12 HUMAN HEALTH EFFECTS – EPIDEMIOLOGICAL STUDIES

It has generally been accepted since the 1970s that there is an association between respiratory health and high levels of particulate air pollution. Early studies focussed on severe pollution episodes, including the Meuse Valley, Belgium, in December 1930; the Manchester and Salfard area, England, 1931; Donora, Pennsylvania, 1948; London, England, 1952; as well as New York City, at approximately the same time. Although the technology of the day has limited the accuracy of reported levels, the associations observed between morbidity/mortality and these episodes of elevated particulate concentrations indicate a clear link between air pollution and adverse health effects. What has not been clear is whether these adverse effects do in fact occur at the much lower concentrations of air pollutants that are experienced today in North America and Western Europe. What has also not been clear is whether these effects were due to air pollution as a whole, or solely to particulate matter, and if so, to which species of particle, or whether the effects were related to one or more other air pollutants which are always present along with particles.

12.1 DESIGN ISSUES

12.1.1 Particle Metrics

Historically, air pollution studies have used different types of measures of particulate matter. One of the commonest of these has been total suspended particulates (TSP); this measure has been superseded in some countries (including Canada, the US, Britain, and some western European countries) by more physiologically-relevant measures of inhalable and/or respirable particles. The TSP method of measurement collects material up to 27-45 µm aerodynamic diameter (d_a) over a 24 h period for assessment by direct weighing. PM_{10}, $PM_{2.5}$, and other less frequently used size selective methods are also gravimetric. Other types of measurements commonly used are the British Smoke Shade or Black Smoke (BS) method and Coefficient of Haze (CoH), which were discussed in further detail in earlier chapters of this document. As a result of these varying methods used for particulate measurement, especially in earlier studies, interpretation and extrapolation of health data for regulatory and air management purposes are difficult. The more inhalable smaller particles (<10 µm in size) have been implicated as more likely to penetrate and deposit themselves in the respiratory passages and lungs (see Chapters 10 and 11). In 1987, the US EPA replaced the previously used TSP standard by PM_{10}. Almost a decade has passed, and many studies have now been published that have measured PM_{10} directly and have attempted to associate these levels with various health effects. Additionally, several studies that measure fine particles, as $PM_{2.5}$ or PM_5, BS, sulphate, and/or particle strong acidity (PSA or H^+) have recently become available, and have been given special consideration in this review. It has been postulated that they may be more dangerous to health than TSP or PM_{10}, since their smaller size means that they are more able to reach the lower respiratory tract and lung (Seaton et al., 1995; Oberdoerster et al., 1995). In addition, some fine particles penetrate more readily than larger particles from ambient air into the indoor environment where most people spend most of their time, thus presenting increased opportunity for exposure (Chapter 6). The role of chemical speciation of particles has been investigated to a very limited extent. In several epidemiological studies, sulphate (SO_4^{2-}) has been used as the particle metric; a smaller number have investigated the role of acidity, as hydrogen ion (H^+). Some laboratory animal studies suggest that numbers of particles may be more important than particle mass, since ultrafine particles have a much greater surface area on which toxic substances such as metals or PAH can be adsorbed (Chapter 10). Very little epidemiological testing of this hypothesis has as yet taken place.

12.1.2 Study Types

Five basic health variables have been examined in these studies: mortality, hospital admissions/emergency department visits, respiratory health (symptoms, medication use, reduced activity days, elementary school absences), pulmonary function, and cancer (the latter in only a few studies, incidental

to other endpoints). All of the epidemiological studies were observational in nature, that is, the investigator had no control over the exposure or treatment of the subjects in the study. These studies contrast with experimental studies (considered in Chapter 11), in which the investigator assigned the subjects to known exposures to particulate matter as well as other experimental conditions (e.g., temperature). It is generally easier to be certain of the cause-effect relationship from results of experimental studies than observational studies. One of the disadvantages with the observational study compared to the experimental study is that it is much more difficult to eliminate potential confounders. While some study designs allow for many of these potential confounders (for example cohort studies can take factors such as cigarette smoking and age into account on an individual basis), it is impossible on theoretical as well as practical grounds to account for all known and unknown potential confounding factors. This inability causes uncertainty with respect to the causal nature of an association between exposure to particulate matter and the observed health outcomes. This uncertainty requires that the data be examined especially carefully if causality is to be entertained, not only with respect to the conduct and results of each study, but with respect to interpretation of the overall findings from all of the studies, including relevant knowledge gained from experimental results.

Observational epidemiology studies fall into two broad categories: longitudinal studies where subjects or populations are followed over time, and cross-sectional studies where subjects are assessed for health outcomes at a particular time, at which time exposure is also ascertained (this can be present or past exposure). Cross-sectional studies usually compare individuals or population in several different locations, in order to be able to sample a wide range of exposures. True cross-sectional studies, in which several populations are compared with respect to health outcome and exposure, are considered to provide the weakest evidence for relationships between adverse health and exposure to particles (or other toxic agents), because differences (e.g., lifestyle factors, occupational exposures, age) between populations make the results highly subject to uncontrolled confounding and bias. Few of the newer studies investigating air pollution have been of this design, although some have retained certain elements of this. For example, the time-series six-city daily mortality study (Schwartz et al., 1996a) and two cohort mortality studies (Dockery et al., 1993; Pope et al., 1995a) both use community-based exposure estimates. The time-series study is not so subject to confounding by differences in populations since they are not correlated with changes in pollutant levels on a daily basis. The cohort mortality studies allow the analysis of the results incorporating most of the known risk factors on an individual basis. Both of these types thus provide stronger evidence for relationships than the true cross-sectional study.

Longitudinal studies are also of two main types: cohort studies and time-series studies. Some additional longitudinal designs have been carried out, such as analysis before, during and after pollution episodes. In a cohort study, subjects are identified and their varied exposures to the agent under investigation is determined, after which they are followed over a specified time to observe the effect of the exposure on health outcomes. Several recent studies have been of this type, in which thousands or hundreds of thousands of individuals in a number of communities have been recruited, categorized with respect to all of the major known potential confounding demographic or lifestyle factors, and their mortality followed over 6 to 16 years with respect to their community exposures to air pollutants. Cohort studies are generally considered to have the strongest design of all the observational studies, since they are able to include controls on an individual basis for most of the important known confounding factors, and to make inferences regarding groups made up of individuals with a given set of measured risk factors.

Most of the recent studies on air pollution have been the second type of longitudinal design, the time-series study. In this type, a time-series composed of changes in daily (or a few days') health indicators such as mortality or hospitalizations (usually data from very large administrative databanks) are followed for periods which have varied between 1 and 19 years, with respect to another time-series of daily variations in pollutant levels. The association of the two series is evaluated after control of other factors (weather, seasons, year-to-year trends, day-to-day and holiday variations, disease epidemics) which also vary with time and which could therefore bias the interpretation of the association. It has been pointed out (Lipfert 1994; Kinney et al., 1995) that the time-series study is less likely than the true cross-sectional study to give results that are potentially confounded due to population differences, since the study population in the time-series analysis is the same over time, and acts as its own "control". It is

subject to confounding due to time-based differences, but these are easier to take into account in the analysis than population risk factors such as smoking status. A major advantage of the time-series study is that it usually provides many more units of observation (typically 1000 days) than cross-sectional studies (2-150 communities), and thus the power of the time-series study to detect effects of low magnitude is usually greater than the power of the cross-sectional study.

All of the observational studies available to date on air pollution are either “ecological” in nature or have some ecological elements. An ecological study is one in which the health outcome is measured for each exposure group and there are no data available on risk factors for individuals in the population (e.g., previous history of disease, diet, smoking, age, race), or on individual exposures (e.g., measurement from a few monitors for the entire city suffice for all members of the population). A direct link between exposure of the individual to the air pollutant and the resulting health outcome is lacking. Therefore no judgements regarding causality or risks to individuals can be made from ecologic studies (the ecological fallacy consists in making inferences from the population to the individual level). Some commentators (primarily from industry) on the research findings from air pollution studies have tried to dismiss the findings from time-series studies on the basis that they were “only ecologic studies”. However, from a public health perspective we are as interested in and concerned about the air quality of the community as we are of the air quality of individual members of the community. Guidelines, objectives and standards are developed for community exposures, on the basis of information from population responses resulting from prior community exposures. Ecological studies can provide important evidence regarding causal relationships between community levels of air pollution and community health.

12.1.3 Time-Series Studies

Most of the recent epidemiological studies considering acute and short-term effects of air pollution on human health have been time-series studies in which the timing of an adverse health event (for example, hospitalizations) is studied in relation to short-term time trends in air pollution within a defined geographic area. Since these form a highly specialized type of epidemiological study, a discussion of their methods, strengths and limitations is included here.

Observational studies try to find relationships between population or community health responses and some characteristic of the environment, in this case air pollution from particulate matter. These relationships are often of low magnitude from a statistical point of view, the relative risk being less than 1.5 in many cases. Moreover, there is intrinsically a high degree of variability in mortality, hospitalizations, and other adverse effects that is unrelated to air pollution. A rigorous statistical analysis is therefore necessary in order to screen out adverse health effects due to non-pollutant-related factors and to have some hope of distinguishing the air pollution “signal” from the background “noise”.

Daily mortality and morbidity (hospitalizations, emergency department visits, etc.) are usually highly cyclic, and undergo strong seasonal fluctuations, with events such as hospitalizations highest in winter and lowest in summer in North America. Ambient particulate matter concentrations can also be seasonal, and their highest levels may or may not coincide with the cyclic fluctuations in health endpoint, depending on location and source of the pollutant. Such seasonal trends could confound the results, and they require some means of adjustment in order to study the question of whether there is any independent association or effect of the pollutant on these health endpoints.

A common method of removing cyclic variations in the data is prefiltering through the use of a multiday (e.g., 15 d or weighted 19 d) moving average, by subtracting from each data point prior to analysis. This is called a “high pass” filter because it allows high frequency fluctuations (daily or weekly) to remain while removing the longer cycles from the data. Regressions with sine and cosine functions of various periodicities are also relatively effective in removing seasonal variations in data. Seasonal dummy variables have been used, but they cannot control for within-season variability. Restriction of the analysis to one season or to a part of a season (1 or 2 months) is another method to overcome seasonal variability (Kinney et al., 1995), but requires large data sets to overcome the loss of part of the data. A fourth method is the use of a nonparametric smoothing technique, such as the STL (Seasonal and Trend decomposition using LOESS, or the locally optimal estimating and smoothing scatter plots) method for estimation (Schwartz, 1996; Cakmak et al., 1996).

Temperature, both high and low, is also associated with adverse health effects, including mortality. Moreover, the strength of the association can be as great or greater than the strength of the particulate-mortality association. For example, a greater part of the variability in mortality was shown to be explained by weather and temperature than by air pollution (Kalkstein and Davis 1989). Temperature can be controlled for in a variety of ways; for example, the non-linear relationship of temperature with disease mortality can be accommodated by separate variables for high and low temperatures, quadratic variables, or by nonparametric smoothing techniques. An additional method of analysis included temperature as one of a number of aspects of weather affecting air masses, grouped as synoptic categories (Kalkstein 1991).

Other weather-related variables include lag time, that is, the time difference between a day with a given pollutant concentration and the day on which the health effect is manifested. Most authors have investigated lag times and included them in the analysis as the data warranted. Autocorrelation is also possible (pollution on one day may not be independent of pollution the next day, or a health outcome on one day may not be independent of health on the following days), and statistical methods are available to test for and overcome this (Schwartz et al., 1996b).

The detrended data are then examined using correlation analysis, regression analysis, or a combination. Regression analysis has commonly been used in recent papers, preceded by correlation analysis in order to give some direction to the regression analysis. It is not obvious at this time which regression model best fits the data, and no one model has been selected as preferential. As stated by Thurston and Kinney (1995), “in time-series analysis, no model is perfect, but some models are more wrong than others”. Poisson regression has been extensively used in the mortality data because mortality is a rare event, following a Poisson distribution. Log normal distributions, and Ordinary Least Squares (OLS) regressions are also common for hospitalization data when large numbers of events are recorded. The results frequently do not appear to be very sensitive to which of these is used (Kinney et al., 1995; Lipfert 1994). Many of the most recent papers using administrative data bases have made use of these more sophisticated statistical techniques, to good effect.

12.1.4 Multiple Pollutants

Airborne pollution alway occurs as a mixture of agents, of which particulate matter is only one. Perhaps the most difficult issue to deal with in drawing any conclusions about the relationship of particulate matter to adverse health outcomes is the presence of other covariate air pollutants and the methods used to disentangle the influence of particulate matter from these other gaseous air pollutants.

Particulate matter, especially in the smaller size fraction, is a primary air pollutant, along with SO_2, NO_x, and CO; these are produced directly from combustion processes (see Chapters 2-4). Sources in North and South America and in western Europe are mostly vehicular traffic, industrial activity and some coal- or oil-fired power generation. Moreover, SO_2 and NO_2 can be transformed into secondary particulates by photochemical processes (into acid or neutral sulphates and nitrates for example) which become part of the fine particle fraction. These four air pollutants are often, (but not always) highly correlated with each other. If variables that are not independent, (i.e., are moderately to highly correlated) are entered into a multipollutant model as independent variables, the basic assumptions of the model regarding independence will be violated and the results will be uncertain and indeed, could be altogether invalid. Therefore, on the basis of common sources and high correlations between them, it would not seem reasonable *a priori* to treat them together in a multipollutant model and expect to obtain accurate estimates of their independent effects on health outcomes. Ozone has a much lower correlation with particulate matter and the other primary pollutants (with the possible exception of NO_2), since it is a secondary air pollutant formed by photo oxidation reactions with NO_x and volatile organic compounds in the atmosphere. Therefore there is some *a priori* reason to expect that models including both ozone and PM would give reasonable estimates of the independent effects of each.

Some investigators (Lipfert 1994; Moolkavgar et al., 1996; Moolkavgar and Luebeck, 1996) have been concerned that the association which has been ascribed to particles is actually reflecting the association of one or more of these other air pollutants that may not have been considered in the analysis or even measured in the study location. These and other investigators have preferred to include several or multiple pollutants together in multipollutant

models, despite the attendant problems of collinearity, in order to allay the suspicion that something has been overlooked.

Other groups of investigators have examined each pollutant alone in models in which the other major non-pollutant variables (weather, season, day-to-day effects) have been accounted for (Dockery et al., 1992; Pope et al., 1992; Schwartz 1993; Pope et al., 1995b; Schwartz et al., 1996b). They have preferred to rely on the association noted in various locations with differing climates, weather patterns, sources and mixtures of air pollutants. However, univariate analyses are considered likely to give biased estimates of effects because of the possibility of more than one causal agent, and because of the high correlations between pollutants.

A modification of this approach has been extension of the analyses to include bivariate regressions with all pollutants that showed associations with adverse health outcomes in the univariate models, accompanied by correlation analyses showing that the correlations between the two are not excessively high (correlations greater than 0.5 would cast doubt on the validity of the results). Pollutants which were not associated in the original univariate analysis were considered unlikely to show associations in pairwise models. This approach is considered to be useful in helping to disentangle the effects of one pollutant from another and in establishing their independent effects within the same locality.

One problem that could occur is modification of the effects of one pollutant by the co-occurring pollutant included in the model. Interaction terms could be developed for the model (Schwartz et al., 1996b), or the effect of high and low levels of one pollutant on the other could be separately analyzed as was done for several of The Air Pollution and Health: a European Approach (APHEA) studies in Europe (Touloumi et al., 1996; Ballester at al., 1996; Sunyer et al., 1996). Another more intractable problem is that of the effect of differential measurement error on the outcome when several pollutants are included together. In all studies, air pollutants have been measured at area monitors, sometimes at only one for an entire city or even larger area (e.g., eastern Tennessee – Dockery et al., 1992). The exposure of individuals in the population will be different than the value give by the ambient area monitor, and will depend on factors such as where they live with respect to the monitor, how evenly spread the pollutant is over the area, whether it has local sources, how much time the individual spends indoors and outdoors, what activities they take part in, and how well the pollutant infiltrates indoors (see Chapter 6). Moreover, the error will be different for each of the measured pollutants that were analyzed since they react differently in the air mass, they may have different local sources, or they may penetrate buildings more or less readily than other pollutants. Lipfert and Wyzga (1995b) have shown that this differential measurement error can bias the interpretation of bivariate or multipollutant analyses, because the pollutant with the least measurement error will have the tightest confidence limits and the effect estimate for the pollutant with the larger measurement error may include zero. This type of error is difficult to recognize or to quantify if suspected, but the possibility should be considered when evaluating the results of bivariate or multipollutant analyses.

While careful analysis and consideration of the results from bivariate analysis in each location are useful in establishing which of several air pollutants have an independent effect on health outcomes in that location, they do not tell us whether particulate matter is really the causal agent, or is acting instead as the best surrogate of the pollutants examined in that location for the air pollution effect. For the overall evaluation of the role of particulate matter versus other air pollutants in exacerbation of adverse health effects, reliance has been placed on the results from a large number of locations in three continents: locations differing in pollutant levels, mixtures of co-occurring air pollutants, climate, and sources. It would be unlikely that co-pollutants could confound the particulate matter-adverse health association in all of these disparate settings.

12.2 ACUTE EFFECTS – MORTALITY

A number of time-series studies, which have used more advanced statistical methods than studies prior to the late 1980s to investigate the association of measures of mortality with increases in daily or several days' concentrations of particulate matter (PM), have been completed in the past decade. The results of these studies have raised questions about the safety of current air quality standards/objectives in both Canada and the United States.

Various measures of particulate matter were used, including total suspended particulates (TSP), $PM_{10/15}$, fine particles or $PM_{2.5}$, sulphates (SO_4^{2-}), and particle strong acidity (PSA or H^+). At the risk of losing valuable information on the nature of the particulate matter-adverse health associations which are provided by studies using TSP as the particle metric, this review on acute mortality effects has concentrated on studies that used inhalable particles, that is, PM_{10} and/or smaller size fractions including $PM_{2.5}$,SO_4^{2-} and H^+. Since the primary purpose of this review was to provide a scientific basis for selection of the National Ambient Air Quality Objectives for PM_{10} and $PM_{2.5}$, and since a relatively large number of studies were available that had used PM_{10}, this was felt to be justified. Particular attention has been given to studies that included both PM_{10} and one or more other measures of fine particles, with the objective of elucidating which of the PM components or properties might be the best indicator for the association of air pollution with adverse health. Studies published by December 1996 from locations in North America, South America and Europe, analyzed by regression techniques that tried to take account of many of the potential confounding factors noted previously, were included. Nineteen studies have been summarized in Table 12.1.

12.2.1 Acute Mortality Studies and PM_{10}

Daily mortality and PM_{10} pollution were studied in the Utah Valley between April 1985 and December 1989 (Pope et al., 1992). During winter temperature inversions, air pollutants were trapped near the valley floor, a situation that often resulted in high concentrations of PM_{10}, primarily due to emissions from a steel mill. The steel mill contributed approximately 82-92% of the PM_{10} emissions in the area. Monitors in Lindon, Provo and Orem collected PM_{10} data along with records of SO_2, NO_2, O_3 and aerosol strong acidity levels, all of which were found to be very low by comparison to other locations. The concurrent-day mean PM_{10} level was calculated to be 47 $\mu g/m^3$ (range: 1-365 $\mu g/m^3$).

Poisson regression with the generalized estimating equation of Liang and Zager was used to estimate mortality associations, correcting for autocorrelations. Adjustments were made for seasonal and yearly time trends, temperature, humidity, and if necessary, for temperature-PM_{10} interactions. A strong statistically significant relationship between PM_{10} pollution and mortality was found. Mortality averaged approximately 4-5% higher for each 50 $\mu g/m^3$ increase in concurrent-day PM_{10} pollution. On days when PM_{10} levels exceeded 100 $\mu g/m^3$, mortality was approximately 11% higher than on days when PM_{10} was less than 50 $\mu g/m^3$. Circumstances also allowed for a comparison of mortality when the mill was open or closed. Actual deaths per day were about 40% higher than expected when the mill was open. The strongest PM_{10}-mortality association was with the 5 d moving average (lag day 0-5) of PM_{10}. An increase in PM_{10} levels of 100 $\mu g/m^3$ (average lag 0-5) was associated with a 16% increase in total mortality (t=4.78). The association was greatest for respiratory deaths, at 43%, followed by cardiovascular deaths at 20%. Dose-response information based on division into quintiles indicated that the relative risk increased monotonically with increasing PM_{10}. The PM_{10} association was robust to a number of alternative model specifications to account for seasonality and weather (Pope et al., 1992). Since the gaseous pollutants were very low in this location, the study has been considered to provide strong evidence for the specific contribution of particulate matter to mortality (Pope et al., 1995b; US EPA 1996). It was noted by Thurston (1996) that CO, which is a risk factor in cardiovascular disease (CV), was not considered in the analysis, although it exceeded the US ambient standards on a number of occasions and thus could have acted partly as a covariate.

In a re-analysis and extension of the Pope et al. (1992) data, Lyon et al. (1995) extended the analysis by three years to 1992, and confirmed the previous findings by Pope that PM_{10} concentrations above 50 $\mu g/m^3$ increased daily mortality by about 4%, However, Lyon et al. maintained that additional analysis of the data by individual year, season, age of decedents, or location at death revealed inconsistencies in the association between PM_{10} air pollution and daily mortality, such that any question of causality was ruled out.

Table 12.1 Summary of Daily Time-Series Mortality Studies

LOCATION (population) (duration, dates) AUTHORS	PARTICLE METRIC, µg/m³ (MEAN; RANGE)	RELATIVE RISK @ 100 µg/m³ increase. (95% CI) (Lag, d)	OTHER POLLUTANTS CONSIDERED (µg/m³ or ppb)	RELATIVE RISK @ 100 µg/m³ (95% CI) (Lag, d)	CO-REGRESSION, INTERACTIONS	COMMENTS, OTHER
Utah Co. US (<500,000) (3.7 y, 1985-89) Pope et al., 1992	PM_{10} (47; 1-365)	1.16 (t=4.8) (all-c.) 5-d moving av.) 1.43 (respiratory) 1.20 (CV)	H^+ (below d.l.) SO_2 (negli.) NO_2 (low) O_3 (low in winter when PM_{10} high	not regressed	not considered to be necessary to correlate or co-regress other air pollutants because of low levels – Analyzed in later work (EPA 1996) O_3 negatively correl. with PM, strengthening PM effect PM_{10} RR 1.38 (0.98-1.94) +O_3	– Strong assoc. between PM_{10} and mortality was robust to changes in model specs., – coherent with morbidity results, same area. – Stat. analysis was careful. – Considered strong support for PM effect – Major criticism is lack of quantitative assessment of other air pollutants. CO, known to be above std., was not tested.
Utah Col US (<500,000 (7.7 y, 1985-92) Lyon et al., 1995	PM_{10} (as above)	1.04 (all-cause) (5d (0.98-1.10) (5d av) 1.13 (CV) (1.04-1.24 1.03 (resp) (0.86-1.3 1.08 (wntr; 0.98-1.2 1.13 (spr., 0.94-1.36 (summer., fall n.s.) (Indiv. years. n.s.)		Not considered		Despite dichotomization of PM_{10} data and consequent loss of data points, PM_{10} RR were signif. or marg. sign. in several cases. – did not succeed in proving that Pope et al. (1992) results were inconsistent
Salt Lake Co, Utah (4.5 y, 1985-1990) Styer et al., 1995	PM_{10} (48; 9-194)	n.s. for year, season (elderly, >65 y)	none considered		wide variety of weather and seasonal corrections included, but no other air pollutants	Complex statistical treatment makes interpretation of negative results difficult
Birmingham US (900,000) (3.4 y, Aug 85-Dec88) Schwartz 1993	PM_{10} (47.9; 21-80 (10th, 90th; 163 max)	1.11 (lag 1,2,3 mean) (1.02-1.20)	none considered			– PM_{10} was assoc. with mortality, warm city – Statistical analysis good; sensitivity analysis done; same results found with different models, different methods of control for weather, temp., epidemics, etc. – Major lack is not considering any other air pollutants which could act as covariates

Table 12.1 Summary of Daily Time-Series Mortality Studies *(continued)*

LOCATION (population) (duration, dates) AUTHORS	PARTICLE METRIC, µg/m³ (MEAN; RANGE)	RELATIVE RISK @ 100 µg/m³ increase. (95% CI) (Lag, d)	OTHER POLLUTANTS CONSIDERED (µg/m³ or ppb)	RELATIVE RISK @ 100 µg/m³ (95% CI) (Lag, d)	CO-REGRESSION, INTERACTIONS	COMMENTS, OTHER
Los Angeles Co. US (6 Million) (6 y, 1985-90) (only 364 d; 6-d monitoring) Kinney et al., 1995	PM_{10} (58±23; 15-177)	1.05 (Lag 0) (1.00-1.11) (RR = 1.03-1.09 for 14 combinations of temporal cycles, model, and weather)	O_3 (Lag 1) CO	O_3 only 1.02 (1.00-1.05) O_3 +PM 1.00 (0.94-1.06) CO only 1.07 (1.01-1.13) CO + PM 1.05 (0.99-1.12)	PM_{10} remained sign. with O_3 incl. PM RR =1.05 (1.00-1.11) with O_3 – O_3 n.s. (But only 364 d of both) CO found in prev. anal to be sign. PM RR 1.04 (0.98-1.09 with CO) – PM assoc weaker, marg. with CO – CO also weaker, marg. with PM	PM_{10} association was robust to different methods of control for cyclic var., weather, type of stat. anal, and other pollutants.RR = 1.02-1.09 for 17 different methods. – O_3 was not indep.assoc. with mortality – CO was independently assoc. But PM remained also indep. assoc. – SO_2 not considered, but low in LA – NO_2 not considered; known to be high
Chicago (Cook Co.) US (5.3 million) (6 y, 1985-90) Ito & Thurston, 1996	PM_{10} 40.7 ± 19.1 (20-65; 10th and 90th centiles (overestim. white suburbs- city monit.)	(Adults, age 15+) 1.05 (Av., L0+1) (1.03-1.08) 1.14 (1.04-1.25) resp 1.12 (1.06-1.18) canc 1.03 (0.98-1.07) circ	O_3 (38 ppb) SO_2 (24.5 ppb) CO (2.05 ppm)	1.10 (1.06-1.15) (lag 1day) 1.10 (0.95-1.3) resp 1.08 (0.99-1.18) canc 1.14 (1.05-1.19) circ. n.s. n.s.	Correlation coefficients: r= PM_{10} – O_3 : 0.37 (moderate) PM_{10} – temp: 0.17 (low) O_3 – temp: 0.33 (moderate) temp – mortality 0.4-0.5 (mod-high) Coregression, PM-O_3 (+temp, etc) PM_{10} 1.04 (1.01-1.07) (L av 0+1) O_3 1.07 (1.01-1.12) (L av 0+1) (both lower than single regression but both significant)	– Provides good evidence that PM_{10} is assoc with mortality. Assoc robust to other pollutants, esp. O_3, which was independently assoc. with mortality. – PM showed cause specificity -elev RR for respiratory, cancer mortality but not CV. – Temperature also had incr. RR and was carefully analysed in several ways. – Authors thought some residual confounding of O_3 by hot temp. remained – Race and gender-specific RRs were developed (elev for blacks, females (B+w)) – Good analysis. Didn't look at NO_2.
Chicago (Cook Co) US (5.3 million) (6 Y, 1985-90) Styer et al., 1995	PM_{10} 38 (median) (3-365) (28-51 IQR or interquartile range)	(Elderly, age 65+) 1.054 ± 0.020 (yr) (n.s. in wint, summer) 1.088±0.03 (spring) 1.138±0.04 (F, 3 tms) 1.158±0.05 (F, 5 tms) (all age mortality.) 1.080±0.04 (Fall, 5) terms included in reg	none		no consideration of interactions with other air pollutants. Complex modelling of temperature, season, year, humidity, day of week, lag temp, tag humidity, lag d-of week. Different terms for each season included in Poisson regression	– Did not provide good evidence that PM_{10} was associated with mortality in the elderly – RR signif. raised in fall and spring but PM_{10} was highest in late spring and summer – Reason for difference between Styer results and Ito & Thurston results may be due to treatment by season. All year mortality RR was similar. I & T (96) didn't analyze by season.

Table 12.1 Summary of Daily Time-Series Mortality Studies *(continued)*

LOCATION (population) (duration, dates) AUTHORS	PARTICLE METRIC, µg/m³ (MEAN; RANGE)	RELATIVE RISK @ 100 µg/m³ increase. (95% CI) (Lag, d)	OTHER POLLUTANTS CONSIDERED (µg/m³ or ppb)	RELATIVE RISK @ 100 µg/m³ (95% CI) (Lag, d)	CO-REGRESSION, INTERACTIONS	COMMENTS, OTHER
Santiago, Chile (4.4 million) (790 d, 1989-91) (43,450 deaths) Ostro et al., 1996	PM_{10} (115; 32-367) winter mean 141 summer mean 76 (large proportion SO_4^{2-}, fine PM, from diesel)	(Poisson, full correct) 1.07 (1.03-1.10) Tot. 1.13 (1.08-1.23) resp 1.08 (1.03-1.12) cvd 1.10 (1.06-1.12) male 1.05 (1.00-1.09) fem. 1.10 (1.06-1.12) 65+ (OLS, min. Temp, tot) 1.10 (1.08-1.1.) (for mean increase of 115) (OLS, no corr, total mortality) @ mean inc 1.16 (1.14-1.18)	O_3 (1 h max) (53 ppb, 11-264) RR for yr. N.s. (OLS or Poisson) summer-1.04 (1.00-1.07) (Poisson) 1.02 (1.00-1.09) (OLS) NO2 (1 h max) (56 ppb, 10-258) RR 1.02 (1.01-1.04) OLS. N.s. Poi SO2 (1 h max) (60 ppb, 4-368)	n.s. for full yr (OLS or Ps) 1.04(Ps), 1.07 (OLS)-su 0.99 (y – Ps) 1.02 (y-OLS 1.04 (1.00-1.07) summer 1.01-1.02 (OLS, y, su, Poisson, yr., (all sign.))	correlation coefficients r = PM-O_3 -0.23; PM-SO_2 0.64 (PM-O_3 0.34-summ) PM-NO_2 0.73 Pairwise regr., OLS- y + su., Poi-y: PM_{10}: 1.04, 1.07, 1.04 (+O_3, NO_2, SO_2) 1.06 (0.97-1.11 – sum.,+ O_3) O_3+ PM: 0.97-0.99 (OLS, Poi, yr) 1.02 (1.00-1.05) (OLS, su 1.04 (1.02-1.09) (Poi, su) NO_2+PM: n.s. yr. or su (0.97-1.03)	– Good evidence that PM_{10} is assoc. With mortality. Robust to diff. methods of analysis. Extensive sensitivity anal. Resp. RR 1.15, CV RR 1.09 (cf total 1.08) Assoc. unchanged or stronger when regressed with NO_2, SO_2, for year or summer. PM_{10} weaker in summer with O_3 – O_3 independently assoc. In summer (RR 1.02-1.04) – comprehensive analysis, careful, except didn't consider CO
Sao Paulo Brazil (16 million) 1 y, May '90-Apr 91 Saldiva et al., 1995 Saldiva et al., 1994 (same as above)	PM_{10} (82.4 ± 38.8) as above	1.082 ± 0.019 (elderly ≥ 65 y) n.s. (children, respiratory mortality)	CO SO_2 NO_2 O_3 CO, SO_2, O_3 NO_2	1.13 ± 0.04 Significant Significant n.s. n.s., all 3 1.24 (1.13-1.34)	All pollutants were co-regressed – PM_{10} RR = 1.083 ± 0.033 in full model (same as alone) – CO, SO_2, NO_2 n.s. in full model correl. coeff. mod-high, 0.55 -0.68 NO_2 mod. highly correl. to others Without NO_2, no consistent relationships evident	– PM_{10} was the only pollutant which remained significant in the full coregr. – no seasonal analysis was done for O_3, which could explain neg. results. – PM_{10} had no effect – NO_2 was only pollutant related to respiratory mortality in children
Lyon, France (410,000) (6 y, 1985-90) Zmirou et al., 1996	PM_{13} 38; 5-98) (by radiometry, said to be equiv. to PM_{10})	n.s. (1.04- all-cause) 1.08 (respiratory) (1.00-1.18) 1.08 (CV) (0.99-1.10) (marg.)	SO_2 NO_2 O_3 (mean 1 h max. <20 all yr)	1.44 (resp) (1.1-1.8) 2.08 (CV) (1.4-3.9) n.s. n.s.	– PM_{13} and SO_2 coregressed – SO_2 sign. with PM_{13} but strength reduced; SO_2 RR=1.27 (PM_{13}<60) SO_2 RR = 1.19 (PM_{13}>60)	PM_{13} was not assoc. with all-cause mort. Weak association with respiratory, CV mortality – SO_2 hadvery strong assoc., slightly. reduced when PM in model – no effect for O_3; central monitor affected by NO_2 scavenging. – No CO (confounder in CV results?)

Table 12.1 Summary of Daily Time-Series Mortality Studies *(continued)*

LOCATION (population) (duration, dates) AUTHORS	PARTICLE METRIC, µg/m³ (MEAN; RANGE)	RELATIVE RISK @ 100 µg/m³ increase. (95% CI) (Lag, d)	OTHER POLLUTANTS CONSIDERED (µg/m³ or ppb)	RELATIVE RISK @ 100 µg/m³ (95% CI) (Lag, d)	CO-REGRESSION, INTERACTIONS	COMMENTS, OTHER
St. Louis, Mo., US (2.3 million) 1 y, Sept 1985-Aug 1986) Kingston-Harriman, Tenn., USA (640,000) (1 y, as above) Dockery et al. 1992	PM_{10} 27.6 (max 97) $PM_{2.5}$ 17.7 (max 75) $PM_{10-2.5}$ SO_4^{2-} 8.0 (max 38) H^+ 9.7 nmol/m³ PM_{10} 30 (max 67) $PM_{2.5}$ 21 (max 58) $PM_{10-2.5}$ SO_4^{2-} 8.7 (max 27) PSA (as H^+) nmol/m³	1.16 (L 1 d) 1.19 (p=0.075) 1.28 (p=0.056) weak pos., n.s. weak pos., n.s. 1.17 (n.s. P=0.28) n.s. n.s. n.s. n.s.	SO_2 (24 h) NO_2 (24 h) O_3 (24 h) as above	n.s. n.s. n.s. Similar to St. L; none of gaseous pollutants significant (reanalysis in EPA 1996: PM_{10} RR including O_3) St L: 1.12 (0.99-1.30) KH: 1.17 (0.97-1.52)	– pollutants regressed singly, except fine and coarse particle ($PM_{2.5}$ and $PM_{10-2.5}$) considered simultaneously – PM_{10}/SO_4^{2-} correl. coeff. = 0.52 – PM_{10}/H^+ correl. coeff. = 0.76	– PM_{10} was only pollutant assoc. with mortality in St. Louis. – $PM_{2.5}$ and CP marg. signif., about equal – SO_4^{2-} and H^+ weakly pos., but n.s. – Order was $PM_{10}>PM_{2.5}=CP>SO_4^{2-}>H^+$ Assoc. not stat. sign. in E Tenn. because of small pop., short time period, exposure missclass. – Effect of gaseous poll. not tested – reason for O_3 n.s. was 24 h averaging
6-CITY study, US St. Louis (2.3 M) E. Tenn (0.6 M) Boston, (2.3 M) Steubenville (0.2 M) Topeka (0.15 M) Portage (0.3 M) (5.9 M; 8 y, '79-87) Schwartz et al., 1996a	PM_{10} 25.0 (8.0-67.8) CP 9.0 (1.0-30.1) $PM_{2.5}$ 14.7 (4.3-431) SO_4^{2-} 5.8 (1.5-22.3) H^+ 10 (0-67) (nmol/m³) (medians, 5th +95th centiles)	1.08 (1.05-1.10 (2 d)) 1.04 (0.90-1.10 (2 d)) 1.15 (1.10-1.19 (2 d)) 1.22 (1.13-1.32) n.s. (t=0.76) indiv. city – $PM_{2.5}$: Bo 1.22 (1.15-1.29) ET 1.14 (1.02-1.26) SL 1.10 (1.04-1.17) St 1.10 (0.90-1.21) Po 1.12 (0.97-1.28) To 1.08 (0.80-1.36)	none (data for SO_2, NO_2, O_3 available)	not calculated	– purposely did not examine interactions between gases and PM – When CP and $PM_{2.5}$ co-regressed, PM RR was unaffected but CP RR was 0. Correlation co-efficents were low, 0.23-0.43, in 5 of 6 cities, but 0.69 in Steubenville, the city in which CP RR was sign. and $PM_{2.5}$ RR was not.	– $PM_{2.5}$ was particle most strongly assoc. with total mortality, also CV, COPD mortality (RR increased to 1.21, 1.33) – CP not assoc. in 5 of 6 cities – CP ruled out for several reasons: weak n.s. assoc.; low correl coeff; poor model fit with $PM_{2.5}$; CM RR prop to PM/CP ratio; low PM_{10} RR in 1 city with high CP – SO_4^{2-} also assoc., but not as strongly, and indep. of $PM_{2.5}$ assoc. – H^+ not assoc. (fewer measurements for H^+, but N=1600+, so enough power) – Carefully conducted, powerful study

Table 12.1 Summary of Daily Time-Series Mortality Studies *(continued)*

LOCATION (population) (duration, dates) AUTHORS	PARTICLE METRIC, µg/m³ (MEAN; RANGE)	RELATIVE RISK @ 100 µg/m³ increase. (95% CI) (Lag, d)	OTHER POLLUTANTS CONSIDERED (µg/m³ or ppb)	RELATIVE RISK @ 100 µg/m³ (95% CI) (Lag, d)	CO-REGRESSION, INTERACTIONS	COMMENTS, OTHER
Philadelphia, US (million) (2 summers, 1992-3) Dockery et al., 1996b	PM_{10} (not given) $PM_{2.5}$ (not given) CP ($PM_{10-2.5}$) (not given) H^+	1.12 (p=0.06, marg) 1.20 (1.04-1.35) (L 1) n.s. (p=0.85) n.s. (p=0.57)	O_3 SO_2 CO	1.09 (sing., but CI n.g.) n.s. (p=0.78) n.s. (neg. assoc.)	no information on whether co-regression or correlation analysis carried out	$PM_{2.5}$ was most strongly and consistently assoc. with mortality – ozone was also independently assoc. with total and non-CV mort. – ozone was not consistent by season, the RR being lowest in summer. – small study, short duration, abstract only
Toronto, Canada (2.5 million) (19 y, 1972-90) Ozkaynak et al., 1995	TSP SO_4^{2-} CoH b-extiction coeff. PM_{10} (meas + est.)	1.07 (from est PM_{10}) (1.05-1.09) (From Thurston 1996)	O_3 SO_2 NO_2 CO	1.047	(abstract; preliminary paper) Thurston 1996 give addit. Info. PM_{10} RR = 1.05 (1.03-1.07) with other pollutants in regression.	– work not fully reported. – PM_{10} was estimated (site-specific) from TSP, monitored PM_{10}, CoH, SO_4^{2-} and Bext. – PM and ozone indep. assoc. with mortality
Amsterdam, NL (700,000) (7 y, 1986-92) Verhoeff et al., 1996	PM_{10} (38; max 163) BS (12; max 81)	1.06 (marg.) (0.99 - 1.14) (L 0d) 1.19 (1.02 - 1.38) (L 0d)	O_3 SO_2 CO	1.05 (1.0 -1.10) (L 2d) n.s. n.s.	PM_{10} RR lowered, n.s. with SO_2, O_3 PM_{10} RR raised, CO BS RR sign. with O_3, SO_2, CO O_3 marginally sign. with BS O_3 significant with PM_{10}	– Supports importance of BS, finer particle size, (but not coregr.with PM_{10}) – PM_{10} effect partly due to O_3, SO_2 – ozone had independent effects – No analysis for NO_2 (possible confounder)
Paris, France (6.1 million) (6 y, 1986-91) (Dab et al., 1996)	PM_{13} (51; 19 – 137) BS (32; 11 – 23)	1.17 (1.04 – 1.31) (L 1d) 1.07 (marg) (0.98 – 1.18) (L 1d)	O_3, 1 h max. O_3, 8 h NO_2 SO_2, 24 h SO_2, 1 h max	n.s. n.s. Sign., in summer (L 1d) n.s. 1.07 (1.015-1.16) (L 1d)	None tested	– Stronger association for PM_{13} than BS which may not include all fine particles – SO_2 may play a role in this location – lack of interaction testing means uncertain of strength of PM association – CO was not tested -no seas. anal. for O_3 – possible reason for lack of significance

Table 12.1 Summary of Daily Time-Series Mortality Studies *(continued)*

LOCATION (population) (duration, dates) AUTHORS	PARTICLE METRIC, µg/m³ (MEAN; RANGE)	RELATIVE RISK @ 100 µg/m³ increase. (95% CI) (Lag, d)	OTHER POLLUTANTS CONSIDERED (µg/m³ or ppb)	RELATIVE RISK @ 100 µg/m³ (95% CI) (Lag, d)	CO-REGRESSION, INTERACTIONS	COMMENTS, OTHER
Athens, Greece (<3 million) (5 y, 1987-91) Touloumi et al., 1996	BS (84; 9 -333) [PM_{10}] [79]	1.05 (1.03 – 1.08) (L 1d) (1.054) (1.033 – 1.087) [site-specific conversion from BS]	SO_2 CO	1.12 (1.07 – 1.16) (L 1d) 1.10 (@ 10 mg/m³) (1.05 – 1.15) (L 0d)	BS RR lowered with SO_2; RR = 1.03 when SO_2<100; RR = 1.02 (n.s.) when SO_2> 100 SO_2 RR incr. To 1.15 (BS>100) BS, CO highly corr. (R=0.79) CO n.s. with BS in previous report (Touloumi et al. 1994)	– BS effect was partly independent of SO_2 – SO_2 plays a more important role than BS, or is a better surrogate for air pollutants – No analysis for NO_2 or O_3 (other possible confounders)
London, UK (8 million) (6 y, 1987-92) Anderson et al., 1996	BS (14.6; 8 – 23)	1.11 (all-cause, year) (1.05 – 1.17) (L 1d) (also sign., summer + winter alone) n.s. – resp. mort. n.s. – CV mort.	O3 1 h max. 8 h av. NO_2 1 h max NO_2 24 h SO_2 24 h	1.08 (all-cause, y) (1.04 – 1.12) (L 0d) CV – 1.04 (year) resp. – 1.07 (year) 1.10 (all-c, summer) sign., CV, summer n.s. sign., all-c., summer	– BS RR (all-c., y.,wi.) increased with O_3. – O_3 RR unchanged with BS (all-c.-su., CV- su..; resp.- y., su., wi.) RR for BS and O_3 unchanged with NO_2 or SO_2	– Both BS and O_3 were independently associated with mortality – O_3 a more important predictor than BS – BS was not assoc. with either respiratory or CV mortality – inconsistency CO was not included in analysis
Barcelona, Spain (million) (7 y, 1985-91) Sunyer et al., 1996	BS (49.7 – winter) (35 – summer)	1.07 (all-cause, y) (1.03 – 1.11) 1.09 – respiratory, y 1.10 (marg.)- CV, y	SO_2 O_3 NO_2	1.13, 1.15, 1.24 (all-c, y; CV, y; resp, su) 1.05, 1.06 (y, all-c, CV) 1.06, 1.09 (su, all-c, CV) sign., all-c., CV, both year + summer	– no bivariate regressions done. – Correlation coefficient for BS-SO_2 was high (r=0.69) – Correlation coeff. for BS-O_3-NO_2 were rel. low, (r= 0.29-0.33)	– BS was assoc. with all-cause, CV and resp mortality in single poll. analysis – SO_2 was more strongly assoc. than BS but high correl. coef. precludes separation of effects for these two pollutants. – Authors sugg. BS not best surrogate for vehicle-related PM pollution – O_3 effect real, and independent of BS – No CO anal.; could be CV confounder)
Valencia, Spain (0.75 million) (3 y, 1991-3) Ballester et al., 1996	BS (68; 5-226) (77 – winter) (58 – summer)	1.09 (1.03 – 1.15) (All cause, year) 1.12 (1.03 – 1.22) (cardiovascular) <1.0 (respiratory)	SO_2	1.07 (0.99 – 1.15) (all cause, summer)	No bivariate regressions. SO_2 -BS correlation 0.24 (relatively low)	

Closer examination of their analyses does not support their case very well. Subdivision of the data by year, season, age, or cause of death probably contributed to lack of significance of many of the outcomes because of low numbers of cases. Analysis of the data by year showed that the risk was not significant for any individual year, or for the total, although the relative risk (RR) reached marginal significance for two of the years and the total. However, when the analysis was carried out using a similar method with continuous data for the same years as the Pope et al. study, the regression coefficients were similar in the two studies. Similarly, seasonal analysis, with the highest risk ratio said to be in spring, was also cited as calling into question the evidence for PM_{10}, which is highest in winter in this location. The data presented indicate that the RR for winter was 1.08 (95% CI 0.98-1.19), while the RR for spring, although higher at 1.13, was more variable and was not significant (95% CI 0.94-1.36).

The authors also cited the evidence that the greatest RR was for people over age 75 years who died in hospitals as further evidence that particulate matter could not have been associated with mortality. They reasoned that exposure to particulate matter would likely be less in hospitals than outside or at home, and therefore could not have been involved. This assumption regarding exposure is not necessarily true, since the PM_{10} in this location was of industrial origin and thus was probably largely in the fine fraction which penetrates buildings quite easily (Chapter 6). In addition, people could be expected to go to hospital for emergency treatment and/or admission, and to die in hospital later, a circumstance which is usually accounted for by allowing for one or more days of lag time (in the Lyon study 3 d and 5 d averaged lag times were used) between the pollutant peak concentration and measurements of mortality. A lack of consistency was also cited with respect to specific cause of death, since the Pope analysis showed respiratory deaths to be most elevated, followed by cardiovascular deaths (CVD), while the Lyon analysis found that the RR for respiratory deaths was not significant and the CVD RR was elevated (RR=1.13; 95% CI 1.04-1.24). As with other analyses in the Lyon et al. study, the results appeared to be affected by high variability introduced by low numbers of events due to splitting up of the available data.

A major difference in treatment of data between the Lyon and the Pope studies, which also could have accounted for a substantial part of the difference in results, was the dichotomization of PM_{10} data using 50 $\mu g/m^3$ as the cutoff, as carried out in the Lyon et al. study (the 5 d moving average was used in both studies), and the consequent loss of data compared to the analysis of continuous data carried out by Pope et al. (1992). Since the fourth quintile average PM_{10} values in Lyon et al. (1995) were below 50 $\mu g/m^3$ but still showed a substantial increase in relative risk, these responses would have been discounted (i.e., given a value of 0) and only the upper 20-25% of data used, thus reducing the significance of the PM_{10} response in most of the subsequent analyses.

The dose-response analysis of Lyon et al. (1995) looking at quintiles of PM_{10} and associated responses, indicated that the RR was not elevated above 1.0 for the first three quintiles, but was elevated at quintile four (mean PM_{10} 47 $\mu g/m^3$) with a RR of 1.046 (no CI given), i.e., that a threshold existed between 36 and 47 $\mu g/m^3$. In contrast, the Pope et al. (1992) study had shown a relatively smooth dose-response curve in a similar quintile analysis without any evidence of non-linearity in response between 17 and 84 $\mu g/m^3$, but for a smaller data set in the same location. While comparison of Lyon's PM_{10} data for the extra three years did not reveal any striking changes in PM_{10} levels from the previous three years analyzed in both studies, the quintile division breakdowns showed substantial anomalies between the two studies. The mean of the first four quintiles in Lyon et al. (1995) were 5 to 9 $\mu g/m^3$ lower that those in the Pope et al. (1992) study, while the mean for the fifth quintile was 15 $\mu g/m^3$ above the fifth quintile of Pope et al. (1992). These anomalies indicate that considerable caution should be taken in weighting the evidence from the Lyon et al. (1995) study in the overall evaluation.

An analysis of PM_{10} and mortality in the elderly was conducted by Styer et al. (1995) for Salt Lake County, Utah, which is the neighbouring area to that considered in the Pope et al. (1992) study. It has approximately the same mean (48 $\mu g/m^3$) and seasonal pattern for PM_{10} as Utah County. A Poisson distribution was assumed for small counts (average 7/d), and factors for year, season, within-season trends, seasonal interactions with PM_{10}, temperature, humidity and barometric pressure were added to the models. Three-day average PM_{10} values accounted for possible lagged effects. In the resulting analyses, PM_{10} was never a significant predictor of elderly

mortality in Salt Lake Co., with or without the addition of barometric pressure which a supplementary semi-parametric analysis indicated was important in Salt Lake. No seasonal or within-season effects of PM_{10} on mortality were indicated. Since the authors in this study used the same general methods as Pope et al. (1992) and other investigators, i.e., testing of various models incorporating the effects of weather, day to day, and season by Poisson regression techniques, the methods used did not suggest any apparent reason to the reviewer for the negative results, other than the suspicion that the models used by Styer et al. (1995) overcorrected for interactions between PM and weather.

Schwartz (1993) studied the impact of air pollution on daily mortality in Birmingham, Alabama, between 1985 and 1988. Daily death counts from detailed mortality tapes of the National Center for Health Statistics were matched to 24 h average PM_{10} levels from all the population-oriented monitors within the city. The reported mean PM_{10} level was 47.9 $\mu g/m^3$, with a maximum of 163 $\mu g/m^3$. No specific sources of the pollution were mentioned. Concentrations were highest in summer and lowest in winter, the opposite of the trend in daily mortality. Significant associations were found between PM_{10} and daily mortality at concentrations below 150 $\mu g/m^{3,}$, the 24 h air quality standard. The relative risk calculated for every 100 $\mu g/m^3$ increase in the mean of the three days' previous PM_{10} was 1.11, with a 95% confidence interval of 1.02-1.20. The RR was virtually unchanged when other regression models or alternative methods of controlling for temperature and seasonality were used. The results were not sensitive to high pollutant levels, and the response was evident down to the lowest level of PM_{10} (20 $\mu g/m^3$). The relative increase in mortality was higher for respiratory and cardiovascular deaths and lower for all other causes, suggesting a similar etiological factor for these two endpoints. This study carefully controlled for seasonal and meteorological variables, and carried out sensitivity analyses to ensure that the associations were not biased. The results of this study thus clearly support the association of air pollution, as represented here by PM_{10}, with increased mortality. However, since this analysis did not consider ozone, it cannot exclude the possiblilty that ozone, which is often not highly correlated with PM due to somewhat differing conditions for formation, is also independently associated with mortality in this community.

Kinney et al. (1995) conducted a study on mortality and daily variations in particulate matter in Los Angeles, California where the mean PM_{10} values were calculated to be 58 $\mu g/m^3$, with a maximum of 177 $\mu g/m^3$. The relative risk for a 100 $\mu g/m^3$ increase in PM_{10} was reported to be 1.05 (95% CI 1.01 to 1.10) when regressed alone. The relative risk and its significance was unchanged for PM_{10} when regressed with ozone, but ozone was no longer significant (RR=1.0). Substantial correlation was reported in this location between ozone and PM_{10}, which made it impossible to separate out any possible independent effects of ozone when they were both included together. The relative risk for PM_{10} dropped to 1.04 (95% CI 0.98 to 1.09) when regressed simultaneously with CO. The relative risk for CO also dropped slightly from 1.07 alone to 1.05 (95% CI 0.99 -1.12) with PM_{10} . The correlation between PM_{10} and CO was somewhat less than that for PM_{10} and ozone. This study showed that air pollution, as measured about equally by both PM_{10} and CO, was associated with mortality in Los Angeles.

An analysis of mortality data for the six years from 1985-1990 for Chicago and Cook Co, Illinois was presented by Ito and Thurston (1996). The mean PM_{10} was reported as 40.7 $\mu g/m^3$ (10th and 90th percentiles 17 and 65.6 $\mu g/m^3$). The relative risk for total non-accidental mortality for a 100 $\mu g/m^3$ increase in PM_{10} was 1.05 (95% CI 1.03-1.08) (single pollutant regression) and 1.04 (95% CI 1.01 to 1.07) for a two-pollutant model including ozone. Ozone was independently associated, but the RR for ozone was reduced more than PM_{10} when both were included. The authors also pointed out that the pattern of associations seen for ozone closely mirrored those for temperature, which was known to be correlated with ozone concentrations, suggesting that the effects noted for ozone could have been explained by temperature effects. Cause specificity was demonstrated with PM_{10}, with elevated relative risks for respiratory and cancer deaths, and marginally elevated RR for cardiovascular deaths, while ozone was not associated with an elevated relative risk for respiratory deaths as might have been expected. CO, SO_2, and the extinction coefficient b_{ext}, a measure highly correlated with fine particulate matter, were also considered but were not as good predictors of an air pollution effect on mortality as PM_{10} , which was the best predictor in this study.

Mortality in the elderly, age 65+ years, was examined by Styer et al. (1995) in a second analysis for Cook

Co., IL (Chicago). For the six years 1985-1990, the median PM_{10} concentration was 38 $\mu g/m^3$ (range 3-365 $\mu g/m^3$), and the interquartile range was 28-51 $\mu g/m^3$. An average of 117 nonaccidental deaths/day (all ages) and 83 deaths/day (age 65+) were recorded, and a total of over 18,000 deaths in the elderly were analyzed. A high degree of association of PM_{10} with meterology (correlation coefficient of PM_{10} with daily mean temperature = 0.52) and a lesser degree of association of PM_{10} with mortality was found. Various treatments for year, season and weather were examined in regression models, including terms for each year, cube of the day of year, polynomial terms for temperature lagged one and two days, humidity on day 0 and lagged two days, barometric pressure and a polynomial term for pressure lagged one and two days. These were examined in a semi-parametric Poisson regression model. The majority of analyses split data by three-month season, and also month-by-month, both of which would have the effect of reducing the number of underlying observations, thus reducing the power of the study to detect an effect.

The whole year estimate for PM_{10} (3 d average, lag 0-3 d) gave a relative risk of 1.055 (95% CI 1.01-1.10 for a 100 $\mu g/m^3$ increase) for persons aged 65 or more, which was similar to the RR estimated by Ito and Thurston (1996). However, the seasonal estimates were significant only in spring and fall, which did not coincide with the season of highest PM_{10} concentration (summer). The spring and fall results could not be explained by high pollen counts, which were available and were accounted for in the analysis. Since PM_{10} in the fall season showed the highest association with mortality, this season was analyzed in greater detail, using various model predictors for each category. The RR for total mortality (all ages), elderly mortality, males aged 65+, whites aged 65+, and cancer deaths were significantly elevated, while RR for females and blacks aged 65+, circulatory deaths and respiratory deaths were not. The authors considered that these results showed inconsistencies, probably due to the lack of ability of regression analysis to deal adequately with weather conditions which may have confounded the results. They concluded that the reported effects of particulate matter on mortality were unconfirmed (Styer et al., 1995). The possibility also exists, and the reviewers considered, that they have overcorrected for season and weather, especially in the analyses by season, race and age which were reduced in size, and therefore in power to detect an effect. This study is therefore also considered to give positive support for the association of air pollution, as measured by PM_{10}, with mortality.

A daily mortality study was carried out in Santiago, Chile during 790 days over a three year period from 1989-1991 (Ostro et al., 1996). 43,450 deaths were recorded over this period, with a mean of 55.0 deaths/day. Air pollution levels were much higher in this city than in comparably sized North American locations. The mean PM_{10} was reported to be 115.4 $\mu g/m^3$, with a range of 35-500 $\mu g/m^3$. The mean PM_{10} in the summer was 76.2 $\mu g/m^3$ and 141.4 $\mu g/m^3$ in the winter. A large proportion of the PM_{10} was stated to be sulphates and other fine fraction PM, from diesel sources (74%) and gasoline vehicles (6%). Analysis was by Poisson and normal (Ordinary Least Squares) regression. Based on an increase of 100 $\mu g/m^3$ in PM_{10}, the relative risk for total mortality was 1.07 (95% CI 1.03 to 1.10), and was 1.08 (95% CI 1.06 to 1.12) for an increase equal to the mean of 115 $\mu g/m^3$ PM_{10} (this was the value reported in the paper, based on Poisson models). The relative risk for respiratory mortality was higher than that for total mortality at 1.13 (95% CI 1.07 to 1.20), while cardiovascular mortality was similar to total mortality at a relative risk of 1.08 (95% CI 1.03 to 1.12) . Mortality was also elevated above the mean for the elderly, age $\geq$ 65 years, with a relative risk of 1.10 (95% CI 1.06 to 1.12) (all were adjusted for yearly, seasonal and temperature variables, and scaled down from increases equal to the mean of 115 $\mu g/m^3$ to increases per 100 $\mu g/m^3$, for easier comparability with results from other studies).

Ozone (lagged 1 day) was significantly and independently associated with mortality in summer (Poisson RR= 1.04; 95% CI 1.00 to 1.09 for a 100 ppb change), but not in winter or over the whole year. In OLS analysis of the summer-only data, the RR for PM_{10} alone was marginally significant (RR=1.07; 95% CI 0.99 to 1.11 for 115 $\mu g/m^3$), but the RR for both PM_{10} and ozone were slightly reduced when both were included together in bivariate analysis (PM_{10} RR=1.06; 95% CI 0.97 to 1.11, and ozone RR=1.02; 95% CI 0.97 to 1.07). SO_2 was marginally significant and NO_2 was not, in univariate analyses, but both were not significant when each was considered with PM_{10} in bivariate Poisson regressions. CO, one of the standard air pollutants, was not considered, although it was undoubtedly very high in this traffic-polluted city. The association of PM_{10} with mortality remained significant in a number of different

regression models with and without other gaseous pollutants, and with extensive sensitivity analyses. This study provides good evidence that air pollution associated with high vehicle traffic, as indexed by PM_{10}, is robustly associated with mortality. Summertime ozone levels also appeared to have an independent association with mortality, along with PM_{10}.

Saldiva et al. (1994) studied children aged < 5 years old and respiratory mortality in Sao Paulo, Brazil. The mean PM_{10} was 82.4 $\pm$ 38.8 µg/m^3 (higher than comparable North American locations) and the mean nitrogen oxides (NO_x) was 127 ppb. The other criteria pollutants O_3, SO_2, and CO were also considered. This study included only one year of data from May 1990 to April 1991, the mean deaths being low at 3/d. PM_{10} was not associated with respiratory mortality in young children (slight negative correlation). NO_x was the only air pollutant with significant effects (odds ratio of 1.24, 95% CI 1.13 to 1.34 for a 100 ppb increase). Moreover, when NO_x was removed from the analysis, no other consistent relationships were observed with the remaining air pollutants. NO_x was moderately to highly correlated with the other pollutants ($r \geq 0.55$ for PM_{10} with NO_x), but not with temperature or humidity. This study indicated that air pollution, in this case best indexed by NO_x and not by any other pollutant, was associated with effects sufficient to induce mortality in children.

In a second study in Sao Paulo, Brazil, Saldiva et al. (1995), examined mortality in the elderly aged 65 years and older. Mean PM_{10} levels were as reported above. Mean daily O_3 was 12.5 ppb with a mean of 1 h daily maximum of 38.3 $\pm$ 29.7 ppb. All five of the usual criteria pollutants were included, but as mentioned above the data were available for only one year. The relative risk for total mortality was 1.082 $\pm$ 0.019 ($p \leq 0.01$) for a 100 µg/m^3 increase in PM_{10} when no other pollutants were included in the regression, and was unchanged at 1.083 $\pm$ 0.033 when all other criteria air pollutants were included together in the model. The dose response was linear, and showed no evidence of a threshold when plotted by quintile of concentration ($p < 0.0001$). CO was associated with mortality ($p \leq 0.05$) when considered alone in the regression, with a relative risk of 1.127 $\pm$ 4.13 for a 7.5 ppm increase, but was no longer associated with mortality when it was considered together with the other pollutants. SO_2 and NO_2 also were associated with somewhat increased relative risks when each was considered alone, but were not predictive of increased mortality when considered at the same time as PM_{10}. Correlation coefficients between PM_{10} and SO_2, NO_2 or CO were high (0.66, 0.68 and 0.55) which makes separation of their effects impossible. Neither O_3 metric gave increased relative risk estimates either alone or with PM_{10} . A seasonal analysis was conducted for PM_{10}, but not for ozone, although ozone has been shown in several analyses to be predictive of increases in adverse health effects in summer, but not in winter (Burnett et al., 1994, 1995; Ostro et al., 1996). In this location and study, bivariate analyses consistently attributed the air pollution-mortality association to PM_{10} , which was clearly the best index for the air pollutant mixture of those examined.

Daily mortality and air pollution were examined in Lyon, France for the six year period from 1985-1990, as part of the European APHEA collaborative study (Zmirou et al., 1996). The mean PM_{13} , which was measured by b-ray atomic absorption, considered here to be equivalent to PM_{10}, was 38 µg/m^3 (range 4.8-97.5 µg/m^3). Particles were lowest in spring and highest in winter. The effects of SO_2, NO_2, and O_3 on mortality were also examined. Meteorological and seasonal factors were considered in the model. The RR for a 100 µg/m^3 increase in PM_{13} was 1.08 (95% CI 1.00 to 1.18) for respiratory deaths and almost the same (RR=1.08; 95% CI 0.99-1.10) for cardiovascular deaths (CVD). Few events, 0.4 deaths/d and 2.0 deaths/d, were recorded for both respiratory and CVD, and this probably contributed to the lack of a robust association. PM_{13} was not significantly associated for all-cause mortality (RR = 1.04; 95% CI 0.94 to 1.10). In this location, SO_2 (daily mean) was the pollutant most clearly associated with respiratory and cardiovascular (CV) mortality; it remained significant when considered together with PM_{13} (data not shown in paper). When PM_{13} was "high", (>60 µg/m^3), the RR for SO_2 was higher (RR=1.27) than when PM_{13} was "low" (RR=1.19). The correlation between SO_2 and PM_{10} varied considerably over the seasons in different monitoring locations, between -0.08 and 0.76, which allowed for an assessment of their interaction. No association was observed between ozone (1 h maximum) and mortality, which the authors suggested could have been due to the central placement of the ozone monitors in central city locations subject to ozone scavenging by traffic-generated NO_2. Thus this study supported a role for SO_2 as the best metric for expressing the association of air pollution with all-cause, respiratory and cardiovascular mortality, and for PM_{13} as a somewhat less effective predictor

for respiratory and CV mortality than SO_2, at least under the conditions prevailing in this city.

12.2.2 Acute Mortality Studies Including PM_{10}, $PM_{2.5}$, and Other Measures of Fine Particulate Matter

Dockery et al. (1992) examined daily deaths from annual mortality data kept by the National Center for Health Statistics for the one year period from September 1985 to August 1986 in St. Louis and the counties of eastern Tennessee surrounding Kingston/Harriman. Particulates were measured daily. A dichotomous sampler was used to separate the particulate matter into fine (<2.5 µm) and coarse (<10 µm) fractions. Mean PM_{10} levels were 27.6 and 30 µg/m^3, with maxima of 97 and 67 µg/m^3 for St. Louis and Tennessee, respectively. $PM_{2.5}$ levels were also reported, with mean levels of 17.7 and 21 µg/m^3 and maxima of 75 and 58 µg/m^3 for the St. Louis and Tennessee regions, respectively. Mean sulphate levels were relatively similar in the two communities, at 8.0 and 8.7 µg/m^3 , with maxima of 38 and 27 µg/m^3 for St. Louis and Tennessee respectively. Particle strong acidity, measured as H^+, was much higher in Tennessee than in St. Louis, with mean levels of 36.1 nmol/m^3 compared to 9.7 nmol/m^3 for St. Louis. Other pollutants considered included 24 h mean SO_2, NO_2 and O_3. Ozone levels were the same in both regions. Carbon monoxide, which always accompanies combustion processes, was not considered. Sources of pollution were not specified, but it was speculated that there exists a mix of vehicular, industrial and natural sources. The association between mortality and air pollution was examined using Poisson regression analysis separately for each pollutant, after adjusting for season and weather variables.

Similar increases in daily mortality were found to be associated with PM_{10} levels on the previous day in both St. Louis (16.2% for a 100 µg/m^3 increase in PM_{10} ; 95% CI 1.01 to 1.30%), and eastern Tennessee (17.4%), but the 95% CI included the null value in the latter location (Dockery et al., 1992). In St. Louis, the proportion of total deaths attributable to PM_{10} during the 1 year study period was 4.2%. Recorded levels of PM_{10} were rarely in violation of the existing standard for the United States. There was a high correlation ($r > 0.5$) between PM_{10} particles and elemental concentrations of aluminum, calcium, chromium, iron and silica, which the authors suggested could have played a role in the observed results. No pollutants were found to have robust associations with mortality in Tennessee, although the regression coefficients were positive for most. This lack of association could have been due to exposure missclassification in Tennessee, since the only monitor was located in Harriman, about 50 miles from the main centre of population in Knoxville. In addition, the population of the Kingston-Harriman area was only 640,000, compared to 2.3 million for the St. Louis census area. Both factors would lead to higher variability in results and wider confidence intervals which included the null value, in the case of Tennessee.

Examination of the regression coefficients for the size-fractionated particulate data for St. Louis showed that both $PM_{2.5}$ and the coarse fraction of PM_{10} above 2.5 µm were positively, but marginally ($0.05 < p < 0.1$) associated with mortality, with RR of 1.19 for a 100 µg/m^3 increase in $PM_{2.5}$ ($p=0.075$) and RR of 1.28 ($p=0.056$) for $PM_{10-2.5}$. When considered simultaneously in the regression, it was not possible to demonstrate a more robust association for one than the other, due to high correlations between them. Although sulfates and particle strong acidity, as H^+, showed some positive regression coefficients in St. Louis, these metrics were less predictive of increased mortality than the other particle metrics. The H^+ measurement error was large in St. Louis because concentrations were low and near the quantitation limit. In Tennessee, no pollutants were found to be associated with mortality. This result is noteworthy with respect to H^+, which was present at much higher concentration than in St. Louis (mean 36 µg/m^3 - Tennessee vs. mean 9 µg/m^3 - St. Louis). Overall, in this study, the association of the different particle metrics with mortality was in the order $PM_{10} > PM_{2.5} = PM_{10-2.5} > SO_4^{2-} > H^+$, with PM_{10} clearly the best metric for predicting increases in mortality, followed by $PM_{2.5}$ and the coarse fraction ($PM_{2.5}$-PM_{10}) equally (Dockery et al., 1992).

The data from St. Louis and (Kingston-Harriman) Tennessee and from the remaining four cities in the Harvard Six City Study have recently been re-analyzed, to examine the relationship between daily total mortality and daily changes in various measures of fine and coarse particulate matter (Schwartz et al., 1996a). This study covered eight years between 1979 and 1987 (the previous study had covered only one year). Mean PM_{10} values ranged from 18 to 46 µg/m^3 (overall median 25 µg/m^3 and median of six locations 29 µg/m^3) and mean

$PM_{2.5}$ ranged from 11 to 30 µg/m^3 (median 17.5 µg/m^3). Sampling data were available only every second day in most cases (n=1140 to 1520). For H^+, measurements were available for only approximately one year (n=159 to 429). Poisson regression analyses were carried out, adjusting for temperature, dewpoint and time trends. Pollutants were not considered simultaneously in bivariate analysis because of high correlations between them, nor was lag structure examined in detail because of the incomplete data set.

The strongest and most robust association was found to be with the fine fraction ($PM_{2.5}$); an increase of 10 µg/m^3 in the 2 d mean $PM_{2.5}$ was associated with a 1.5% increase in daily deaths (95% CI 1.1% to 1.9%). The individual city estimates for a 10 µg/m^3 increase in $PM_{2.5}$ (2 d mean) ranged from 0.8% to 2.2% for the six cities. While results were statistically significant for three of the six cities, results for Steubenville and Portage were only marginally significant, and Topeka results were not significant. The association with $PM_{10/15}$ was less marked, with an overall increase of 0.8% (95% CI 0.5 to 1.1%) for each 10 µg/m^3 increase in $PM_{10/15}$ (2 d mean). and with the increases in the individual cities from -0.5 to +1.2% for a 10 µg/m^3 increase (RR=0.95 to 1.12 for 100 µg/m^3). The association was negative for Topeka and positive but not significant (marginal) for Portage. The most interesting results were those concerning the analysis for the coarse mass fraction of particles (CP). In contrast to fine particles or to PM_{10}, CP showed no association with mortality in the overall six-city results, with an estimated increase per 10 µg/m^3 of 0.4% (95% CI -0.1 to 1.0%; t=1.48) In addition, it was also shown to be not associated with mortality in five of the six cities in individual analyses, the one exception being Steubenville, where a 2.4% increase (95% CI 0.5 to 4.3%; t=2.43) was estimated. In this city, the $PM_{2.5}$ result was marginal, and the correlation between the two PM measurements was very high (r=0.69), in contrast to low-moderate correlations for the other five cities (r=0.23-0.43). In simultaneous regressions, coarse particles did not make any independent contribution to the observed association of $PM_{2.5}$ with mortality. In this study, sulphate was also related to mortality, but had a weaker association than $PM_{2.5}$ Particle strong acidity, as H^+, was not related to daily mortality. In this study, the gaseous pollutants were not addressed because of relatively high correlations with PM and the probable confusion that could result during the particulate metrics analysis (Schwartz et al., 1996a).

Daily mortality and air pollution in Toronto, Ontario from 1972-1990, was examined in a preliminary report by Ozkaynak et al. (1995). PM_{10} concentrations (mean 40 µg/m^3) were estimated from TSP, CoH, SO_4^{2-}, and some limited PM_{10} monitoring. Ozone, SO_2, NO_2, and CO were also considered. Multiple regressions were conducted, after detrending the mortality and the air pollution data to remove the effect of seasonal, meteorological and day-to-day variations that were unrelated to air pollution (for example, the effect of Mondays in increasing the official recording of deaths). Either TSP or PM_{10} explained about 2.3% of the deaths that occurred. The relative risk per 100 µg/m^3 increase in PM_{10} was 1.07 (95% CI 1.05 to 1.09) in a single-pollutant regression. Ozone was also associated with mortality, with a relative risk per 100 ppb increase of 1.05, which gave an estimate of 1.5% as the contribution to mortality at the ozone mean of 36 ppb. Thurston (1996) gave further details of the results for PM_{10} of multi-pollutant simultaneous regression, in which the relative risk for PM_{10} was reduced only slightly from 1.07 to 1.05 (95% CI 1.03 to 1.07). The results of this study were therefore consistent with other similar studies in pointing to the independent effects of particulate matter on mortality, but could not distinguish the effects of any one particle measurement.

Dockery et al. (1996b) have recently examined a small mortality data set for Philadelphia, for the summers of 1992 and 1993. Of the PM metrics examined, $PM_{2.5}$ was the most strongly and consistently associated with total and cardiovascular mortality. A 2% increase in mortality per 10 µg/m^3 $PM_{2.5}$ was calculated (95% CI 0.4 to 3.5%; p<0.01), while the increase associated with the coarser particle fraction PM_{10} was considerably less, at 1.2% (95% CI not given, but p=0.06, i.e., marginal). No association was found for H^+, SO_2, or CO. A positive association (0.9% per 10 µg/m^3) was found for O_3, which was independent of, and additive to $PM_{2.5}$.

Although a very small study, this adds to the number of results showing that the $PM_{2.5}$ fraction is the one most strongly associated with mortality and other adverse health effects.

12.2.3 Acute Mortality Studies with PM_{10} and BS

There is some uncertainty inherent in comparison of PM_{10}, a gravimetric measurement, with Black Smoke or British Smoke Shade (BS), an optical-based measurement, used commonly in Europe. BS is generally

considered to represent a carbon-based dark fraction intermediate in size between PM_{10} and $PM_{2.5}$, with a cutoff size of about 7 µm and a median of 4.5 µm aerodynamic diameter (D_a) (UK Dept. of Environment 1996; US EPA 1996). Moreover, other light-coloured particles such as sulphates, nitrates or acid aerosols would not be included, and would therefore be underestimated, although they may be of importance for adverse health effects (Walters et al., 1994; Anderson et al., 1996). Several recent European studies have included both PM_{10} (or sometimes PM_{13}, which is considered very close to PM_{10}) and BS as particle metrics, thus enabling a limited comparison with results for BS.

Air pollution and its relationship to total mortality was examined in Amsterdam, the Netherlands (population 700,000) for the seven year period 1986-1992 (Verhoeff et al., 1996). Pollution levels were considered relatively low at this time, with mean BS of 12 µg/m^3 (90th centile 23 µg/m^3 and maximum 81 µg/m^3) and mean PM_{10} of 38 µg/m^3 (90th centile 67 µg/m^3 and maximum 163 µg/m^3). Meteorological and temporal variables as well as influenza epidemics were considered in the models. When each was considered separately in the model, both the finer particle measure (BS) and PM_{10} (lag 0 or current day measures for both) were associated with increases in mortality, but BS appeared to have a slightly greater magnitude of association than PM_{10} when considered over their respective interquartile ranges (IQR). The increase per 10 µg/m^3 BS (also the interquartile range (IQR) for this pollutant) was 1.9% (95% CI 0.2 to 3.8%) The increase per 10 µg/m^3 PM_{10} was 0.6% (95% CI -0.14 to +1.4%), and represented a somewhat smaller increase of 1.3% (95% CI -0.3 to 3.1%) for the IQR range of 22 µg/m^3. The relative risk associated with BS was reduced slightly when a one day lag was considered, but the risk associated with PM_{10} was considerably reduced, to about 27% of the original magnitude. In univariate analysis, ozone (1 h max) was also associated with increased mortality when lagged 2 d, with a 0.5% increase (95% CI 0.1 to 1.0 %) per 10 µg/m^3 increase, and a 1.9% increase (95% CI 0.04 to 3.9%) for an IQR increase of 39 µg/m^3. SO_2 and CO were also considered separately, but were not found to be important predictors of mortality. (NO_x was not considered).

When BS or PM_{10} were considered in bivariate analyses separately with with each of the other three gaseous pollutants in turn, BS had a more robust association than PM_{10} with mortality, and the RR for BS remained the same or was increased over the univariate RR, but was reduced for ozone, SO_2 and CO. The association of PM_{10} appeared to be unstable when the three gaseous pollutants were included, and its RR was reduced somewhat with ozone and SO_2, but increased with CO in bivariate analyses. Overall, this study gives support for particulate matter as the best predictor among the air pollutants SO_2, CO or ozone, of an adverse effect of air pollution on mortality. For ozone, the RR remained almost the same as in the univariate analysis at 0.5% (for 10 µg/m^3) when regressed with PM_{10}, but was reduced somewhat to 0.3% when regressed with BS. These results gave some suggestion of an additional association of ozone with mortality that was independent of the association with particulate matter or other air pollutants.

The results of this study were consistent with the findings of other studies that finer particles are more strongly associated with adverse health outcomes than larger particles, based on the more robust association of BS with mortality than PM_{10} when each was considered in bivariate analysis with the individual gaseous pollutants, and on the somewhat greater magnitude of association of BS (1.9%) than PM_{10} (1.3%) with mortality when each was considered with respect to its IQR increase.

As part of the European APHEA collaborative air pollution study, Dab et al. (1996) examined acute mortality from respiratory disorders. In Paris, France (population 6.1 million), over a period of six years, 1987 to 1992, with respect to associations with BS and PM_{13} (measured by radiometry and stated (Zmirou et al. 1996) to be essentially identical to PM_{10}). (See also hospitalization analysis from this study in section 12.3.3) The mean (24 h) BS was 32 µg/m^3 (5th to 99th centile 11-23 µg/m^3) and the mean (24 h) PM_{13} was 51 µg/m^3 (5th to 99th centile 19-137). Data were analyzed using Poisson regression models, adjusted for meteorological variables (mean daily temperature and relative humidity), season, influenza epidemics, weekly and daily patterns and holidays. An increase of 10 µg/m^3 in PM_{13} (lagged by 1 d) was associated with a 1.7% increase in daily deaths (95% CI 0.4 to 3.1%) while a 10 µg/m^3 increase in BS (also lagged 1 d) was associated with a 0.7% increase (95% CI -0.25 to 1.8%). These corresponded to an increase of 8.6% in mortality for an increase in PM_{13} equal to the mean of 51 µg/m^3, and an increase of 2.3% for an increase in

BS equal to the mean of 32 µg/m^3. No conversion factors were provided to relate BS to PM_{10}, PM_{13} or TSP, but a factor of 0.63 between means of BS (~PM_{5-7}) and PM_{10} would give approximately 0.45% increase for a 6.3 µg/m^3 increase in BS compared to a 1.68% increase for a 10 µg/m^3 increase in PM_{10}. Thus, in this location, PM_{13} appeared to be a much better particulate matter predictor than the smaller measure of BS for increased respiratory mortality. The lower association found for BS than for the larger size fraction PM_{13} may reflect the lack of suitability of BS in this location for capturing the non-coloured fraction of fine particles secondarily produced from vehicle combustion, as suggested by Anderson et al. (1996).

SO_2 (1 h maximum, lagged 1 d) was also associated with increased respiratory mortality when analyzed separately in the basic model, with a 0.85% increase in mortality (95% Cl 0.15 to 1.6%) for a 10 µg/m^3 increase, or about half that seen for the same increase in $PM_{13.}$ In separate analyses, neither 1 h nor 8 h ozone (lagged 0 d) was significant as a mortality predictor, and 24 h mean NO_2 and SO_2 (both lagged 1 d) were also not significant. The robustness of the BS, PM_{13} or SO_2 mortality associations were not tested by considering SO_2 in bivariate analyses with either of the particulate measures. Respiratory mortality was not associated with any particular season, and individual pollutants, including ozone, were not regressed in seasonal analyses, although ozone was three to four times higher in summer than in winter, and has been shown in some studies (Burnett et al., 1994) to demonstrate associations only in the warm season.

Air pollution and mortality in Athens, Greece (population >3 million) has been investigated in several reports (Katsouyanni et al., 1990; Touloumi et al., 1994) and is included as part of the European APHEA collaborative study (Touloumi et al., 1996). Although BS was the only PM measurement, a site-specific analysis and conversion factor for the BS —> PM_{10} metric was made available (Katsouyanni, 1996; to L. Grant, US EPA, reported in Thurston 1996). Over the five year 1987-1991 period, mean BS was 84 µg/m^3 (range 9-333 µg/m^3) and 42% of days exceeded the WHO air quality guideline. This mean corresponds to a PM_{10} mean of 78 µg/m^3 and a maximum of 306 µg/m^3. SO_2 and CO measurements were also available, and were also relatively high, with means of 51 µg/m^3 for 24 h SO_2 and 6.6 µg/m^3 for 8 h CO. Meteorological (double quadratic function of temperature with a changing point at 22^{o}C, plus relative humidity), seasonal and other daily and long-term variables were adjusted for in the modelling.

A 10 µg/m^3 increase in BS (lagged 1 d) was associated with a 0.5% increase in mortality (95% Cl 0.3 to 0.8%). This was calculated to be equivalent to 0.54% (95% Cl 0.3 to 0.87%) for an equivalent increase in PM_{10} (based on the formula PM_{10} = 8.70 + 0.832 BS). However the strongest association was with SO_2 (lagged by 1 d) and a 10 µg/m^3 increase was associated with a 1.2% increase in total mortality (95% Cl 0.7 to 1.6%). CO (current day) was also associated with increased mortality, and a 10 µg/m^3 increase gave a 1.0% increase in mortality (95% Cl 0.5 to 1.5%). The estimated increases in mortality were greatest for SO_2 (10%), followed by BS (8%) and CO (5%) when considered according to their respective ranges of increase from the 5th to the 95th percentile in Athens (87.2, 150, and 7600 µg/m^3 respectively).

When BS was included in a bivariate regression with SO_2 the regression coefficient for BS was reduced and that for SO_2 was increased, indicating that SO_2 was the better predictor of the two. The RR for BS was reduced from 1.05 to 1.03 when SO_2 was <100 µg/m^3 and to 1.02 (and was no longer significant) when SO_2 was above 100 µg/m^3. High concentrations of BS (>100 µg/m^3) appeared to act synergistically with SO_2 , with the RR associated with SO_2 rising from 1.12 to 1.15 (12 to 15%). CO was not co-regressed with either of the other two measured pollutants in the APHEA analysis for 1987-91, but was co-regressed in the previous analysis for 1984-88. It was found to be no longer significant (Touloumi et al., 1994), although high correlation (r =0.79 for BS/CO) precludes any conclusion in this regard. No data were available on ozone or NO_2. Air concentrations of all three pollutants BS, CO and SO_2 were highest in late fall and winter, and a significant interaction with season was found for SO_2, but not for BS or CO. The strongest effect of SO_2 was in the winter.

12.2.4 Acute Mortality Studies with BS Only, as the Particle Metric

All-cause, respiratory and cardiovascular mortality and their possible associations with air pollution were investigated in Greater London England (population 8 million), as part of the 14-centre European APHEA collaborative study (Anderson et al., 1996). Particles (BS), ozone, NO_2 and SO_2 (but not CO) were

investigated in autoregressive log-linear Poisson regression models, adjusted for time trends (year, season, day of week, bank holidays), seasonal variations, influenza epidemics, and weather (relative humidity and temperature, which was found to have a U-shaped relationship to mortality and was adjusted by using three separate linear terms, for <5°C, 5-20°C, and >20°C). The 24 h average BS was 14.6 $\mu g/m^3$ (10th-90th centiles 8-37 $\mu g/m^3$ and interquartile range 10-18 $\mu g/m^3$).

An increase of 10 $\mu g/m^3$ BS (lag 1 d) was associated with a 1.1% (95% CI 0.55 to 1.72%) increase in all-cause mortality, equivalent to 0.9% (95% CI 0.4 to 1.2%) for an interquartile range increase of 16 $\mu g/m^3$ (reported as 1.7% (95% CI 0.82 to 2.6%) for a 31 $\mu g/m^3$ increase, which was the 10th to 90th centile range). All-year, cool season and warm season BS were all significantly correlated ($p<0.01$) with total mortality when data were subdivided into the cool and the warm seasons. The increases for cardiovascular deaths (CVD) and respiratory mortality were smaller and non-significant, an anomalous finding, not wholly consistent with other studies, and not explainable because of small numbers of daily deaths for these causes, since deaths/day were 78.6 (CVD) and 22.5 (respiratory deaths).

However, the strongest associations with mortality occurred with ozone, when considered as both the 1-h maximum and the 8-h average. A 2.6% increase in all-cause mortality (95% CI 1.3 to 3.8%) was associated with a 10th-90th centile (31 ppb) increase in 1-h ozone, and the increase rose to 3.5% in the warm season (34 ppb increase, the 10th-90th centile range). The all-year, all-cause increase was equivalent to a 0.84% (95% CI 0.4 to 1.3%) increase per 10 ppb ozone, and to 1.3% (95% CI 0.7 to 2,0%) for an interquartile range increase of 16 ppb. The 10th-90th centile increase (24 ppb) in 8 h average ozone gave about the same magnitude of association, 2.4% (95% CI 1.1 to 3.8%), as 1 h ozone with all-cause mortality, and a slightly greater magnitude, 1.0% (95% CI 0.5 to 1.6%) for a 10 ppb increase. Respiratory mortality associated with ozone (1 h max. and 8 h average) were higher than all-cause mortality in the all-year, cool and warm seasons, and respiratory mortality rose to 6.4% for all-year ozone (1 h max) and 6.0% for 8 h ozone. Increases in cardiovascular (CV) mortality were associated in the warm season with increases in both 1 h maximum values and 8 h averages, but all-year CV mortality was asssociated only with 1 h max. ozone. SO_2, which had previously been associated with mortality in the early London Fog episodes (Thurston 1996), was associated with all-cause mortality, but not with CVD or respiratory mortality, in the warm season only (RR 1.52%, 95% CI 0.08 to 2.98% for a 10th to 90th centile increase of 25 ppb). NO_2 (1 h max.) was associated with increases in all-cause, CVD and respiratory mortality in the warm season only, while 24 h NO_2 was associated only with CV mortality, also in the warm season.

In two-pollutant models, both BS and 8 h ozone were found to be independently associated with mortality. The associations with all-cause, respiratory and CV mortality were the same or slightly increased for ozone (8 h) in the all-year and warm-season analyses when BS was included. For BS, all-cause mortality was almost doubled for all year and cool season analyses, and unchanged for warm-season effects when ozone was included in bivariate analyses. The effects of SO_2 and NO_2 were attenuated by inclusion of either BS or ozone in the model, while the latter two both remained significant (Anderson et al., 1996). The effects of CO on mortality and its possible effects on BS and ozone results were not investigated (a re-analysis of the London results including CO has been completed but was not available in time for this document).

The results of this study support an association of daily variations in air pollution with increased mortality. Both ozone and particles, as BS, were shown to have independent associations with all-cause mortality, and summertime ozone with respiratory and CV mortality as well. The magnitude of the associations with ozone were greater than those associated with BS for an equivalent 10th to 90th centile range increase. The associations of either BS or ozone with mortality could not be explained by two other gaseous air pollutants, SO_2 and NO_2, suggesting that particulate matter is the best representative of the three air pollutants arising from primary sources, (i.e., direct combustion) that were examined here.

The acute relationship between air pollution during the six year period from 1985 to 1991, and all-cause, respiratory and cardiovascular mortality in Barcelona Spain was assessed as part of the European APHEA collaborative air pollution study (Sunyer et al., 1996), and also as a supplement to previously conducted morbidity studies (Sunyer et al., 1991, 1993). Results were analyzed using APHEA methodology, with linear regression and autoregressive Poisson models with corrections for temporal variations (year of study,

day of week, holidays), seasonal variables, and meteorological factors (linear and quadratic terms for temperature and humidity, terms for high humidity and very hot days). The median number of total deaths was 48/day in winter and 43/day in summer (total number of days 2557). The median 24-h BS was 49.7 μg/m^3 in winter and 35 μg/m^3 in summer, and represented one of the higher values in western Europe. SO_2, NO_2 and ozone were also investigated. Most values were calculated for a lag of 1 d.

A 0.7% increase in total mortality was associated with a 10 μg/m^3 increase in all-year and winter BS (95% Cl 0.3 to1.1%). As predicted, the increase was greater for cardiovascular (CVD) and respiratory mortality, at 0. 93% and 0.97% respectively, but was of marginal significance in the case of respiratory mortality, possibly due to increased variance from low numbers of cases (median 5/d compared to 21/d for CV mortality).

The greatest magnitude of association with mortality in all categories was with SO_2 (24 h average 46 and 36 μg/m^3 in winter and summer respectively). Increases of 1.27% (total mortality, all year) and 1.45% (CVD, all year) were observed per 10 μg/m^3, although respiratory mortality increases were not significatly associated except in summer (the increase was 2.4%, but note that SO_2 is lower in summer than winter). However, SO_2 was the only pollutant associated with respiratory mortality in this study, (the association with BS being of marginal significance), which agrees with earlier findings for Barcelona on hospitalizations (Sunyer et al., 1991, 1993). The results for SO_2 were also more robust than those for BS in sensitivity analyses incorporating various trends and potential seasonal or weather confounders. The ozone findings were of interest in this study, and contrast to the earlier morbidity studies (ibid.). A 0.48% increase in total mortality and a 0.58% increase in CV mortality were associated with a 10 μg/m^3 increase in (all year) ozone, while respiratory mortality was not significant, probably for the reason above. The magnitude of the relationship was slightly greater for summertime ozone (median 86.5 μg/m^3 compared to 55.2 μg/m^3 in winter). For NO_2, increases were significant for total and CV mortality in all-year and summer analyses, but the increases were not as marked as for SO_2, BS, or ozone.

No pollutants were considered together in bivariate analyses; BS and SO_2 were highly correlated (r=0.63), and thus their effects cannot be separated in regression analyses. The correlations between BS, ozone and NO_2 were weak-moderate (r= -0.33 to 0.29), and the effects of ozone could have been independent. The authors pointed out the possibility of CO exerting a confounding effect, particularly on CV mortality, with which it has been unequivocally associated. The authors also pointed out the weaknesses of using BS as the only surrogate to measure the particle effect, and suggested this as part of the reason for the weaker association of BS with mortality than SO_2. This study also examined whether the mortality was predomintly in the elderly, over age 70 years, or in a younger age group. There was little evidence that overall, total mortality was increased in the elderly by any of the pollutants (reduced for BS and ozone; slightly increased , <0.1%, by NO_2 and SO_2, except 0.2% for SO_2 in winter, all for 10 μg/m^3 increase) (Sunyer et al., 1996).

The relationship of air pollution, measured as BS and SO_2 was also examined for the three year period 1991-93 in Valencia, a second APHEA centre in Spain (population 750,000) with a warm Mediterranean climate similar to Athens, but with low concentrations of air pollutants, primarily due to vehicle combustion (Ballester et al., 1996). Analyses were undertaken with core models selected by least squares analysis incorporating corrections for season, temperature and humidity, long term trends, day-of the week and holiday effects, and influenza epidemics. Poisson regression was used for each pollutant in separate analyses with two different lag times and warm and cold seasonal adjustments. The mean BS was 67.7 μg/m^3, and was slightly higher (77.4 μg/m^3) in winter and lower (58.0 μg/m^3) in summer. Mean SO_2 was 39.9 μg/m^3, and did not vary much from winter to summer.

A positive association was found between BS (lagged 3-4 d) and total, CVD or elderly ($\geq$ 70 y) mortality, the RR for a 10 μg/m^3 increase was 0.9% (95% Cl 0.3 to 1.5%) for total mortality, virtually the same for elderly mortality, and 1.2% (95% Cl 0.3 to 2.2%) for CV mortality. There was no association with respiratory mortality, likely due to the small number (1.59 deaths/d) of respiratory deaths compared to larger numbers per day (17.5, 11.7, 6.9/d) for total mortality, elderly mortality, or CV mortality. The association with SO_2 was less clear; the relative risk per 10 μg/m^3 SO_2 over the entire year for total mortality was 0.7% (95% Cl -0.3 to 1.5%). SO_2 during the warm months was however, associated with increased CV mortality and with total mortality in the elderly. Introduction of an interaction term

between BS and SO_2 in the form of a dummy variable for "low" versus "high" exposure to BS below and above 100 µg/m^3, did not have any effect on the results for SO_2. Pollutants were considered in univariate analyses in order to avoid collinearity, but no correlation coefficients were given (Ballester et al., 1996). These results indicate a positive relationship between air pollution and mortality. This relationship appeared to be more stable for BS than for SO_2 in this locality, and was more similar to results from North American cities than from other European cities. Since no measurements were available for any air pollutants other than BS and SO_2, no further conclusions on which air pollutant is the best indicator of the air pollution effect can be made from these results.

12.2.5 Summary of Results on Acute Mortality

Nineteen studies which investigated the relationship of daily variations in mortality with particulate air pollution using modern time-series methods were reviewed in detail. These have been summarized in Table 12.2. In all of the 15 North and South American locations, studies that used inhalable particulate matter less than 10 µm in diameter (PM_{10}) were selected. Seven recent studies also investigated other, finer fractions, as $PM_{2.5}$ and as sulphate particles. Six European locations measured BS, a fine particle measure with a mean diameter less than 4.5 µm, and in four locations, PM_{10} or PM_{13} (very similar to PM_{10}) was used, sometimes in addition to BS. Most of these studies also examined one or more gaseous pollutants in addition to particulate matter.

Virtually all these studies demonstrated consistent associations between air pollution and acute mortality. These associations could not be explained by the influence of weather (temperature and humidity were most commonly found to have independent associations with mortality), season, yearly trends, day-to-day variations and variations due to holidays, epidemics, or other non-pollutant factors, since all the analyses looked for some or all of these potential biases and accounted for them in various ways in the analysis.

Overall, particulate matter, as PM_{10}, $PM_{2.5}$, BS, and/or sulphate, was clearly associated with all-cause mortality in most of the analyses. These associations were found in North America in 13 locations across the continent, in two locations in large South American cities, and in seven locations across Europe, and showed remarkable consistency with each other despite the widely varying climatic conditions and pollutant mixtures encountered in these cities. In addition, despite a wide range of mean PM_{10} concentrations for these communities, from 18 µg/m^3 (Portage WS) to 115 µg/m^3 (Santiago Chile), the RR range was narrow, indicating highly consistent results under differing PM_{10} exposure conditions. While five of the 23 PM_{10} locations (Salt Lake County, UT, Kingston-Harriman, TN, Topeka, KN, Portage, WS, and Lyon, France) did not show a positive association of PM_{10} with acute all-cause mortality, and marginal associations were found in a further six analyses on all PM metrics (Philadelphia and one of the Utah valley results with $PM_{10,}$ three of the same cities for $PM_{2.5}$ as for PM_{10}, and in Paris, France with BS), the small size of the population studied and/or the low number of "events" (deaths) included (Salt Lake, Kingston-Harriman, Topeka, Portage, Utah Valley) as well as inexact exposure measurements (the earlier study in Kingston-Harriman, and probably others as well) could have been responsible for some of these inconclusive results.

For PM_{10}, the relative risks for mortality from all causes except accidents (calculated for a 100 µg/m^3 increase) varied from 0.95 to 1.17, with a mean of 1.082 ± 0.056 and a median (n=23) of 1.08. The RR were therefore on the low end of the range previously reported (Dockery and Pope 1994; Schwartz 1994e; Pope et al., 1995c) of 1.07 to 1.16 for each 100 µg/m^3 PM_{10} increase. For the fine fractions $PM_{2.5}$, and BS, the unweighted mean relative risks were also elevated with concentration means (1.15 (n=9) and 1.10 (n=6) respectively). Only one study provided a combined quantitative estimate for sulphate for six US cities, and the mean RR (100 µg/m^3 increase) was 1.22. These results mean that an increase in daily deaths of about 0.8% can be predicted for each 10 µg/m^3 daily increase in $PM_{10,}$, and a 1.0% and 1.5% increase for similar size increases in BS and $PM_{2.5}$. While this increase is of very low magnitude, it signifies substantial numbers of avoidable deaths due to the very large size of the population that is impacted by air pollution.

Table 12.2 Summary of Relative Risks for Particulate Matter: Total Mortality

LOCATION	PM METRIC (MEAN; RANGE)	RR (100 ug/m^3 increase) (95% CONFIDENCE LIMITS)	RR + OTHER POLLUTANT IN MODEL (95% CI) (95% Confidence Limits with other pollutant in model)	REFERENCE
St. Louis, US	PM_{10} (28; max 97)	1.16 (1.01 – 1.30)	1.12 (0.96 – 1.15) (+O_3) (US EPA 1996)	Dockery et al., 1992
Kingston-Harriman US	PM_{10} (30; max 67)	1.17 (0.88 – 1.50)	1.17 (0.88 – 1.52) (+O_3) (")	Dockery et al., 1992
Utah Valley US	PM_{10} (47; 1-365)	1.16 (1.10 – 1.22)	1.14 (1.04 – 1.24) (+O_3) (Pope & Kalkstein 1996)	Pope et al., 1992
Philadelphia US	PM_{10} (not given)	1.12 (0.99-; upper CI not given) (p=0.06)	—	Dockery et al., 1996b
Birmingham US	PM_{10} (48; 21-80, max 163)	1.11 (1.02 – 1.20)	—	Schwartz 1993
Toronto Canada	PM_{10} (40; not given in text)	1.07 (1.05 – 1.09)	1.05 (1.03 – 1.07) (+ "other pollutants") (Thurston 1996)	Ozkaynak et al., 1995
Los Angeles US	PM_{10} (58; 15-177)	1.05 (1.00 – 1.11)	1.05 (1.00 -1.11) (+O_3) 1.04 (0.98 – 1.09) (+ CO)	Kinney et al., 1995
Chicago (Cook Co.) US	PM_{10} (38-median; 28-51 IQR)	1.055 (1.01 – 1.10) (>65 y)	—	Styer et al., 1996
Chicago (Cook Co) US	PM_{10} (41 +19)	1.05 (1.03 – 1.08)	1.04 (1.01 – 1.07) (+O_3)	Ito and Thurston 1996
Utah Valley US	PM_{10} (47: 1-365)	1.04 (0.98 – 1.10)	—	Lyon et al., 1995
Salt Lake Co US	PM_{10} (48: (9-194)	1.008 (≈0.8 – 1.08) (> 65 y)	—	Styer et al., 1995
6-city study, (combined) St. Louis (US) K-H, Tenn. Boston Steubenville Topeka Portage	PM_{10} (25; 8-68) 30.6 ± 14.5 24.5 ± 12.8 45.6 ± 32.3 26.7 ± 16.1 17.8 ± 11.7	1.08 (1.05 – 1.11) 1.06 (1.01 – 1.10) 1.09 (1.01 – 1.18) 1.12 (1.07 – 1.17) 1.09 (1.01 – 1.16) 0.95 (0.80 – 1.09) 1.08 (0.96 – 1.17)	—	Schwartz et al., 1996a
Sao Paulo Brazil	PM_{10} (82 + 39)	1.13 (1.07 – 1.19) (>65 y)	1.13 (1.03 – 1.23) (+O_3, SO_2, NO_2, CO)	Saldiva et al., 1995
Santiago Chile	PM_{10} (115; 32-367)	1.07 (0.99 – 1.11) (OLS, summer) 1.08 (1.06 – 1.12) (Poisson, all year)	1.06 (1.00 – 1.09) (+O_3, OLS, summer) 1.04 (1.01 – 1.08) (+ SO_2, Poisson, all year) 1.07 (1.03 – 1.11) (+ NO_2, Poisson, all year)	Ostro et al., 1996
Paris France	PM_{13} (51: 19-137)	1.17 (1.04 – 1.31)	—	Dab et al., 1996
Lyon France	PM_{10} (38: 5-98)	1.02 (0.94 – 1.10) total deaths-accidents (1.04; 1.02 – 1.09 respiratory deaths)	RR for PM n.g. with SO_2	Zmirou et al., 1996
Athens Greece	PM_{10} (78; 8-300)	(1.063 (1.033 – 1.09) – estimate from BS)	[1.03 (1.01 – 1.06) (SO_2<100) – estimate from BS] [1.02 (0.97 – 1.07) (SO_2>100) – estimate from BS]	Touloumi et al., 1996

Abbreviations: RR – relative risk; C.L. -confidence limits; IQR – interquartile range; n.g. – not given; OLS – Ordinary Least Squares regression;

Table 12.2 Summary of Relative Risks for Particulate Matter: Total Mortality *(continued)*

LOCATION	PM METRIC (MEAN; RANGE)	RR (100 ug/m^3 increase) (95% CONFIDENCE LIMITS)	RR + OTHER POLLUTANT IN MODEL (95% CI) (95% Confidence Limits with other pollutant in model)	REFERENCE
Amsterdam NL	PM_{10} (38; max 163)	1.06 (0.99 – 1.14)	1.03 (0.94 – 1.13) (+O_3) 1.02 (0.93 – 1.13) (+ SO_2) 1.10 (1.01 – 1.20) (+ CO)	Verhoeff et al., 1996
Unweighted rel. risk: PM alone (n=23) mean 1.082 ± 0.056 (95% CI range 0.80 – 1.50) median 1.08 ; bivariate analysis, PM + other gases (n=16): median 1.05; mean 1.069 ± 0.047				
Amsterdam NL	BS (12; max 81)	1.19 (1.02 – 1.38)	1.18 (1.01 – 1.37) (+O_3) 1.27 (1.07 – 1.49) (+ SO_2) 1.20 (1.01 – 1.44) (+ CO)	Verhoeff et al., 1996
London England	BS (15; 8-22, 10th-90th percentile)	1.11 (1.05 – 1.17)	1.19 (1.11 – 1.) (+O_3)	Anderson et al., 1996
Barcelona Spain	BS (50,35; winter, summer)	1.07 (1.03 – 1.11)	—	Sunyer et al., 1996
Valencia Spain	BS (68 + 29)	1.09 (1.03 – 1.15)	—	Ballester et al., 1996
Paris France	BS (32:11-123; 5th-95th percentile)	1.07 (0.98 – 1.18)	—	Dab et al., 1996
Athens Greece	BS (84; 9-333)	1.05 (1.03 – 1.08)	1.03 (1.01 – 1.06) (SO_2<100) 1.02 (0.97 – 1.08) (SO_2>100)	Touloumi et al., 1996
Unweighted mean relative risk 1.096 ± 0.050 (95% CI range 0.98 – 1.38) median 1.08 (95% CI 1.03 – 1.16)				
St. Louis, US	$PM_{2.5}$ 17.7 (max 75)	1.19 (p=0.075) (95% CI not given	—	Dockery et al., 1992
Kingston-Harriman US	$PM_{2.5}$ 21 (max 58)	1.17 (p=0.28) (95% CI not given)	—	Dockery et al., 1992
Philadelphia, US	$PM_{2.5}$ (not given)	1.20 (1.04 – 1.35)	RR for PM + O_3 not stated (both independent)	Dockery et al., 1996b
6-city study, (combined) St. Louis (US) K-H, Tenn. Boston Steubenville Topeka Portage	$PM_{2.5}$ 14.7 (4.3-431)(IQR 14.0) 18.7± 10.5 20.8 ± 9.6 15.7 ± 9.2 29.6 ± 21.9 12.2 ± 7.4 11.2 ± 7.8	1.15 (1.11 – 1.19) 1.11 (1.04 – 1.17) 1.14 (1.02 – 1.26) 1.22 (1.15 – 1.29) 1.10 (0.99 – 1.21) 1.08 (0.80 – 1.36) 1.12 (0.97 – 1.28)	"same" (+ CP or $PM_{10-2.5}$) CP – RR=1.24 (1.05-1.43) correlation=0.69	Schwartz et al., 1996a
Unweightled mean relative risk (6 individual cities + 3 cities) 1.148 ± 0.049 median 1.14 (95% CI range 0.8 0- 1.36)				
St. Louis Mo. US	SO_4^{2-} 8.0 (max 38)	weak pos., n.s.	—	Dockery et al., 1992
Kingston Tenn. US	SO_4^{2-} 8.7 (max 27)	n.s.	—	Dockery et al., 1992
6-city study US (combined)	SO_4^{2-} 5.8 (1.5-22.3)	1.22 (1.13 – 1)	SO_4^{2-} RR strong, (t=4.66) but less than $PM_{2.5}$ (t=7.41)	Schwartz et al., 1996a
Too few data points for comparison				

Abbreviations: RR – relative risk; CI -confidence limits; IQR – interquartile range; n.g. – not given; OLS – Ordinary Least Squares regression;

These increases in relative risk due to air pollution were observed at particulate matter concentrations substantially below the current international and Canadian 24-hour objectives/standards. Canada currently has objectives only for TSP, as a 24-h acceptable level of 120 $\mu g/m^3$, approximately equivalent (depending on location) to PM_{10} of 60-80 $\mu g/m^3$ and to $PM_{2.5}$ of about 30-50 $\mu g/m^3$. In the majority of the studies examined the mean/median (24 h) concentrations of PM_{10} were below 50 $\mu g/m^3$ (median of 22 locations 43 $\mu g/m^3$), and $PM_{2.5}$ means were below 20 $\mu g/m^3$ (median of 8 locations 18 $\mu g/m^3$). The lowest mean concentrations at which PM_{10} mortality associations were positive were in Boston MA at 24.5 $\mu g/m^3$, and in the overall results for six cities (including Boston) at 25 $\mu g/m^3$ PM_{10} and 14.7 $\mu g/m^3$ $PM_{2.5}$ (Schwartz et al., 1996a).

There was little evidence in these data that the dose-response curve included a threshold, and the response was observed to increase monotonically (in the concentration range below 80-100 $\mu g/m^3$) with increasing concentration (all PM_{10} data) in both nonparametric analyses (Birmingham AB – Schwartz 1993; Santiago – Ostro et al., 1996; Utah Valley – Pope and Kalkstein 1996) and quartile or quintile analyses (Utah Valley – Pope et al., 1992; Birmingham, AB – Schwartz 1993; Sao Paulo, Brazil – Saldiva et al., 1995) The quintile results for St. Louis, MO and Kingston, TN (Dockery et al., 1992) were also roughly monotonic when taken together, but not separately, due to relatively poor exposure information and (in Tennessee) to low population. A curvilinear response, with high slope at low concentrations, leveling off at higher concentrations, was observed above 100 $\mu g/m^3$ in Santiago, Chile, and possibly also in the Birmingham data, above about 50 $\mu g/m^3$. Although the quintile analysis of Utah Valley by Lyon et al. (1996) indicated a definite threshold at the mean for quintile 4 of 47 $\mu g/m^3$, discrepancies were evident in the quintile means, and caution was indicated in interpretation of these data. The lack of a threshold down to low concentrations suggests that it will be difficult to select a level at which no adverse effects would be expected to occur as a result of exposure to particulate matter.

There was evidence from the six-city acute mortality study that the fine fraction of particulate matter ($PM_{2.5}$) was consistently associated with mortality, and that the association was of greater magnitude than that with PM_{10} or sulphate for increases equivalent to the IQR for each (2.1% for $PM_{2.5}$ versus 1.8% for PM_{10} and 1.5% for SO_4^{2-}). Moreover, the coarse fraction of PM_{10} above $PM_{2.5}$ in diameter was not associated with mortality in the overall analysis (0.4%; 95% CI -.01 to 1.0% for IQR), or in the five individual cities in which the correlation coefficents between fine and coarse fractions were below 0.46 (the association was positive in the one city with a high correlation coefficient of 0.69). This association of the fine fraction was supported by results from a small study in Philadelphia and by one of the two European studies which measured both BS (relatively fine) and PM_{10} or PM_{13} (Dockery et al., 1996b; Dab et al. 1996). Sulphate, which forms a part of the fine fraction, has been suggested as the best index for fine particle effects (Lippmann and Thurston 1996), but the results from the six-city study do not support this hypothesis when both measures are available, since the magnitude of effect for $PM_{2.5}$ was substantially greater than the magnitude of effect for sulphate for an equivalent concentration range. Moreover, the US EPA analyzed the non-sulphate portion of $PM_{2.5}$ separately from sulphate and found that the relative risk was as high or higher for the non-sulphate fraction as for the sulphate fraction (US EPA 1996).

The elderly and those with pre-existing respiratory and cardiovascular diseases have been suggested as being at increased risk from exposure to particulate matter (Schwartz 1993, 1994d; Lipfert 1994). A slight increase (13%) in relative risk from 1.5 to 1.7% for a 10 $\mu g/m^3$ increase in $PM_{2.5}$ was observed for those aged $\geq$ 65 years in the six-city daily mortality study (Schwartz et al., 1996). The RR for the elderly aged $\geq$ 70 years was virtually unchanged (an 11% decrease) in Barcelona and Valencia Spain (Sunyer et al., 1996; Ballester et al., 1996), using BS as the particle metric. In Santiago, Chile a 43% increase in the RR (per 100 $\mu g/m^3$ increase) over the all-cause RR was observed for the elderly $\geq$ 65 years, while in the Lyon et al. (1995) analysis for the Utah Valley and in the Styer et al. (1995) results for Chicago, IL, the risk appeared to be doubled for those over age 65. The increases in RR for the various age groups in the Lyon study appeared to be unstable, probably because of the low number of respondents (n=4036), but this was not the explanation for the Chicago study, which presented detailed results for deaths in the fall season only. Overall, the results suggest only a surprisingly modest increase in relative risk for the elderly compared to the whole population. This does not support the suggestion that it is only the elderly who are being affected and dying from air pollution,

and that their lives are being shortened by air pollution episodes only by a few days or weeks before they would have died anyway.

A number of investigators looked at the specificity of the air pollution effect on the causes of mortality. Deaths from respiratory disease were moderately to strongly elevated compared to all-cause deaths in the six-city daily study, and in Chicago, IL, Birmingham, AB, Santiago, Chile, Barcelona, Spain and Lyon, France (Schwartz 1993; Schwartz et al., 1996; Ostro et al., 1996; Sunyer et al., 1996; Zmirou et al., 1996). Only in three studies, in London England (Anderson et al. 1996), Valencia Spain (Ballester et al., 1996) and in the Lyon et al. (1995) analysis for the Utah Valley, was a decrease noted in RR for respiratory deaths compared to total mortality. In the latter two locations, the few deaths per day could have contributed to the lower non-significant RR, but this could not have been the explanation for London. In the six-city study, both chronic obstructive pulmonary disease (COPD) and pneumonia were found to exhibit strongly increased relative risks over the total mortality RR. For COPD, the risk was almost doubled, and for pneumonia, the risk was 2.7 times the RR for total mortality of 1.5% for a 10 $\mu g/m^3$ increase in $PM_{2.5}$

The association between air pollution and cardiovascular disease was also clear. Modest increases over the total mortality RR were noted in the relative risk for death due to cardiovascular diseases in the six-city study (RR increased from 1.5% to 1.7% for a 10 $\mu g/m^3$ increase in $PM_{2.5}$), Barcelona, Spain (RR increased from 0.7 to 0.9%) and in Valencia, Spain (RR increased from 0.9 to 1.2% for a 10 $\mu g/m^3$ increase in BS). Substantial increases were observed in Birmingam, AB (55%) and the Utah Valley (300%) (Schwartz 1993; Lyon et al., 1995). The RR declined from the total mortality RR in only two locations, Chicago (RR for a 10 $\mu g/m^3$ increase in PM_{10} decreased from 0.5 to 0.3%) and in London, England (RR decreased from 1.7 to 0.6%) (Ito and Thurston 1996; Anderson et al., 1996). Overall, the association with cardiovascular disease was well marked but was only modestly increased by comparison to total mortality. Moreover, the association with cardiovascular disease was often of lesser magnitude than the association with respiratory disease, particularly in all the large cities, (six-city study, Chicago, IL, Santiago, Chile) with the exception of London, England.

Particulate matter is not the only air pollutant that could be associated with increases in mortality. Because of the strong intercorrelations often demonstrated between the primarily produced air pollutants PM, SO_2, NO_2, and CO, as well as correlations between SO_2, NO_2, and secondarily produced fine PM as sulphates and nitrates, it has been difficult or impossible for any one study to attribute the air pollution effect to any single one of these agents to the exclusion of others. A bivariate or multipollutant regression model treats each variable as independent, an assumption that is invalid if these variables are highly correlated with each other as they often are. The best method available thus far has been examination of single pollutant models in regression analyses which tried to account for all non-pollutant-related factors and any potential confounders such as temperature before examining the relationship of the pollutant to mortality. If positive relationships with several pollutants were found, bivariate analyses could then be carried out, bearing in mind that the validity of the results would depend (inversely) on the degree of correlation of the two pollutants. Some investigators have also looked for interrelationships between pollutants by examining the effects of one pollutant at high and low levels of the other pollutant, for example the effect of SO_2 above and below 100 $\mu g/m^3$ on the association of BS with mortality in Athens (Touloumi et al., 1996). Many investigators examined at least one other air pollutant in addition to PM, in order to determine if any other air pollutant was a better predictor of increased mortality than was PM, or was independently associated with an increased relative risk. The results of bivariate analyses with SO_2, NO_2, CO and ozone on the estimates of relative risk associated with PM_{10} and BS are shown in Table 12.2. In the only study which quantitatively examined fine particles as $PM_{2.5}$ and sulphate, no bivariate regressions were undertaken because none of the other pollutants were associated in single analyses, and there was potential for correlation problems as well (Schwartz et al., 1996b).

Overall, although the particulate matter coefficients were slightly reduced, they retained their association with acute mortality in bivariate analyses (and in one preliminary multivariate analysis for Toronto (Ozkaynak et al., 1995)). The mean and median RR for PM_{10} (per 100 $\mu g/m^3$ increase) was reduced from 1.08 (n=23) to 1.05 (n=16).The mean and median RR for BS of 1.10 and 1.08 respectively (n=6) rose to a mean of 1.15 and median of 1.19 in three analyses with SO_2, two with ozone and one with CO, but this result is biased upward by consideration of three

of six results from a single location and study in which relative risks were estimated to be high for BS with or without the inclusion of other air pollutants in the analysis (Verhoeff et al., 1996).

The possible relationship of SO_2 with mortality was considered for 14 locations, since it had in the past been associated with wintertime peaks in PM and episodes of mortality and morbidity (the London Fogs and other episodes of the 1950s). In general, while SO_2 appeared to be the best predictor of air pollution effects on mortality in a few European locations, in most locations its effects were attenuated in regressions which included a particulate matter metric, and in several locations, it did not appear to be associated with mortality even in single pollutant analyses. However, it should be noted that a number of studies investigating TSP (not reviewed here) have also reported positive associations with SO_2. Sulphur dioxide was the air pollutant most strongly associated with mortality in Lyon, France, Athens, Greece and Barcelona, Spain, remaining significantly associated in Lyon and Athens after inclusion of PM_{13} in Lyon (Zmirou et al., 1996) and BS in Athens (Touloumi et al., 1996). A high correlation coefficient with BS (0.63) precluded pairwise comparision in Barcelona (Sunyer et al., 1996), and calls for caution in interpretation of the results of the other two studies also, with respect to the role of SO_2 (the PM-SO_2 correlation coefficient varied with season between -0.08 and +0.76 in Lyon, and was reported in an earlier paper (Touloumi et al., 1994) as “substantial” in Athens). In single-pollutant regression analyses, SO_2 was found to have positive associations with mortality in Santiago, Sao Paulo, Paris, London and Valencia (Ostro et al., 1996; Saldiva et al., 1995; Dab et al., 1996; Anderson et al. 1996; Ballester et al., 1996), but pairwise analyses with PM_{10}, BS or both attenuated the effects of SO_2 while having little effect on the PM coefficients. SO_2 was not associated with mortality in univariate analyses in Chicago IL (Ito and Thurston 1996), St. Louis, MO and Kingston-Harriman, TN (Dockery et al., 1992), Philadelphia, PA (Dockery et al., 1996b), Toronto (Ozkaynak et al., 1995) and Amsterdam (Verhoeff et al., 1996). Thus, particulate matter is considered to be more robust predictor of the air pollution-mortality effect compared to SO_2, in the great majority of locations.

Nitrogen oxides (usually NO_2) were examined in nine locations. Overall, the evidence for an association of NO_2 with mortality is considered weak. In four locations (Lyon and Paris, France, St. Louis, MO and E. Tennessee US) no association between mortality and NO_2 was found in single pollutant analyses. In Sao Paulo, Brazil and Santiago, Chile, the association of NO_2 with mortality in the single-pollutant model was reduced to non-significance in bipollutant models, while the coefficient for PM_{10} remained high. Correlation coefficents between NO_2 and PM_{10} were high in both locations, 0.55-0.68 in Sao Paulo and 0.73 in Santiago. NO_2 was also not associated with mortality in Toronto in a multi-pollutant analysis (no single-pollutant results were presented) (Ozkaynak et al., 1995). In London, England, NO_2 (1 h maximum) was associated with increased risks due to cardiovascular disease, in summer only. The relative risks associated with (1 h) NO_2 were smaller and less consistent than for BS or ozone, and (1 h) NO_2 was not included in bivariate analyses in this study (Anderson et al., 1996). No association was found for 24 h NO_2 (Anderson et al., 1996). In Barcelona, NO_2 (1 h max.) was associated with total and CV mortality as well as with mortality in the elderly $\geq$ 70 years old. No pairwise regression with other pollutants were undertaken, although the correlation coefficients for BS-O_3-NO_2 were relatively low at 0.29-0.30. The authors suggested a confounding effect with (unmeasured) CO, in view of the CVD increases rather than respiratory increases as might have been expected from what is known of the pulmonary toxicity of NO_2 (Sunyer et al., 1996). Particulate matter, as BS or PM_{10}, was the air pollutant most strongly and consistently associated with mortality in all these studies except in London, England, where the strongest associations were with ozone (Anderson et al., 1996), and in Barcelona, Spain, where the air pollutant which best predicted increases in mortality was SO_2 (Sunyer et al., 1996).

Carbon monoxide (CO), which is a primary vehicular combustion product like PM and NO_2, was considered in two European and five North and South American locations. CO was associated with mortality in Los Angeles, CA and in Athens, Greece. In Los Angeles, the regression coefficients for both CO and PM_{10} were reduced only slightly in bivariate regresssions, which could indicate that each was a good, independent predictor of the air pollution effect on mortality, but no correlations between them were given (Kinney et al., 1995). In Athens, the increase associated with CO was 10% (95% CI 5 to 15%) for a 10 $\mu g/m^3$ increase, compared to 12% for SO_2 and 5% for BS. Based on equivalent 5th-95th percentile range increases, the increase associated with CO was 7.6% (95% CI 3.8 to 11.4%), about the same as

with BS and lower than SO_2 at 10.5%. The BS-CO correlation coefficient was 0.79, too high for bivariate regressions to be undertaken (Touloumi et al., 1996). CO was not associated with all-cause mortality in Chicago, Philadelphia or Amsterdam when regressed singly (Ito and Thurston 1996; Dockery et al., 1996b; Verhoeff et al., 1996), or in Sao Paulo or Toronto in multiple-pollutant regressions (Saldiva et al., 1996; Ozkaynak et al., 1995). Although particulate matter was the best index of air pollution in these five cities, further work is warranted on the possible association of CO with mortality, in view of the high correlations between them which could obscure any relationship, and of the biological plausibility of a link between CO and cardiovascular disease.

The possibility of an association between ozone and acute mortality was examined in 13 locations. Ozone toxicity is known to occur after short periods (one to six hours) of exposure, and ozone concentrations are also most frequently highly cyclic in a diurnal pattern. Therefore the results for ozone are often more sensitive than particles or other air pollutant gases to the duration of the measurement, with 1 h maximum and 5 to 8 h daytime values for ozone more likely to be more strongly associated with adverse health than 24 h values, which tend to smooth out the effect of diurnal peaks. The manner of its secondary formation via photochemical oxidation of primary combustion products means that it is also highly seasonal, with highest concentrations observed in summer. Therefore an analysis on a yearly basis is less likely to demonstrate associations than an analysis on a seasonal basis. However this type of formation also means that it is usually not highly correlated with particulate matter, making it easier to detect independent associations. These factors were taken into account in weighing the evidence for an effect of ozone on mortality that was independent of other air pollutants.

The relationship of ozone, as one of several air pollutants, to acute mortality was examined in 13 locations. Ozone (1 h daily maximum) was associated with mortality in single-pollutant regression models in 8 of these cities: London, England (also the 8 h daily average), Barcelona, Spain, Amsterdam, NL, Santiago, Chile, Chicago, IL, Philadelphia, PA, Toronto, ON and Los Angeles, CA (Anderson et al., 1996; Sunyer et al., 1996; Verhoeff et al., 1996; Ostro et al., 1996; Ito and Thurston 1996; Dockery et al., 1996b; Ozkaynak et al., 1995; Kinney et al., 1995). The relative risks on a yearly basis ranged from 0.2 to 2.6% for a 10 ppb or a 10 $\mu g/m^3$ increase. Separate analysis for the cool and warm seasons in London, England and Santiago, Chile demonstrated that risks were higher for summertime than when the entire year was included (Anderson et al., 1996; Ostro et al., 1996). In all these cities except Barcelona, two-pollutant analyses were carried out with the inclusion of both particulate matter and ozone in the model. In Los Angeles, there was a reduction to a RR of 1.0 for ozone and no change in the RR for PM_{10} based on only 364 days of simultaneous measurement (Kinney et al., 1995). In the remaining seven cities, the relative risks for both ozone and PM remained the same or were slightly, but not greatly, reduced in magnitude and the confidence limits widened. Thus both ozone and particulate matter (PM_{10} in most locations, BS in London and Amsterdam) appeared to act as independent factors in the association of air pollution with daily mortality. This conclusion is strengthened by the fact that the correlations between ozone and PM were very low to low-moderate, ranging from -0.29 to +0.37 in five of these cities. No association of total daily mortality with ozone was found in single-pollutant models in five additional cities: Sao Paulo, Brazil, Lyon and Paris, France, St. Louis, MO and eastern Tennessee, US (Dockery et al., 1992; Saldiva et al., 1995; Zmirou et al., 1996; Dab et al., 1996). In the two US locations, 24 h measurements and poor placement of monitors with respect to the place of residence of most of the potential responders could have been partly responsible for the negative results for ozone. No obvious reason for the lack of association of ozone was evident in the other three cities, for which both 1 h and 24 h monitoring results were available. In 10 of the 13 locations that investigated the relationship of mortality to ozone in additon to other air pollutants, particulate matter appeared to have the strongest association with mortality of the several air pollutants that were examined. The exceptions were London, England, where the RR for an increase in ozone equal to the 10th to 90th percentile range was found to be 2.4% (95% CI 1.1 to 3.8%), compared to 1.7% (95% CI 0.8 to 2.6%) for BS (Anderson et al., 1996), Barcelona, Spain and Lyon, France where SO_2 was the best predictor of increased mortality compared to BS and ozone (Barcelona) or PM_{13} and ozone (Lyon) (Sunyer et al., 1996; Zmirou et al., 1996). The weight of evidence is here considered to be relatively strong that ozone has an association with daily mortality that is independent of the PM association.

In all of the analyses that examined one (or more) air pollutants together in the same model with particulate matter, the association of particulate matter with daily mortality was remarkably robust, despite the problems of disentangling the effects of PM from other air pollutants. This was the case for all four of the normally considered gaseous pollutants, SO_2, NO_2, CO and ozone. Moreover, in most locations the magnitude of the PM association was greater than any other air pollutant considered, the exceptions being ozone in London and SO_2 in Lyon and Barcelona. The magnitude, robustness and consistency of this association across so many locations with differing air pollutant mixtures indicates that PM is the best indicator of the air pollution effect on mortality, and is considered to give some support to PM of some kind, possibly acting together with other air pollutant(s) as a causal agent. An attempt to address the question of which metric of particulate matter might be the best indicator for the "PM effect" was made in one study, which provided strong evidence that it was the fine fraction ($PM_{2.5}$) that was most closely associated with mortality.

12.3 ACUTE EFFECTS – HOSPITALIZATIONS AND EMERGENCY DEPARTMENT VISITS

A number of studies, mostly longitudinal time-series analyses of acute or short-term effects, have examined hospital admissions for respiratory disease as an indicator of health, and a few have examined cardiovascular outcomes as well. The data presented show a wide range of geographical locations and particulate sources. The studies which included only PM_{10} as the particle metric have been considered separately from studies which examined the relationship of hospitalizations to various measures of fine particles, often in addition to PM_{10}.

12.3.1 Hospital Studies and PM_{10}

Pope (1991) examined the association between monthly respiratory admissions and PM_{10} air pollution for three populated areas in the state of Utah: the Utah Valley, (population 188,000); the Cache Valley (population 72,500) and the Salt Lake Valley (population 780,000) over the four year period between April 1985 and March 1989 (Pope 1991). Annual mean PM_{10} concentrations were 53, 55, and <40 µg/m^3 for Utah Valley, Salt Lake and Cache Valley respectively, and were highest in winter, at 95, 71 and <60 µg/m^3. The main source of particulate pollution in the Utah Valley was a steel mill, which contributed approximately 50 to 70% of the PM_{10} pollution in this area. This steel mill only slightly affected PM_{10} levels in the Salt Lake Valley, about 60 km to the north. Sources of PM_{10} pollution in the Salt Lake Valley were varied. Particulate levels in the Cache Valley were generally low, so admissions data from this location were used as a reference level or control. Overall levels of SO_2 and NO_2 were said to be low and in compliance with EPA standards, but, as demonstrated by other studies with PM, this is no guarantee that associations with adverse health would not be found. Although no quantitative data were presented, SO_2 was reported to be near the limit of detection, and ozone was low in winter when PM_{10} concentrations peaked. Smoking rates were also low. Hospital admissions were recorded for pneumonia, bronchitis and asthma. Total respiratory admissions in these categories were 4144 for Utah Valley, 7373 for Salt Lake, and 1468 for Cache Valley. Admissions were regressed using ordinary least squares (OLS) estimates with autoregressive models using maximum likelihood estimation (statistical references given). A trend variable for each month of study, monthly mean low temperature, PM_{10}, and lagged PM_{10} and temperature were regressed.

Average hospital admissions (all ages) for pneumonia, asthma and bronchitis were higher in the Utah Valley when the steel mill was open than when it was closed for 13 months. The rates of admissions were 1.17, 1.40 and 1.14 for pneumonia, bronchitis and asthma respectively, and were higher than those in the Cache Valley (RR= 0.95, 0.92 and 1.24, the latter of marginal significance). The preschool age group was identified as a potential susceptible subgroup. When the steel mill was open, ratios for bronchitis and asthma were twice as high for children aged 0-5 years (RR= 2.09 and 2.01 for bronchitis and asthma respectively). These differences were not observed in either the Salt Lake or the Cache Valley. During periods when the steel mill was in operation, the ratio of hospitalization rates for bronchitis or asthma in the Utah Valley was twice as high in the Utah Valley as in the Cache Valley (Pope 1991). While this study is not strictly comparable to daily time-series studies since it examined monthly changes, it provides the results of an interesting "natural experiment" in which hospitalization rates were demonstrated to be reduced when the source of much of the PM_{10} pollution was removed, i.e., a cause-effect relationship was demonstrated on a population basis. The cross sectional comparison within the design acted to provide a

control population and confirmed this rise in rates. An additional point of interest was the much stronger effect on preschool children than on the population as a whole with respect particularly to bronchitis and asthma. The results of this study are highly consistent with the hypothesis that particulate matter pollution, as here measured by PM_{10}, plays an important role in the incidence and severity of respiratory disease.

A daily time-series was conducted in the Seattle area comparing daily PM_{10} measurements with hospital emergency department visits for asthma, with gastroenteritis as a control diagnosis, in eight hospitals over a 13 month period from September 1, 1989 to September 30, 1990 (Schwartz et al.,1993). Measurements were also collected for SO_2 and O_3 (no data were presented for O_3, and the length of the monitoring period was also not stated). The maximum and mean PM_{10} concentrations were 103 µg/m^3 and 29.6 $\pm$ 18 µg/m^3, respectively. PM_{10} levels were measured from a residential site in a wood-burning area where wood smoke (fine particulate matter) was thought to be the main source of the particulate pollution. Ozone was measured from a site 20 miles east of the city, which would likely have had higher levels than the city itself, due to NO_x scavenging in the area with more vehicular traffic. There were 2955 visits for asthma during the study period (mean 7.1/d).

Results showed a highly significant association between PM_{10} concentrations and asthma admissions, at low environmental levels. A relative risk (RR) of 1.12, (95% CI 1.04-1.20), was calculated for an increase equal to the mean of 30 µg/m^3 PM_{10}. This estimate was robust to differences in model specifications for temperature adjustment, relative humidity, or for cold dry days. Division of the results by quartile of PM_{10} demonstrated a dose response, with RR increasing from the second (mean 20 µg/m^3) to the fourth quartile (mean, 30 and 55 µg/m^3) by comparison to the first (mean 13 µg/m^3) (RR and confidence intervals not presented except as a graph). No associations were found for gastroenteritis, or for the other air pollutants examined, SO_2 and ozone (RR=0.99 and 0.97 respectively). However, the association with light scattering (km^{-1}), which is a measure of fine particles less than 2.5 µm, was of the same magnitude as PM_{10}, with a RR of 1.11 (95% CI 1.04-1.18 for a change of 7 km^{-1} equivalent to the change in PM_{10}) (Schwartz et al., 1993). Despite the small size of this study (one year, relatively few visits), it suggests that particulate air pollution from the small size fraction produced by wood smoke may play a role in exacerbation of asthma. The investigation of other air pollutants which could also have been associated with respiratory illnesses was weak, especially for ozone, which has been shown in other studies to have such an association independently from PM_{10}.

In Birmingham, Alabama, daily counts of hospital admissions for the respiratory illnesses pneumonia and chronic obstructive pulmonary disease (COPD) were recorded in the elderly ($\geq$ 65 y) for the five years 1986 to 1989 inclusive (Schwartz 1994a). The admission means were 5.9/d for pneumonia and 2.2/d for COPD. Twenty-four-hour PM_{10} pollution data were collected at three monitoring sites for 1369 (94%) of the possible days throughout the study period. The mean PM_{10} level for the study period was 45 µg/m^3, (10th to 90th percentile range: 19 µg/m^3 and 77 µg/m^3). Ozone (1 h peak levels and 24 h average) was also considered. Data were analyzed in Poisson regression models controlling carefully for yearly trends, season, and weather. For pneumonia, the relative risk calculated for a same-day PM_{10} increase of 100 µg/m^3 was 1.19 (95% CI 1.07-1.32). The relative risk for COPD was 1.27 (95% CI 1.08-1.50). It was also calculated that inhalable particles were responsible for 8% of the pneumonia admissions and 12% of the COPD admissions at the mean concentration of 45 µg/m^3. Results were not sensitive to several different methods of controlling for seasonality or weather, or to extremes of temperature. In a quartile analysis of the same data, a monotonic response was observed, with no evidence for a threshold from 13 to 55 µg/m^3 (means for quartile 1 to quartile 4). A similar yet weaker significant relationship was found with COPD admissions. It was also calculated that inhalable particles were responsible for 8% of the pneumonia admissions and 12% of the COPD admissions at the mean concentration of 45 µg/m^3. Ozone was weakly associated with pneumonia admissions two days later; the relative risk for a 50 ppb increase in 24 h ozone was 1.14 (95% CI 0.94-1.38) and for 1 h peak ozone was 1.04 (95% CI 0.97-1.12). Peak ozone was also weakly associated with COPD admissions; the relative risk was 1.07 (95% CI 0.96-1.20). No attempt was made to assess the interactions or the independence of the associations with PM_{10} and ozone in bivariate regressions, although the correlation coefficients between them were relatively low (r=0.29). The correlation between ozone and temperature was also negligible (r=0.04) in this city.

Using data from hospitals in Detroit, Michigan (total population 4 382 000 in 1990, population base 517 000 for those age 65 and older), daily admissions for three categories of respiratory diseases (pneumonia, chronic obstructive pulmonary disease (COPD) including asthma, and asthma alone: means 15.7/d, 5.8/d and 0.75/d respectively) were recorded for the four years 1986 to 1989, for persons aged 65 and older, and compared with daily pollution data available through various monitoring stations in Detroit (Schwartz 1994b). Pollution variables included ozone as well as PM_{10}. PM_{10} levels ranged from a 10th percentile of 22 $\mu g/m^3$ to a 90th percentile of 90 $\mu g/m^3$, with a mean of 48 $\mu g/m^3$. After control for season and weather (temperature and dew point), associations were found in bivariate regressions between both PM_{10} and ozone and hospital admissions for pneumonia. The relative risk for pneumonia with concurrent-day PM_{10} levels was 1.012 (95% CI 1.004-1.019 for a 10 $\mu g/m^3$ increase in PM_{10}). The relative risk of pneumonia for a 5 ppb increase in 24 h ozone was 1.026 (95% CI 1.015 to 1.04). When analyzed by quartile of PM_{10} and ozone, a linear dose response was evident for PM_{10}, the RR increasing from 1.0 at 22 $\mu g/m^3$, (quartile 1) to 1.075 at a mean of 88 $\mu g/m^3$ (quartile 4). The dose response was not so evident for ozone, and the RR was not increased until quartile 3 (mean ozone about 25 ppb) Both PM_{10} and ozone were significantly associated with COPD admissions (other than asthma) as well. The increased risk for PM_{10} and COPD (RR = 1.020, 95% CI 1.004-1.032 for a 10 $\mu g/m^3$ increase) was higher than for pneumonia. The RR for ozone in the same pairwise model was 1.03 (95% CI 1.007-1.045 for a 5 ppb increase) The inclusion of both PM_{10} and ozone in the same model did not appreciably lower the coefficients for either pollutant with either endpoint (data not shown), and the correlation coefficient between them was 0.35, or moderately low. These results suggested that both were independently associated with respiratory disease. Sensitivity analyses indicated that extremes of high or low temperature or the methods of controlling for seasonality were not responsible for the associations observed with PM_{10}. The associations seen with 24 h ozone were also seen with 1 h maximum ozone but the effect was weaker. Neither PM_{10} nor ozone were associated with increases in asthma (Schwartz, 1994b), possibly because of the low number of daily admissions recorded for this disease, and also because this disease is less prevalent than COPD or infectious diseases in older persons. This study provides evidence that both PM_{10} and ozone are independent risk factors for respiratory disease, and that the associations, at least for PM_{10}, are not due to bias introduced by the treatment of seasonal or weather effects.

The association between daily counts of hospital admissions for cardiovascular disease in the elderly was also examined, again using Detroit data during the four years 1986 to 1989 (Schwartz and Morris 1995). Admissions categories examined included ischemic heart disease (44/d), dysrhythmias (13/d) and congestive heart failure (27/d). The same pollution data set was used as described in the above study, with the addition of data on SO_2 and CO. After careful control for temperature, dewpoint, seasonal and day-to-day variations, PM_{10} (mean of current and previous day) was found to be a significant predictor of admissions for ischemic heart disease (IHD) in single pollutant regressions (RR = 1.056, 95% CI = 1.016-1.10), as well as for admissions for congestive heart failure (CHF) in a bivariate regression with CO (RR = 1.075, 95% CI 1.013-1.14) (both relative risks calculated for a 100 $\mu g/m^3$ increase based on relative risks, for an interquartile increase of 32 $\mu g/m^3$, of 1.018 (95% CI 1.005-1.032) for IHD and 1.024 (95% CI 1.004-1.044) for CHF.) A curvilinear dose-response was shown for quartile analysis of the results for IHD and PM_{10}, with steeply rising slope at low concentrations (approximately 22 to 36 $\mu g/m^3$) and lower slope at higher concentrations (approximately 55 to 85 $\mu g/m^3$).

Although ozone was not associated with ischemic heart disease (IHD) admissions in single pollutant analysis, associations were observed for SO_2 and CO, but neither SO_2 nor CO remained associated with IHD in bivariate analyses with PM_{10}. CO was strongly associated in single pollutant regression with admissions for congestive heart failure (CHF). In bivariate regressions, the regression coefficients and relative risks remained constant for CO (RR=1.022; 95% CI 1.010-1.034 for IQR increase of 1.28 ppm) and were reduced somewhat from 1.032 to 1.024 for an IQR increase in PM_{10}, indicating an independent association for both pollutants with CHF (CO and PM_{10} correlations were moderately low, at 0.30). The results for PM_{10} for IHD and for both PM_{10} and CO in bivariate analyses were subjected to sensitivity analyses; the results could not be explained on the basis of the extreme temperatures, pollutant levels above the US standards, other temperature lags, or various regression types (robust Poisson regression, Generalized Additive Model with nonparametric smooth functions of time, temperature and humidity).

Data on influenza and other non-air-pollutant-related epidemics were not available and could not be controlled for. Little association was observed between PM_{10} levels and admissions for dysrhythmias. (Schwartz and Morris, 1995).

This study was one of the first to show associations between PM_{10} air pollution and cardiovascular disease, in addition to respiratory disease outcomes that had previously been shown for this city (Schwartz 1994b) and elsewhere. It also provides evidence that ozone is not associated with cardiovascular disease, and supports the hypothesis that it is associated specifically with respiratory disease. A major finding was the association between CO and admissions for congestive heart failure; these associations, for both CO and PM_{10} , were found to be independent of each other, and the results were robust to alternate methods of estimation and weather control.

Hospital admissions for respiratory illnesses in the elderly (aged 65 years and older) and PM_{10} levels were examined in the metropolitan area of Minneapolis-St. Paul, Minnesota (population 2.46 million in 1990) for the four years 1986 to 1989 (Schwartz 1994c). Mean admissions were 6/day for pneumonia and 2/d for chronic obstructive pulmonary disease (COPD). Mean PM_{10} concentrations were 36 $\mu g/m^3$ and the interquartile range was 23 to 44 $\mu g/m^3$. Ozone (24 h average) was also examined. After control for time trends, season, and weather in Poisson regression analyses, the results for models including both pollutants showed that current-day PM_{10} levels were significantly associated with hospital admissions for pneumonia (RR=1.17, 95% CI 1.03-1.33 for a 100 $\mu g/m^3$ increase). Ozone had a similar relationship (RR=1.15; 95% Cl 0.97-1.36 for a 50 ppb increase), which changed from marginal to significant when a different temperature control was used. When both pollutants were considered simultaneously, both were considered to have made independent contributions to explaining pneumonia hospitalizations, but the ozone result were not as consistent after sensitivity analysis for the effects of extreme temperature, high pollutant levels or model specification. The correlation between PM_{10} and ozone was low, 0.18, but the correlation between ozone and temperature was high, 0.51, making it difficult to separate out the effects of temperature from ozone. For COPD hospital admissions, both concurrent and previous-day PM_{10} levels were again significantly associated with hospital admissions (RR=1.22, 95% CI 0.99-1.52 and RR=1.37, 95% CI 1.12-1.68, respectively, for 100 $\mu g/m^3$ increases), the effect being greater with a one-day lag. A weighted average of the current and previous day's PM_{10} levels captured the sum of both effects on COPD (RR=1.57, 95% CI 1.20-2.06). Ozone (24 h and 1 h maximum) was not associated with COPD in this study. Seasonal patterns, weather conditions, misclassification of disease and high air pollution episodes were all reported to have been controlled for. The association found with hospital admissions for pneumonia and ozone, but not COPD and ozone (Schwartz 1994c) is consistent with results from previous studies in Birmingham and Detroit by the same author (Schwartz, 1994a,b).

Daily counts of hospital admissions for respiratory disease for people aged 65 years old and older during three years from 1988 to 1990, were compared to average daily concentrations of PM_{10}, SO_2, and O_3 in two cities, New Haven, Connecticut and Tacoma, Washington (Schwartz 1995). Mean respiratory admissions were 8.1/d in New Haven and 4.2/d in Tacoma. Mean, interquartile range, and 90th percentile concentrations for PM_{10} were 41, 25 and 67 $\mu g/m^3$, respectively for New Haven, and 37, 27 and 67 $\mu g/m^3$, respectively for Tacoma. After inclusion of a 19 d moving average filter to remove cyclic variations, and further adjustments for temperature including extremely hot days, humidity, and day of the week effects, results from Poisson regression analyses showed that all three pollutants were positively associated with hospital admissions for respiratory disease in both cities, the most consistent association being with PM_{10}. Both cities were also found to be consistent regarding the lag of two days for the association of PM_{10} with respiratory hospital admissions. Calculated relative risk estimates (and 95% confidence limits) for each increase of 50 $\mu g/m^3$ PM_{10} in single pollutant regressions were 1.06 (1.00-1.13) for New Haven and 1.10 (1.03-1.17) for Tacoma. In New Haven, inclusion of either of the other pollutants with PM_{10} did not reduce the estimated magnitude of either the PM_{10} effect estimate, or the estimates for ozone and SO_2, indicating the strong possibility of independent effects for all three pollutants in this city (no correlation analysis results were given). In Tacoma, the magnitude of the PM_{10} effect was the same or slightly larger in two-pollutant analyses with SO_2 and ozone, similar to New Haven, but in Tacoma, the relative risk for a 25 ppb increase in ozone remained the same in the bivariate analysis (RR=1.20; 95% CL 1.06-1.37) while the relative risk for PM_{10} included 1.0 (RR=1.12; 95% Cl 0.97-1.29). In Tacoma, SO_2 was no longer associated in the

bivariate analysis that included either PM_{10} or ozone (Schwartz 1995). While no correlations between pollutants were provided, the consistency of the results overall provide some support for an independent association for both PM_{10} and ozone in Tacoma well as in New Haven. On the other hand the SO_2 association was attenuated by ozone in both cities, and by PM_{10} in Tacoma.

Hospital admissions for respiratory disease and air pollution were examined in Spokane, Washington for patients aged 65 and older for the three years 1988 to 1990 (Schwartz, 1996). Mean respiratory admissions were 3.9/d, and the two largest hospital admission subcategories were pneumonia (1.9/d) and chronic obstructive pulmonary disease (1.0/d). Air pollution data were collected for particulates (PM_{10}) every 24 h and for ozone (O_3) on both a 24 h and an hourly basis. The mean level of (24 h) PM_{10} was 46 $\mu g/m^3$, with an interquartile range of 24 to 57 $\mu g/m^3$, and a 10th to 90th percentile range of 16 to 83 $\mu g/m^3$. Results were analyzed using Poisson regression with the Generalized Additive Model, which allowed the fitting of non-linear functions for weather (temperature and dew point), day of study, season and day of the week, and interactions between these variables, with smoothing functions for each that were chosen based on minimization of Aikaiki's information criterion (statistical references given in paper). This type of model had the advantage of not trying to force a linear shape to the variables, which showed non-linearities in data. An association between same-day PM_{10} and respiratory admissions was found, with a relative risk (for a 50 $\mu g/m^3$ increase) for all respiratory categories of 1.085 (95% Cl 1.036-1.136), for pneumonia, 1.053 (95% CI, 0.985-1.126) and 1.171 (95% CI, 1.079-1.272) for chronic obstructive pulmonary disease. Peak ozone (1 h maximum) was also associated with an increase in all respiratory admissions (RR=1.24; 95% Cl 1.002-1.544 for a 50 $\mu g/m^3$ or 25 ppb increase), but not with the subcategories.The results for PM_{10} were robust to changes in the model to control for temperature, but the ozone results were more sensitive to the handling of temperature. This was not surprising in view of the negligible correlation (0.034) between PM_{10} and temperature, and the moderate ozone-temperature correlation (0.44). While the correlation between ozone and PM_{10} was relatively low at 0.26, no bivariate analyses could be undertaken with both pollutants in the model because there were only 115 days in which both pollutants were measured togther. Nonetheless, the author rightly considered that this study added support to other studies that suggested the existence of an (independent) association (Schwartz 1996). While data were not presented on SO_2, its stated virtual absence in this location precludes confounding by this pollutant. Moreover, the lack of correlation between PM_{10} and temperature suggests that the positive findings for PM_{10} cannot be explained by temperature.

Gordian et al. (1996) studied the association, for the period May 1, 1992 to March 1, 1994 (22 months), between particulate pollution and the incidence of acute respiratory diseases as measured by daily outpatient visits for specific respiratory diagnoses in Anchorage, Alaska, an area without significant industrial pollution. The population of Anchorage is approximately 240 000 and it is located on the seacoast, in a bowl surrounded by mountains. The main sources of particulates were unpaved roads, road sanding, vehicular traffic, and ashfall from volcanic eruptions. The authors stated that wood-burning was not a major source of PM in Anchorage because wood was too expensive to use as a heating fuel. Limited monitoring for $PM_{2.5}$ carried out intermittantly over several years indicated that the fine particle fraction of PM_{10} ($PM_{2.5}$) formed an unusually low portion of the total PM_{10}, the ratio $PM_{2.5}$/coarse fraction of PM_{10} being 0.26 on average, and as low as 0.14 in some years. Daily mean, (plus range) air pollution measurements for PM_{10} and carbon monoxide (winter season only for CO) were recorded as 45.5, (5 to 565) $\mu g/m^3$ and 2.5, (0.5 to 7) $\mu g/m^3$, respectively. Health data were grouped using ICD (International Classification of Diseases) codes to identify upper respiratory problems such as sore throat, earaches, sinusitis, rhinitis, and other nonspecific upper airway problems. The bronchitis group included lower airway diseases such as bronchitis, tracheitis, and nonspecific cough. The asthma group included all reactive airway disease, bronchospasm, and asthma. Diarrhea was selected as a control diagnosis. The number of people eligible for the study was approximately 14 000 workers and their families employed by the state of Alaska and the city of Anchorage, who were covered by a single health insurance company. Claims for emergency visits were analyzed using both Poisson and multiple linear regression analyses, the latter detrended using a 19 d moving average (Shumway filter), adjusted for long-term cyclic variations, seasonal effects, day of the week effects, and temperature.

Researchers found statistically significant associations between either same day or previous day PM_{10} and outpatient visit for illnesses due to asthma and upper respiratory illness (URI), but no association with bronchitis after adjustment for several factors. The increase was about 3.5% for asthma and 1.2% to 2.7% for URI, both for a 10 µg/m^3 increase in PM_{10}, in a location where the primary sources of PM_{10} were not combustion or secondary aerosols. However, the association found between PM_{10} and asthma-related doctors' visits was not significant during the period that was affected by volcanic activity from Mt. Spur, 60 miles west of Anchorage (Gordian et al., 1996). This study thus gave mixed signals regarding the importance of the particle fraction between $PM_{2.5}$ and PM_{10} ("coarse particle" (CP) fraction), and indicated that silicaceous or volcanic crustal coarse particulate pollution may have less than expected adverse acute respiratory effects, but that the urban CP fraction may also be associated with adverse repiratory effects , even in a healthy, young, working population. Wintertime CO was also found to be associated with outpatient visits for bronchitis and upper respiratory tract infections, but not with asthma. These associations might have been explained by the high correlation between CO and automobile exhaust emissions, but models including both PM_{10} and CO produced results essentially the same as the single pollutant regression models. However, due to the small number of days on which CO was measured, the authors advocate caution in interpretation of the CO results. Only sporadic measurements were available for SO_2, NO_2, and ozone. However, the authors considered it unlikely that any of these could have been responsible for the associations since SO_2 measurements were less than 10% of the US EPA standard, and NO_2 and ozone measurements were less than 33% of that standard. This argument is open to question considering the results of others showing adverse health outcomes at very low levels of pollutants. Overall, the most intriguing findings from this study have to do with the effects of a particulate mass composed largely of coarse particles, >2.5 µm.

In three communities in eastern Washington State (1990 population 101 623), the number of Emergency Department visits in 1991 for respiratory disorders such as otitis media, bronchitis, upper respiratory tract infections, pharyngitis, sinusitis, croup, pneumonia, asthma, influenza, bronchiolitis, and chronic obstructive pulmonary disease were compared to daily PM_{10} levels (Hefflin et al., 1994). Dust storms are a major source of PM_{10} in Washington State, the particulates being coarse, volcanic in origin, and belonging to the plagioclase (glass) mineral class of aluminum silicates and other oxides. The coarse fraction ($PM_{10-2.5}$) thus makes up a greater proportion of PM_{10} than usual. The total number of emergency visits for all respiratory disorders was 23 349 or 64/d. For a total of 278 daily PM_{10} samples, the daily mean value was 40 µg/m^3, with a daily range of 3-1,689 µg/m^3. The results showed a relationship between PM_{10} levels and the number of emergency room visits during 1991 for bronchitis and sinusitis. No association was found between PM_{10} and asthma despite the expected prevalence of asthma in such a community. A 10 µg/m^3 increase in PM_{10} was associated with a 0.35% increase in visits for bronchitis ($p=0.03$). In October 1991, two dust storms occurred, during which PM_{10} levels went above 1000 µg/m^3 on several days. Although the odds ratio for bronchitis was raised to 1.2 in the dust storms, this was less than expected on the basis of the high PM_{10} levels experienced, thus indicating that crustal dust is less toxic than finer particles, which are usually produced as a result of combustion processes.

12.3.2 Hospital Studies and TSP

The relationship between pollution levels and hospital emergency room visits were studied in the industrial town of Steubenville, Ohio, during the spring months of March and April, and fall months of October and November during 1974-1977 (Samet et al., 1981). Records of emergency room visits covering 10 categories (asthma, emphysema and/or chronic bronchitis, pneumonia, lower respiratory infection, upper respiratory infection, other respiratory infection, other respiratory disease, cardiac disease. cardiac and respiratory disease, trauma, and miscellaneous) were collected and compared to air pollution data. Monitored pollutants included total suspended particles (TSP), sulphur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO), and ozone (O_3). The 24 hour average was utilized as the index of pollution exposure. The TSP mean was measured at 156 µg/m^3 with a range of 14-696 µg/m^3. Analysis of the resulting data showed no consistent correlation of lagged and unlagged pollutant levels with either total emergency room visits or with visits for diagnoses other than trauma (Samet et al., 1981). Since this was an early study, the negative results might have been attributed to the less rigorous statistical treatment given to the data, by comparison to later time-series analyses, but a later re-analysis, by the original

author, of these data using contemporary statistical methods yielded the same results as the original (Samet 1997, personal communication.) The negative results could also have been due to use of the TSP metric, which has a coarse particle size cutoff above the inhalable range, and thus does not provide as close a match to the real exposure of individuals in the population as a smaller size fraction.

The effects of low levels of pollution and weather conditions on the number of patients admitted to hospital for exacerbation of chronic bronchitis or emphysema were studied in Helsinki, Finland during a three-year period (1987-1989) (Ponka and Virtanen 1994). In addition to total suspended particulates (TSP), other air pollutants monitored included SO_2, NO_2, and O_3. The main source of air pollutants in the Helsinki area is coal-fired and oil-fired power plants, road traffic, and industrialization. Pollution data collected were daily mean concentrations and the ranges, the results for TSP being 76 µg/m^3 and 6-414 µg/m^3, respectively. Final analysis showed no significant effect of either temperature or relative humidity, or of TSP or O_3 on the daily number of hospital admissions. However, it was also explained that approximately one-third of the TSP air pollution data were missing, and therefore had to be estimated (Ponka and Virtanen, 1994). The previously described study excluded any hospital admissions for asthma. A separate report was published using the same air pollution data on the association between asthma and ambient air in pollution in Helsinki (Ponka and Virtanen 1996). No association was observed between asthma and TSP levels. However, associations were observed between some of the other air pollutants and asthma. Due to some unexplained results, the method of analysis was deemed unsatisfactory as was the collection of data for TSP, (Ponka and Virtanen, 1996).

The above studies were all conducted after an initial examination of the association between asthma and air pollution by the same author in the Helsinki region (Ponka 1991). Hospital admissions were examined over a three-year period between 1987 and 1989. During this period, 4,209 admissions to hospital for acute asthma were recorded. Pollutant levels were reported for NO_2, NO, SO_2, CO, O_3, and TSP. Mean TSP levels were 76.3 µg/m^3 with a range of 6.0-414.0 µg/m^3. Admissions were increased 28%, 29%, 15% and 18% associated with periods of high NO, NO_2, CO, and TSP pollution respectively, compared to periods of lower pollution. No clear cut limits could be observed on the basis of health effects, but it was observed that as pollution increased so did health effects. It should also be noted that it was not the incidence of asthma that was considered in this study, but rather, the frequency of acute attacks among persons with pre-existing bronchial asthma that was recorded (Ponka, 1991).

12.3.3 Hospitalization Studies with Various Fine Particle Measures

Thurston et al. (1994) conducted a daily time-series in the city of Toronto, Ontario, (population 2.5 million) utilizing measured TSP, PM_{10}, $PM_{2.5\text{-}10}$, $PM_{2.5}$, SO_4^{2-}, H^+, O_3, SO_2 and NO_2 and evaluating the association with daily respiratory effects-related hospital admissions for 22 Metropolitan Toronto-area hospitals. Monitoring was carried out for six weeks in July and August of the years 1986-1988, (n=40-42 days x 3 years). The 24 hour average PM_{10} level ranged from 30 to 39 µg/m^3, wih a maximum of 86 µg/m^3, $PM_{2.5}$ ranged from 15.8 to 22.3 µg/m^3, with maximum values ranging from 50.7 to 66.0 µg/m^3, and SO_4^{2-} means were 74, 38 and 124 nmol/m^3 (7.1, 3.6 and 11.9 µg/m^3) for 1986-88 respectively. When regressed singly, ozone, H^+, fine particles ($PM_{2.5}$), PM_{10} and sulfate were all associated with hospital admissions; for a 10 µg/m^3 increase in SO_4^{2-}, $PM_{2.5}$, and PM_{10} , respiratory hospitalizations increased 8.0% (0-16%), 3.2% (-3.0 to 9.3%) and 4.7% (0.5-8.8%) respectively (95% CI in brackets). Coarser particles between 2.5 and 10 µm in diameter, and TSP were found to have weaker marginal associations with hospital admissions, and association with the very coarse fraction above PM_{10} to be non-existent (associations with SO_2 and NO_2 were also non-significant). When each particle metric was regressed simultaneously with ozone, only H^+ remained significant (p=0.04), and sulfate was also marginally significant (p=0.09). Regression coefficients for all PM fell 20-50% in the bivariate regressions and the ozone coefficient remained about the same (with H^+) or was reduced 20-25%. Because of high intercorrelations (r=0.64-0.73) between ozone and all PM pollutant measures except H^+ (moderately high), the authors considered that it was not possible to establish whether ozone and the particle metrics had independent effects or whether any one pollutant was the best index of the adverse health effects of air pollution. However, the results suggested that particle strong acidity was an important contributor to respiratory admissions, at least in this location. It was also observed that associations

generally became stronger as particle size decreased (i.e., TSP < PM_{10} < $PM_{2.5}$) and that chemical composition of the particle mass (acidity and SO_4^{2-}) had an influence on daily summertime respiratory and asthma hospital admissions.

In a well conducted study on summertime respiratory hospital admissions, the daily number of unscheduled respiratory admissions was recorded for 168 acute care hospitals in southern Ontario (population 8.7 million, or over 90% of the entire population of the province) for the six years between 1983 and 1988 (Burnett et al., 1994). Mean respiratory admissions were 107.5/d. The only particle metric available over the entire area was sulphate. The yearly mean was 4.37 µg/m^3 (range 1-31 µg/m^3) and the warm period (April-September) mean was 5.13 µg/m^3. Mean annual ozone (1 h maximum) was 36 ppb and the summertime mean was 50 ppb. Data were analyzed by multiple regression, taking account of day-of-week variations in hospitalization rates, inter-hospital variations, and longer or seasonal variations making use of a 19 d weighted filter to remove all cyclic variations in the data for health outcomes and exposure variables.

The investigators found significant associations during the May-August summer period, between hospital admissions (all ages) for asthma, COPD, and infections, and both ozone and sulphates recorded on the day of admission and up to three days previously, with the highest association on the previous day (lag 1 d) for both pollutants. In summer, ozone was more strongly associated than sulphates when the two were included in the same model . Five percent of daily admissions were associated with a 50 ppb increase in ozone while a further 1% could be ascribed to a 5.3 µg/m^3 increase in sulphates. However, the high correlation between these two (0.38-0.65 among various stations) indicates that caution is needed when assigning effects to each pollutant. When plotted by decile of concentration (lagged one day), the dose-response appeared to increase monotonically from 0 to 20 µg/m^3 for sulphate and from 20 to 95 ppb for ozone. Other particulate metrics (TSP, PM_{10}, CoH) could not be investigated because daily data were not available, and/or there was insufficient area coverage of the monitoring network. Two other air pollutants (SO_2, NO_2) were considered, but insufficient monitoring stations were available to give monitoring data representative of the entire 900 km long area. Relatively low correlations between SO_2, NO_2 and the two pollutants sulphate and ozone, that were included in the regression analysis provide some assurance that SO_2 and NO_2 were not likely to bias the association for sulphate (Burnett et al., 1994).

Burnett et al. (1995) further analyzed this database with respect to sulphate and other particle metrics estimated from sulfate and expanded the study to include hospital admissions for cardiovascular cases as well as respiratory admissions. Groups of diagnoses thought to be unrelated to air pollutants (gastrointestinal, genitourinary, nervous system, and blood system) were also included as controls. As before, the daily number of unscheduled admissions was recorded for 168 acute care hospitals for the six years between 1983 and 1988. Data were analyzed by multiple regression, taking account of day-of-week variations in hospitalization rates, inter-hospital variations, and longer or seasonal variations making use of a 19 d weighted filter for admission data. Regressions were performed for winter and summer separately, adjusting for temperature and ozone, which were highly correlated with sulphates (for temperature, r=0.35, 0.15, and 0.43 for the year, cool and warm seasons respectively; for ozone, r=0.47, -0.04, and 0.53 for the year, cool and warm seasons respectively) and were considered as potential confounders. Adjustments for temperature and ozone were done separately for the warm and the cool season. Yearly sulphate levels averaged 4.4 µg/m^3 with a median of 3.1 µg/m^3 ; the 95th and 99th percentiles were 13.0 and 23.0 µg/m^3 respectively. As with ozone, sulphate levels were higher in the warm season (April-September) than in the cold season. The predicted values of PM_{10} based on a sulphate level of 13 µg/m^3 were 47.0, 52.1 and 44.5 µg/m^3 for the Toronto, Windsor and Ottawa regions, respectively, (also central, western and eastern limits of the entire area) with an average of 48.0 µg/m^3 , which would represent very well the more than half of the population living in the central region. Note, however, that a concentration of 32 µg/m^3 was reported in the paper by Burnett et al. (1995, page 21) which could be due to an intercept effect.

For both respiratory and cardiovascular illnesses, hospitalization rates were found to increase with increasing sulphate concentration. A 13 µg/m^3 increase in sulfate concentration (the 95th percentile) was associated with a 3.7% increase in respiratory admissions (95% CI 2.3 to 4.7%), and a 2.8% increase in cardiac admissions (95% CI 1.7 to 4.8%) ($p < 0.0001$ for both). The associations were almost

the same after adjustment of ozone, square ozone, temperature, and square temperature: the increase was 3.5% (95% Cl 2.3-4.7%) for respiratory admissions and 3.3% (95% Cl 1.7-4.8%) for cardiac admissions. The relationship appeared linear for respiratory effects-related admissions; however, the concentration-response appeared to be curvilinear for cardiovascular illnesses (i.e., the increase in rate tended to diminish for cardiovascular illnesses as the sulphate concentration increased. When the total sample was divided into four groups according to increasing SO_4^{2-} concentration, the adjusted daily average hospitalization rate for the lowest half of the sample, with an average sulphate concentration of 1.55 µg/m^3, was statistically different from the corresponding average hospitalization rate for the next higher group (the 25% around the average, at the 4.13 µg/m^3 sulphate concentration) for both respiratory and cardiovascular illnesses ($p < 0.01$).

Positive associations were observed for all age groups, sexes, and time periods for cardiac diseases including coronary artery disease (2.3%) and heart failure (3.0%) (but not dysrhythmias) and respiratory diseases including asthma (3.2%), COPD (4.8%), and infection (3.3%). For respiratory diseases, excess hospitalizations were calculated to be 2.7% for children <15 y, compared to 3.8% and 3.7% for adults 15-64 y and ≥65 y. Cardiac admissions were increased more for the elderly (≥65 years) than for those under age 65, at 3.5% for the former versus 2.5% for the latter. Increases in both respiratory and cardiac admissions were similar in the winter and the summer period, after adjustment for temperature and ozone. The results were robust to application of 15 different regression models (Burnett et al., 1995).

This study clearly demonstrated that sulphates, despite the low levels experienced in southern Ontario (the sample median was 3.07 µg/m^3), are associated with excess hospitalizations for both respiratory and cardiac diseases. Although the correlation between ozone and sulphate was moderately high (r=0.53), these associations can not be explained by ozone, since the effect of sulphates was observed over the entire year as well as in summer, and persisted in winter when the correlation was low. The method of adjustment for temperature also appeared to be satisfactory. A major strength of this study is its size – about one-third of the population of Canada, over a period of six years. Its weakness is perhaps in the lack of ability to consider the role of other measures of particulate matter (PM_{10}, $PM_{2.5}$) or other air pollutants – SO_2, NO_2, CO – some of which could have had high correlations with sulphates as well as associations with increased adverse health outcomes.

Summertime respiratory and cardiac admissions to Metro Toronto hospitals during June to September 1992-94 (388 days) were examined in a preliminary study by Burnett et al. (1997) with respect to possible associations with a suite of particulate matter metrics as well as the four criteria gaseous pollutants. Fine particle metrics included $PM_{2.5}$ (mean 14 µg/m^3; range 4-40 µg/m^3), SO_4^{2-} (mean 33 nmol/m^3 or 3.2 µg/m^3; range 5-229 nmol/m^3 or 0.5-22 µg/m^3), particle strong acidity as H^+ (mean 1 nmol/m^3; range 0-23 nmol/m^3), and coefficent of haze (CoH: mean 0.8 x 10^3 lin. ft.). Coarse particle metrics included CP or $PM_{2.5-10}$ (mean 10 µg/m^3; range 4-23 µg/m^3) and PM_{10} (mean 25 µg/m^3; range 10-58 µg/m^3). Correlation coefficients between the various particle metrics and NO_2 were moderate to high (0.34 to 0.61) except for H^+ (r=0.25). Correlation coefficients with SO_2 were moderate (0.42 to 0.55), and correlation coefficients between particles and ozone were moderately low (0.23 to 0.34) except for SO_4^{2-} (r=0.53).

After adjustment for long term temporal trends, seasonal variations, short term epidemics, day of the week effects and ambient temperature and dew point, positive associations were observed in Poisson regressions carried out individually for each of the PM metrics. For respiratory admissions, relative risks for the observed particulate pollutant interquartile ranges, adjusted for temperature and dew point, were 1.023 to 1.037, all significant. The magnitude of the association was highest for CoH and fine particles and least for H^+ and coarse particles. When regressed pairwise with each gaseous pollutant, the relative risks for all the particle metrics were slightly to moderately reduced, but all retained significance except PM_{10} with NO_2 (for which the correlation coefficient was high, 0.61). Ozone retained its significance, and its magnitude of association was the same or slightly lower in all the pairwise analyses, while the relative risk for CO was reduced to half or less of its univariate value and was not significant with any of the particle metrics. While the relative risks for SO_2 and NO_2 dropped and were no longer significant for regressions with CoH, the RRs dropped more moderately in pairwise regression with the other particle metrics and retained their significance.

For cardiac admissions, all particle metrics except $PM_{2.5}$ and SO_4^{2-} were significantly associated in the single regressions, again with CoH having the high-

est magnitude of association (RR for CoH =1.062; t=5.6). In the pairwise regressions, CoH retained its association with each of the gases (CoH-gas correlation coefficients were 0.2, 0.3, 0.5 and 0.6 for CO, O_3, SO_2 and NO_2). Relative risks for SO_4^{2-}, PM_{10} and fine particles were no longer significant with any of the gases in bivariate models. The relative risk for H^+ retained its magnitude with NO_2 (r=0.25), and the coarse particle relative risk was increased with ozone (r=0.20); otherwise, the relative risks for H^+ and coarse particles were all reduced to non-significance with NO_2 or SO_2 (H^+ r=0.25-0.45; CP r=0.44-0.57). Ozone was again the only gas that consistently retained significance when regressed with the various PM matrics (Burnett et al., 1996). The negative results for cardiac disease observed for sulphate and fine particles in this much smaller summer-only study contradict the previous findings of the much larger multi-year southern Ontario study (Burnett et al., 1995), and are considerd to be due to the limited size of the data set (only 388 days versus 2000+ days in the earlier 1995 study). Due to the high correlations between most of the particle metrics (0.6-0.9 for all except CoH, 0.3-0.5), inter-particle comparisons are doubtful, since the effect of one is likely to be attributed in the regression to another highly correlated metric. Combined regression of the four gaseous air pollutants with and without PM was attempted for both respiratory and cardiac admissions, but the results should be interpreted extremely cautiously in view of the above-mentioned high correlations.

The relationship of hospital admissions for respiratory illnesses to the air pollutants PM_{10}, sulphate, and ozone was examined in Montréal (population almost 3 million) for five summers, from May to October, 1984-1988 (n=911 days) (Delfino et al., 1994). The means and 90th percentile values for PM_{10} and SO_4^{2-} were 29.5 and 45.7 µg/m^3 (PM_{10}) and 4.2 and 8.2 µg/m^3 (SO_4^{2-}), well below international standards for PM_{10} (no objectives exist for sulphate). The 1 h and 8 h ozone values were 36.7 and 60.3 ppb for 1 h O_3 and 30.4 and 51.5 ppb for 8 h O_3, also well below the current Canadian objective of 82 ppb. For five of the six day sampling period for particles, it was necessary to estimate PM_{10}, using the light extinction coefficient, temperature, O_3, NO_x, and barometric pressure. This meant that PM_{10} was actually acting partly as a surrogate for fine particle air pollution from photochemical episodes. The correlation coefficients between PM_{10}, SO_4^{2-}, and ozone were high, as expected, with r=0.90 for SO_4^{2-} and r=0.68 for ozone. The SO_4^{2-}-ozone coefficient was also high, r=0.66. Temperature was also highly correlated with all three of the pollutant variables examined: correlation coefficients were 0.66, 0.58 and 0.72 for PM_{10}, SO_4^{2-}, and ozone. Since the analysis was confined to the warmer season, the variability in the pollution measures aproached a normal distribution, and linear regression methods using Ordinary Least Squares was carried out. A 19 d weighted moving average (Shumway filter) was used to remove longer-wave cyclic yearly and seasonal variations in outcomes (hospitalization counts) and exposures. Temperature, relative humidity and day of the week effects were also controlled. Data were examined for both a longer warm season (May-October) and a shorter summer season (July, August). The effect of high air pollution days on adverse respiratory effects was examined by carrying out the regression after dichotomizing data at days above the 90th percentiles, which were >46 µg/m^3 for PM_{10}, >8.2 µg/m^3 for SO_4^{2-}, and > 60 ppb for ozone (1 h maximum). Pollutants were first examined singly in the models and then other explanatory variables were added. Finally, pollutants which remained significant predictors of hospitalizations were regressed in the same model together.

During May-October, an increase of 10 µg/m^3 PM_{10}, lagged 3 d, was associated with a 2.1% increase in asthma admissions (95% CI 0.6 to 4.0%). After inclusion of ozone, the PM_{10} regression coefficient changed only minimally, but the standard error was markedly inflated resulting in marginal significance, probably due to the high correlation between these two pollutants. For the 46 days in July and August with high air pollution (SO_4^{2-} > 8.2 µg/m^3), non-asthma respiratory admissions associated with sulphate lagged 4 d were 9.6% higher (95% CI 0.5 to 18.7%) than for days that were below 8.2 µg/m^3, the 90th percentile. Asthma admissions and non-respiratory admissions were not affected by SO_4^{2-}.

While ozone (lagged 4 d) was significantly associated with respiratory admissions during July and August when regressed alone, its coefficient dropped by 40% and it lost significance when temperature was included. Temperature itself (lagged 0 and lagged 1 d) was correlated with hospital admission in the all respiratory, respiratory non-asthma and non-respiratory categories, and thus could potentially act as a counfounding factor for ozone, with which it was also highly correlated (r=0.7). Due to the estimation technique for missing PM_{10} values, this study was plagued by the high correlations between the three

pollution metrics (PM_{10}, SO_4^{2-}, and O_3), that were examined,as well as the temperature correlations. Therefore, the effects observed on hospital admissions cannot be ascribed to any one component of particulate matter or to particles rather than ozone. The modelled variables should be looked upon as a reasonable expression of the mix of air pollutants affecting respiratory health (Delfino et al., 1994).

Delfino and colleagues attempted to further delineate the effects of the various particle metrics in a smaller study, also in Montréal, in which daily emergency room visits for respiratory illness were examined for the summers of 1992 and 1993 ($n \leq 98$ for each year) (Delfino et al., 1997). There were 10 659 visits for respiratory diseases and over 13 000 visits for non-respiratory causes (the reference group) recorded in 1993. Mean emergency department (ED) visits in 1993 were 98/d for total respiratory diseases, all ages, and 27/d for the elderly. Mean and 90th percentile values for PM_{10} were 22 and 38 µg/m^3, and for $PM_{2.5}$, 12 and 22 µg/m^3. Mean and 90th percentiles for sulphate were 3.3 and 7.8 µg/m^3, for H^+, 4 and 10 nmol/m^3, for ozone (8 h), 31 and 46 ppb, and for 1 h maximum ozone, 36 and 57 ppb. As in the previous study, high correlations were observed between most of the air pollutants. Sulphate made up a large fraction of both $PM_{2.5}$ and PM_{10}, and the correlation coefficients were 0.93 and 0.87. Maximum temperature was highly correlated with both measures of ozone (r=0.7), and moderately correlated with the particle measures (r=0.4-0.5). The data were treated as previously by ordinary least squares (OLS) regressions after detrending with a 19 d weighted filter and applying various corrections for season, weather, and day of week effects.

No associations were found for 1992, although both pollutant levels and ED visits were significantly different between years. The authors noted that about one-third of the PM data were lacking for 1992, which could have accounted for the lack of significance in this year, due to increased variance and reduced statistical significance. While no associations were found for most age groups, respiratory visits for the elderly were associated in 1993 with increased O_3 (1 h max. and maximum 8 h moving average), PM_{10}, $PM_{2.5}$, and SO_4^{2-}, all lagged 1 day (corrected for temperature and humidity effects). An increase to the mean level (36 ppb) of (1 h) ozone was associated with a 21% (95% CI 8 to 34%) increase in ED visits. The effects of particulates were smaller with mean increases of 16% (4 to 28%) for 22 µg/m^3 PM_{10}, 12% (2 to 21%) for 12 µg/m^3 $PM_{2.5}$, and 6% (1 to 12%) for 3.3 µg/m^3 SO_4^{2-}. Acidity (H^+) was not associated with ED visits in adults. In pairwise regressions of ozone with PM_{10}, $PM_{2.5}$ and SO_4^{2-}, the regression coefficients for the PM metrics were reduced by half or more, and the the coefficient for ozone was also reduced by about 25%. However, it is not reasonable to assume that the respiratory association with particulate matter was due to ozone, because of the high correlations between PM and ozone (r=0.57-0.63), and it appears more likely that particles and ozone are both independently associated with respiratory ED visits. Tests for statistical interactions between ozone and PM were negative. An isolated effect was found for children under the age of two years with respiratory visits associated with H^+, which the authors suggested was spurious based on internal inconsistencies (Delfino et al., 1997). This study provides limited evidence for an independent association of ozone and three of the four measures of particulate matter with respiratory disease. Acidity did not appear to play a role in exacerbation of disease leading to outpatient visits. The small data sets in this study, combined with the high correlations among all of the air pollutants make it problematic to discern which of the pollutants was the best predictor of adverse respiratory outcomes.

A two-year study of air pollution and respiratory hospital admissions was conducted in the cities of Buffalo, Albany, Metropolitan New York City and suburban N.Y.C. (White Plains) in June to August 1988 and 1989 (Thurston et al., 1992). Air pollution measurements were collected for particulate phase aerosol strong acidity (H^+), sulphate (SO_4^{2-}) and ozone (O_3). Hospital admissions data employed in this study were counts of unscheduled (emergency) hospital admissions with a primary diagnosis of respiratory illness in New York State acute care hospitals in selected counties. The range of mean and maximum SO_4^{2-} values for all areas were 6.9-9.6 µg/m^3 and 26.0 to 41.8 µg/m^3, respectively. Acidity measurements showed a range of means and maximums from 2.2-3.3 µg/m^3 and 7.5-18.7 µg/m^3, respectively.

For the summer of 1988 in Buffalo, a 9% increase in respiratory hospital admissions per 10 µg/m^3 SO_4^{2-} and a 28% increase per 10 µg/m^3 H^+ was calculated from Poisson regression, after adjustment for cyclic and seasonal variations, day of the week effects, and maximum temperature. Ozone was also highly significantly associated. Results for New York City

were similar to those for Buffalo. The relative risks for H^+ were consistently higher than those for SO_4^{2-}. Results were not significant for 1989, when pollutant levels were lower than in 1988, nor for Albany or White Plains, N.Y. In the case of Albany, a combination of small population and lower air pollutant values could have been responsible for the lack of association, while in White Plains, the explanation offered was the high socioeconomic status of this population, which tends to mitigate the effects of outdoor pollutants, through use of air-conditioning and remaining indoors during pollution episodes. The results of the present study indicated that summertime haze pollution appeared to play a role in the occurrence of respiratory admissions during that particular season, especially for asthma admissions, for which air pollution was estimated to account for an average of 6-24% of Buffalo and New York City 1988 summertime admissions. At the same time, the relative risk of admissions in these cities increased by a factor of 1.19-1.43 on maximum summertime pollution days in 1988. Because of the high correlation coefficients between ozone and the two particle metrics (r= 0.51-H^+; r= 0.67-SO_4^{2-}), and between SO_4^{2-} and H^+ (r=0.77), the effects of these pollutants cannot be distinguished from one another. The authors considered that the results were consistent with the hypothesis that H^+ acts to exacerbate the effects of ozone on the respiratory disease process (Thurston et al., 1992). Measurements for PM_{10}, and $PM_{2.5}$ were lacking in this study. These PM metrics are usually highly correlated to SO_4^{2-} and H^+. If this were the case in this location, the hospitalization increases noted with SO_4^{2-} and H^+ may well have also been seen with fine particles and PM_{10}.

An extension of the previous study on respiratory admissions in Buffalo, N.Y. has recently been completed (Gwynn et al., 1996). During the summers of 1988 to 1990, PM_{10} (missing days estimated from SO_4^{2-} and CoH data) and three fine particle measurements were investigated (SO_4^{2-}, H^+ and CoH), but their means and ranges were not given. Poisson regression techniques were followed, with filtering to remove cyclic and seasonal variation, and adjustments for day of the week, linear time trends, quadratic hot and cold temperature terms, and a heat and humidity interaction term. For total admissions, a 1 to 2% increase (statistically significant) per equivalent range of $\mu g/m^3$ was calculated (note that means and ranges were not given), for all except CoH, which was only marginally significant. For respiratory admissions, the increases (per the range for each, which was not given) were 20%, 38% and 1-2% (n.s.) for SO_4^{2-}, H^+ and CoH respectively, and for the larger particle size (PM_{10}) the increase was also significant at 18%. All four of the criteria pollutant gases were also significantly correlated with respiratory hospital admissions in single-pollutant regressions (t= 4 to 7.5, except for CO, t= 2), and they remained significant (NO_2 and CO were marginal) although with a reduced relative risk when co-regressed with acidity (H^+). Acidity was the most consistently associated of the PM metrics when included in models with each of the gases in turn. Based on data presented thus far in this preliminary paper, the order of significance for the four particle metrics was $H^+ > SO_4^{2-} \sim PM_{10} >$CoH. The particle metrics were said to be all highly correlated with each other, but correlation coefficients were not presented. The high correlations noted would make it impossible to determine the true size of the various PM regression coefficients and thus the metric with the best predictive power for respiratory disease. This paper provided some potentially interesting results but was poorly documented and presented.

Ponce de Leon et al. (1996) investigated the effects of air pollution levels in London, England by recording daily counts of hospital admissions and adjusting for all variables (trend, season and other cyclic factors, day of the week and holidays, influenza epidemics, temperature, humidity, and autocorrelations) in Poisson regressions. Pollution data recorded were Black Smoke (BS), SO_2, O_3, and NO_2, lagged 0-3 d. The study period began in April 1987, ending in February 1992 (1,796 days) and included all ages in three groups, the 0-14, 15-64, and 65+ age groups. Daily average levels of BS and SO_2 were obtained for four monitors, with data for more than 75% of the study days. The reported mean level of BS was 14.6 $\mu g/m^3$ with 5th and 95th percentile values of 6 $\mu g/m^3$ and 27 $\mu g/m^3$, respectively. No relationship between BS and hospital admissions was observed in any age group either for the whole year or for separate analyses of summer and winter. However, ozone was found to be significantly associated with respiratory admissions; an increase of 10 ppb ozone in the warm season was associated with a 1.7% increase (95% CI 0.85-2.5%). The ozone regression coefficient was little changed by addition of BS, NO_2, or SO_2 in bivariate regressions. Although statistically significant health effects in the elderly were associated with NO_2 exposure in the summer, this was attributed to the higher correlation between ozone and NO_2 in summer than in winter or in the entire

year. Although some sporadic associations were noted between SO_2 and respiratory admissions in some age groups, the effects were not consistent. The results for particulate matter, despite pollution levels in London within the range associated with effects in other cities, did not appear to be consistent with most other current evidence based mainly on North America. Some explanations were offered for these results including too few monitors (only four) to cover as wide an area as the city of London, and the possibility that BS represented either a less toxic type of particulate than PM_{10} in North America, or BS measurements, which are optically determined based on dark soot particles, may not accurately capture concentrations of the secondarily-formed sulphates and nitrates that are uncoloured. The level of BS in London was one-half or less the values in other European cities in which positive associations were observed.

A daily time-series analysis was conducted on the association between BS, PM_{13}, O_3, SO_2 and NO_2, and hospital admissions for all respiratory diseases, COPD, and asthma in Paris, France for the six-year period 1987-1992 (Dab et al., 1996). Mean BS was 32 $\mu g/m^3$; concentrations were higher in winter (mean 40 $\mu g/m^3$) than in summer (mean 25 $\mu g/m^3$). PM_{13} concentrations were less seasonal, with 51, 54 and 48 $\mu g/m^3$ for yearly, winter, and summer means respectively. The increase in all respiratory admissions was 0.41% (95% CI 0.07 to 0.75% for a 10 $\mu g/m^3$ increase in BS, and almost the same, 0.45% (95% CI 0.04 to 0.87%) for a similar increase in PM_{13}. Increases were not significantly associated with either BS or PM_{13} for the specific asthma and COPD categories of respiratory disease. SO_2 was associated with all three endpoints (RR for a 10 $\mu g/m^3$ increase = 1.10 (24 h) and 1.05 (1 h) for COPD, and 1.07 for asthma), while NO_2, both 24 h and 1 h, was associated with asthma, with the RR for a 100 $\mu g/m^3$ increase at 1.18 (95% CI 1.06-1.30) for 24 h NO_2 and 1.08 (95% CI 1.02-1.15) for 1 h NO_2. Ozone was not significantly associated with any endpoint in this analysis, although the RR for a 100 $\mu g/m^3$ increase in 1 h ozone was 1.03 (95% CI 0.997-1.073) for all respiratory admissions. No correlations between pollutants were given, and no pollutants were co-regressed (Dab et al., 1996).

In Athens, Greece, during the year 1988, the daily numbers of emergency outpatient visits for all causes, and hospital admissions for cardiac and respiratory causes (diagnoses at time of admission) were examined with respect to BS, CO and NO_2 (Pantazopoulou et al., 1995). Mean resiratory admissions were 41.8/d in winter and 41.4/d in summer (total over 15 000 admissions). Mean cardiac admissions were 73.8/d in winter and 63.9/d in summer (total over 25 000 admissions). Mean emergency visits (all causes) were 592/d (winter) and 575/d (summer). Recorded mean values for six area monitoring locations for BS were 75 $\mu g/m^3$ and 55 $\mu g/m^3$ for winter and summer, respectively, with 5th and 95th percentile values of 26 $\mu g/m^3$ and 161 $\mu g/m^3$, and 29 $\mu g/m^3$ and 90 $\mu g/m^3$, respectively. After adjustment for month of year (5 dummy variables), day of week, temperature (linear) and relative humidity, a positive association was found between the number of visits and air pollution levels for both BS and CO, in winter only. The resulting effects of BS exposure were more pronounced for morbidity of the respiratory system (20-29% increase from 5th to 95th percentile pollution levels) and to a somewhat lesser extent of the circulatory system (15-17% increase from 5th to 95th percentile pollution levels). A 10 $\mu g/m^3$ increase in BS was associated with a 1.2% increase in respiratory-related visits and a 0.96% increase in cardiac disease-related visits. Division of the area into three, based on high, medium and low (the above metropolitan area) BS mean concentrations, (wintertime mean daily averages for BS of 135, 112, and 75 $\mu g/m^3$) gave poor dose-response information. Results with NO_2 were statistically significant when wintertime NO_2 from the central monitoring station was used as an air pollution indicator. A 10 $\mu g/m^3$ increase in NO_2 was associated with a 1.4% increase in respiratory hosital admissions and a 2.0% increase in cardiac admissions in winter. A 10 $\mu g/m^3$ increase in CO (in winter) was associated with a 4.0% increase in respiratory admissions and a 2.3% increase in admissions for cardiac disease. The relationship between air pollution and total emergency outpatient visits for all causes (not specifically cardiorespiratory) was also examined but no association was observed with any of the three pollutants. The three measured air pollutants were noted to be highly correlated with each other, but no values were provided. Potential sources of bias in the data were noted such as a lack of a definition of a “real” emergency case, use of admission diagnosis rather than discharge diagnosis, and inclusion of admission cases from outside the Athens area (Pantazopoulou et al., 1995). The high correlations between pollutants precludes assignment of the air pollution effects on cardiorespiratory health to any single pollutant.

As part of the APHEA collaborative European project, Schouten et al. (1996) assessed the short-term relationship between air pollution and the daily number of emergency hospital admissions for respiratory disease in the Netherlands (cities of Amsterdam and Rotterdam) between 1977 and 1989. Pollution parameters used were 24 h daily means for BS, SO_2, and NO_2, one hour maxima for SO_2, NO_2, and O_3, and 8 h maxima for BS, O_3, SO_2, and NO_2. In Amsterdam, black smoke pollution data were available only for the years 1986-1989 and measurements were taken about 20 km west of the city. The annual mean level for BS in Amsterdam was 11µg/m^3 with 5th and 95th percentile values of 1 and 37 µg/m^3. Concentrations were almost twice as high in winter as in summer. In Rotterdam, the annual mean BS level was 26 µg/m^3, with 5th and 95th percentiles of 6 and 61 µg/m^3. Concentrations in Rotterdam were more even throughout the year, with somewhat higher levels in winter (95th percentile values 72 and 54 µg/m^3 in winter and summer respectively). Emergency hospital admissions data were collected for all respiratory admissions (6.7 and 4.8/d in Amsterdam and Rotterdam respectively), chronic obstructive pulmonary disease (1.74/d – Amsterdam and 1.13/d – Rotterdam), and asthma (1.13/d – Amsterdam and 0.53/d – Rotterdam) for all ages, and data were subdivided for adults in the age groups 15-64 years and >65 years. It was observed that the daily counts of emergency hospital admissions due to all diseases of the respiratory system were low in both cities, for all age categories.

Neither BS nor the other pollutants were significantly associated with respiratory disease admissions in Amsterdam, although the RR associated with BS was somewhat elevated for some categories. In Rotterdam, BS (100 µg/m^3 increase) was associated positively but not significantly with all respiratory admissions for all ages (RR 1.24, 95% CI 0.88-1.76), and positively with an increase in RR to 1.37 (95% CI 1.09-1.73) for all respiratory admissions in the age group 15-64 years. The association was significant in summer but not in winter, a finding inconsistent with the somewhat lower concentrations of BS in summer. Ozone was also associated with significant increases in relative risk for all respiratory admissions in the 15-64 and the 65+ age groups (RR for younger adults was 1.15 (95% CI 0.97-1.38) for 8 h ozone averaged over days 0-5; RR for elderly adults aged 65+ in the 1977-1981 period only were 1.25 (95% CI 1.04-1.50) for 8 h ozone and 1.27 (95% CI 1.09-1.49) for 1 h ozone). NO_2 was associated with increased relative risks for all respiratory admissions in the 65+ age category in the 1982-84 period only and for COPD in all age groups together (RR 1.05 to 1.20 for 1 h, daily mean, lagged 2 days or averaged over day 0-2). The low number of admissions, both total and by category, combined with subdivision into age categories, probably contributed to the inconsistent results found in this study. The lower BS concentrations recorded for Amsterdam compared to Rotterdam could also have contributed to the lack of significance in the Amsterdam results. Analysis of the results by summer and winter seasons did not show any consistent pattern. Although some regressions showed higher relative risks in certain categories for the elderly, the pattern was also not consistent. Specificity of effects was also weak, since only NO_2 was asociated with COPD, and it was not associated with all respiratory admissions. Analysis of results for the whole Netherlands (population 14 million), in which very little spatial variation in pollutant levels occurred, indicated a relative risk for respiratory admissions, all ages, in the winter season of 1.10 (95% CI 1.024 to 1.184) for an increase of 100 µg/m^3 in BS. The RR was slightly lower, and was not significant in summer, as expected. The relative risks for SO_2, and NO_2 were also significantly elevated in winter, during the period when their concentrations were also highest. The RR for ozone was elevated in summer, when its highest concentrations were recorded. No correlations between pollutants were shown, nor were any bivariate regressions undertaken (Schouten et al., 1996).

BS was again used as the particle metric in Barcelona, Spain, examining the association between the daily number of emergency department (ED) admissions for chronic obstructive pulmonary disease (COPD) and air pollution in the five years between 1985 and 1989 (Sunyer et al., 1993). SO_2 levels were also collected to help determine whether its association with COPD was independent of the role of BS. Summer and winter pollution data were collected separately to help control more adequately for weather and influenza epidemics. Mean BS concentrations were estimated to average 63.2 µg/m^3 over the study period, and were 48 µg/m^3 in summer and 68 µg/m^3 in winter (data from Castellsague 1995). Numbers of daily hospital admissions for Barcelona residents over the age of 14 with COPD were collected and recorded for the study period. In single pollutant analyses, both BS and SO_2 were associated with COPD emergencies in both winter and summer although the association with BS in the summer was not significant. A 2.3% increase (t=5.0)

in visits for COPD per 10 μg/m^3 increase in BS and a 2.5% increase per 10 μg/m^3 SO_2 was predicted for winter. In a bivariate analysis, the increases in hospitalizations were reduced but remained significantly different than zero for both pollutants, to 0.94% (t=2.7) with SO_2 and 0.81% for BS (t=2.6) (no confidence limits were provided). The correlations between BS and SO_2 were high,(r=0.7), but the similar reductions for both lend support to the hypothesis of the researchers that both pollutants have independent associations with COPD in Barcelona. Stratification by tertile of each pollutant also showed that both pollutants remained significant, but that there were some inconsistencies. Statistics for other air pollutants were not given. SO_4^{2-} was said to form 38% of BS, but co-regression of SO_4^{2-} with SO_2 did not reduce the SO_2 association. The authors pointed out that BS is not a good measure of particulates in the summer as there is less heating than in winter and therefore less burning of fossil fuels. The ratio of total suspended particulates to BS was also found to be much higher in the winter than in the summer (Sunyer et al., 1993).

Castellsague et al. (1995), also for Barcelona, assessed the relationship between levels of black smoke, SO_2, NO_2, O_3 and adult emergency room visits for asthma during the same five year period from 1985-1989. Analysis was performed separately for the winter (January 1 to March 31) and summer (July 1 to September 30). Mean Black Smoke (BS) was 48 μg/m^3 in summer and 68 μg/m^3 in winter. After adjusting for weather and time-related variables, current day and lagged day 1-3 average summertime BS were associated with a 3.3% (95% CI 0.4-6.3%) and a 4.6% (increase, respectively, per 10 μg/m^3 increase in BS. The increase was small and was not significant in winter. NO_2 was associated with small but significant increases in asthma in both summer (1.8%; 95% Cl 0.4-3.2%) and winter (2.2%; 95% Cl 0.4-4.2%), while SO_2 and ozone were not significant in this analysis in either season. Because of high collinearity between variables, no co-regressions were undertaken. Therefore it is not possible to ascertain the independent relationship of BS with emergency hospital visits for asthma in this study.

Walters et al. (1994) examined the relationship between BS and SO_2 with hospital admissions for asthma and all respiratory diseases in Birmingham, UK for the two years April 1988-March 1990. No measurements of NO_2, O_3 or other pollutant gases were available. The mean daily BS level was low, at 12.7 μg/m^3 (max. 188), and mean daily (24 h) SO_2 was 39 μg/m^3 (max. 126), averaged for seven sites. Both SO_2 and BS peaked in concentration from October to December. The relationships were examined seasonally, by stepwise Least Squares regression, after inclusion of temperature, humidity and temperature. Since admissions lagged behind peaks in pollution, lags of 0 and 2 d, and the 0 to 3 d moving average lag were examined. BS was found to be more closely association with all respiratory disease admissions than with asthma admissions, and was also more strongly associated than SO_2. Associations were significant for the winter season, and to a limited extent in the summer (although it was pointed out by the authors that this could be the result of confounding with unmeasured pollutants including ozone and pollens). In winter, 25% and 20.5% increases in respiratory admissions, lagged 2 d, were associated with increases of 10 μg/m^3 BS and SO_2 respectively. Increases of 21% and 17% in asthma admissions, also lagged 2 d, were associated with BS and SO_2 respectively (per 10 μg/m^3). Acidity did not appear to play a role in exacerbation of disease leading to patient visits. Co-pollutant regression revealed that BS, but not SO_2, was the independent determinant of increased respiratory and asthma admissions (complete data not presented) (Walters et al., 1994). The authors did not comment on the lack of correlation between autumn admissions and the highest yearly pollutant levels at that time.

12.3.4 Summary of Acute Hospitalization and Emergency Department Studies

These studies cover a wide range of circumstances surrounding exposure to particulate matter. Summaries of the findings for PM_{10} and BS are presented in Tables 12.3 and 12.4. Results for $PM_{2.5}$ are shown in Table 12.5, while results for sulphate are shown in Table 12.8.

Of the 16 studies that examined PM_{10} and respiratory endpoints (Table 12.3), all showed associations of PM_{10} in univariate analyses with one or more respiratory endpoints, at means between 25 and 55 μg/m^3. The total respiratory hospitalizations category was considered in eight studies. The relative risk, as a percentage increase per 10 μg/m^3, varied from 0.45% (Paris, France) to 4.7% (Toronto, Thurston et al., 1994) with a median of 1.7 μg/m^3 , and was higher for emergency department visits, at 7.3% in Montréal.

Black Smoke (BS), a particle metric that is intermediate in size between PM_{10} and $PM_{2.5}$, has been used

extensively in Europe. In six of eight studies (Table 12.4), the relative risk for respiratory hospitalizations varied widely from 0.4% (95% CI 0.07 to 0.75%) to 12.3% (95% CI 5.8-18.2%) per 10 μg/m^3 increase in BS. The range of means in positive studies was from 12.7 to 75 μg/m^3. The different airborne concentrations recorded in the various cities, as well as the relative importance of other co-occurring air pollutants, could have accounted for some of these differences. In Amsterdam, NL, no air pollutants were found to be associated with hospitalizations, possibly a reflection of low numbers of hospitalizations and consequent low power of the study to detect such effects, while in London, UK, only ozone (not BS, NO_2, or SO_2) was consistently associated with increased respiratory hospitalizations. In both cities, ambient BS concentrations were quite low, less than 15 μg/m^3 versus higher than 26 μg/m^3 for all of the other locations except Birmingham, in which only BS and SO_2 were measured and BS was associated in bivariate regressions with increased hospitalizations.

Overall, there is some evidence for an association of BS with increases in respiratory disease, despite the variations observed in the strength of the association and in its statistical significance, and the lack of data on its significance when included with the range of gaseous pollutants known to occur with it. BS is an optical measurement of dark-coloured particles, predominantly from power generation, heating fuel and diesel combustion. It does not measure uncoloured particles such as sulphates or nitrates secondarily formed in the atmosphere after primary combustion. It may not, therefore, be a particularly good indicator of the type of particulate matter air pollution which has been prevalent since the 1980s in urban areas, and which is due predominantly to vehicular fuel combustion (Anderson et al., 1996; Walters et al., 1994).

Only three hospitalization studies, two in Toronto and one in Montréal, directly examined the association between fine particles as $PM_{2.5}$ and respiratory or cardiac effects. Positive associations between $PM_{2.5}$ and respiratory effects (2.5 to 9.6% per 10 μg/m^3) were seen in univariate analyses in all three studies (Table 12.5). The association was slightly reduced from 2.5 to 1.8% in Toronto (Burnett et al., 1997) when ozone was included in the analysis, but was no longer significant in the earlier Toronto study (Thurston et al., 1994) or in Montreal (Delfino et al., 1996) after inclusion of ozone. The high correlation between ozone and $PM_{2.5}$ in these two studies (r=0.7 – Thurston et al. (1994) and r=0.46 to 0.63 – Delfino et al. (1996)) makes it difficult to separate out the individual effects of $PM_{2.5}$ from ozone. However, in the larger Toronto study by Burnett et al. (1997) in which the correlation coefficent was lower (r<0.34), the $PM_{2.5}$ association remained after including ozone. The Burnett et al. (1996) study also examined cardiac effects, and found that the relative risk was not significantly elevated in association with $PM_{2.5}$, regressed either singly or with ozone. Additional information on the magnitude of the risk of respiratory hospitalizations associated with $PM_{2.5}$ is given by the large study on sulphate and ozone in southern Ontario (Burnett et al., 1995) (Table 12.5). An overall site-specific conversion factor for sulphate to $PM_{2.5}$ was determined (see Appendix; $PM_{2.5}$ =6.973897 + 1.917519 SO_4^{2-}), and indicated that the relative risk for respiratory causes (adjusted for ozone, temperature, etc.) of 3.5% (95% CI 2.3-4.7%) for a 13 μg/m^3 increase in sulphate was equivalent to a 31.9 μg/m^3 increase in $PM_{2.5}$, or 1.1% (95% CI 0.7 to 1.5%) for a 10 μg/m^3 increase in $PM_{2.5}$, which was slightly lower than the above previous estimates, but within their confidence intervals.

All eight studies (Table 12.8) which examined SO_4^{2-} found positive associations with respiratory endpoints (2 to 9%, and up to 18.2% in an emergency department study), at mean concentrations between 3.3 (Montréal) and 11.9 μg/m^3 (Toronto, summer 1988). The association became marginal or disappeared in the two Toronto studies and in the Montréal ED visit study when ozone was included in the regression with SO_4^{2-}. However, the association remained significant but somewhat reduced in strength in the ozone-adjusted regressions in the two southern Ontario studies, which were by far the largest and most reliable of those available. The correlations between ozone and SO_4^{2-} were high in all studies, 0.5 to 0.8, which causes difficulties in separating out the effects of one from the other. Overall, SO_4^{2-} has good evidence for an association with respiratory hospitalizations and is considered to be a good surrogate for fine particles from combustion sources. Cardiac effects were significantly associated with SO_4^{2-} in the southern Ontario study, with an ozone-adjusted increase of 2.5% (95% CI 1.3-3.7%) in cardiac-related hospitalizations for a 10 μg/m^3 increase in SO_4^{2-} (data analyzed over the whole year) (Burnett et al., 1995). In a second, smaller study on data for three summers in Toronto, a 4.4% increase per 10 μg/m^3 increase in sulphate was observed in the univariate analysis, but was no longer seen in the bivariate analysis with ozone (Burnett et al., 1997).

Table 12.3 Summary of Findings on Hospital Admissions and Emergency Department Visits Associated with PM_{10}

Location Reference	PM_{10} mean, (range) µg/m³	Endpoint	% increase per 10 µg/m³	Other pollutants considered
Utah Valley +Cache, Salt Lake Valleys Pope et al., 1991	53, 55, <40 (3 locations) (max 365)	respiratory, all ages (total 4144 admissions) pneumonia bronchitis asthma	Rates doubled in Utah Valley compared to Salt Lake or Cache Valley when steel mill open or when PM_{10}>50 1.7% (RR=1.17) 4.0% (RR=1.40) 0% (RR=1.14, not significant)	No other pollutants considered (SO_2 was low, near detection limit)
Seattle, WA Schwartz et al., 1993	29.6 (6 -103)	(ED visits, all ages) -asthma (7.1/d)	3.7% (1.2 to 6.4%) (<65 y) (n. signif., >65 y)	SO_2, O_3 not significant (RR = 0.99 for SO_2) RR= 0.97 for O_3) β_{ext} also assoc, RR=1.11 (1.04-1.18) Main source of PM was wood smoke
Birmingham, AB Schwartz 1994a	45 (19, 77) (10th, 90th percentile)	(>65 y) -pneumonia (5.9/d) -COPD (2.2/d)	1.9% (0.7 to 3.2%) 2.7% (0.8 to 5.0%)	O_3 (24 h) pneum RR=1.14 (0.94-1.38) O_3 (1 h) COPD RR=1.07 (0.96-1.20) No bivariate regression. (PM_{10}-O_3 correlation =0.29)
Detroit, MI Schwartz 1994b	48 (22, 90) (10th, 90th percentile)	(>65 y) -pneumonia(15.7/d) -COPD (5.8/d)	1.2% (0.4 to 1.9%) (+O_3) 2.0% (0.9 to 3.2%) (+O_3)	O_3 (24 h) positive; Pneumonia RR=1.052, COPD RR=1.054 (per 10 ppb) Bivariate regression did not alter coefficients for PM_{10} or O_3, i.e. both independently associated. (PM_{10}-O_3 correlation =0.35)
Detroit, MI Schwartz & Morris 1994	48 (22, 90) (10th, 90th percentile)	cardiovascular, >65 y -ischemic heart disease (44/d) -congestive heart failure (27/d)	0.56% (0.2 to 1.0%) CHF not significant.	PM_{10} RR 0.75% (0.13-1.4%) + CO. O_3 not sign. CO RR=1.22 (1.01-1.03) but n.s. in bivariate regr. SO_2 RR=1.014 (1.003-1.026 for IQ range) but n.s. + PM_{10} (i.e. CO, SO_2 not independent of PM_{10}.)
Minneapolis, MN Schwartz 1994c	36 (18, 58) (10th, 90th percentile)	(>65 y) -pneumonia (6/d) -COPD (2/d)	1.7% (0.3 to 3.3%) 5.7% (2.0 to 10.6%)	PM_{10} RR same or higher + O_3 O_3 indep. assoc. (RR=1.15) with pneum. in co-regression with PM_{10} (i.e. both independently assoc.)
New Haven, CT Schwartz 1995	41 (67, 90th percentile)	(>65 y) respiratory (8.1/d)	1.2% (0.0 to 2.6%; p<0.05)	PM_{10} + O_3: PM 1.8%, O_3 1.4% (10 ppb). PM+ SO_2: PM_{10} same, SO_2 0.8% PM_{10} and O_3 indep. assoc., SO_2 probably not (SO_2 n.s. with O_3)

Table 12.3 Summary of Findings on Hospital Admissions and Emergency Department Visits Associated with PM_{10} *(continued)*

Location Reference	PM_{10} mean, (range) $\mu g/m^3$	Endpoint	% increase per 10 $\mu g/m^3$	Other pollutants considered
Tacoma, WA Schwartz 1995	37 (67, 90th percentile)	(>65 y) respiratory (4.2/d)	2.0% (0.6 to 3.4%)	PM_{10} + O_3: PM n.s. (p>0.1), O_3 RR same PM_{10} + SO_2: PM_{10} RR same, SO_2 n.s. (RR=0.99). Ozone dominates over PM_{10} and SO_2
Spokane, WA Schwartz 1996	46 (83, 90th percentile)	all respiratory (>65 y) (3.9/d) -Pneumonia (1.9/d) -COPD (1.0/d)	1.7% (0.7 to 2.7%) 1.1% (-0.03 to 2.5%) 3.4% (1.6 to 5.4%)	SO_2 negligible in Spokane. 1-h O_3 also assoc., 9.5% for 10 ppb. Not co-regr. because only 115 days measured together.
Anchorage, AK Gordian et al., 1996	45.5 (5-565)	(Doctors= visits) -asthma, -upper respir. tract infections	3.5% (p<0.01) 1.2% (p<0.05)	CO assoc.with URI, bronchitis. Benzene high. Limited data for other pollutants. O_3 max=40 ppb (2y). SO_2, NO_2 low.
E. Washington State Heflin et al., 1994	40 (3-1700)	-bronchitis -asthma	0.35% (p=0.03) not significant	No other pollutants considered Dust storms resulted in increased otitis, UR infections.
Toronto, Ont. Thurston et al., 1994	30,30,39 (3 yrs.)	-respiratory -asthma	4.7% (p=0.015) 0.44% (not significant)	O_3 also associated in bivariate regression with all PM metrics. H^+ remained significant, SO_4^{2-} marginally so.
Toronto, Ont. Burnett et al., 1997	25 (10-58)	-respiratory -cardiac	2.5% (t=3.42) 2.3% (t=2.24)	PM_{10} coefficient retained value when regressed with all gases except NO_2 (but r high). Strength of association: CoH >$PM_{2.5}$ >SO_4^{2-} > PM_{10}>H^+>CP. O_3 was indep. associated in bivariate regressions with all PM
Buffalo, NY Gwynn et al., 1996	not given	-respiratory	~18% (12 - 24% for range)	H^+>SO_4^{2-} ≈ PM_{10}>CoH
Montréal, Qué. Delfino et al., 1994	31.5 (July-Aug)	-asthma -respir. non-asthma	2.1% (0.6 to 4.0%) 1.0% (t=1.83; n.s.)	PM_{10} RR for asthma reduced to 1.8% (marg. sign) in bivariate regression with O_3 and O_3 also reduced (n.s.), but r=0.63 SO_4^{2-} included
Montréal, Qué. Delfino et al., 1996	30.1, 21.7 (2 y)	(Emerg. Dept.visits) -respiratory	7.3% (1.95 to 12.7%)	PM_{10} reduced to 4.5% (n.s.) with O_3. O_3 significant with all PM (H^+,SO_4^{2-}, $PM_{2.5}$, PM_{10}). Limited evidence for independent associations of O_3 and 3 of 4 PM, but PM-O_3 and O_3 - temperature correlations high.
Paris, France Dab et al., 1996	50.8 (max 138) (PM_{13})	-all respiratory -COPD -asthma	0.45% (0.04 to 0.87%) -0.5% not significant -0.025% not significant	SO_2 significant, all 3 endpoints NO_2 significant for asthma BS ~ PM_{13}

Table 12.4 Summary of Findings on Hospital Admissions and Emergency Department Visits Associated with Black Smoke (BS)

Location	Reference	BS mean, (range) µg/m^3	Endpoint	% increase per 10 µg/m^3	other pollutants considered
London, England	Ponce de Leon et al., 1996	14.6 (6-27)	-respiratory disease	-2 to +2% (n.s.)	O_3 RR unchanged (independent) in bivariate regr. with BS. Correlation = 0.3 to 0.45). NO_2, SO_2 n.s.
Birmingham, Eng.	Walters et al., 1994	12.7 (IQR 5-15; max 188) 12.3 (winter)	-respiratory dis. -asthma	12.3% (5.8-18.2%) – winter 2.8% (0.3-5.3%) – winter	BS+SO_2: BS sign., resp.+ asthma, SO_2 neg. Alone, SO_2 sign, resp; marg asthma
Amsterdam, NL	Schouten et al., 1996	11 (1-37)	-respiratory dis. -COPD -asthma	1.3% (-3.1 to 8.7%- 65+) 4.7% (-1.9 to 16.5%) -2.0% (-5.6 to 4.8%)	No correlations or co-regressions. O_3 , SO_2 and NO_2 also not signif.
Rotterdam, NL	Schouten et al., 1996	26 (6-61)	-respiratory dis. -COPD -asthma	3.7% (0.9 to 7.3%) 2.4% (-1.2 to 7.6%) n.s. (Not given)	No correlations or co-regressions. O_3 marg, resp (adults), NO_2 sign., COPD (all ages). SO_2 not signif.
Paris, France	Dab et al., 1996	31.9 (max 268) 40 – winter; 25 – summer	-respiratory -COPD -asthma	0.41% (0.07 to 0.75%) -0.05% (n.s.) 0.43% (n.s.)	No correlations or co-regres. PM_{13} similar to BS. O_3 n.s.; SO_2 +ve all endpts. NO_2 +ve, asthma.
Athens, Greece	Pantazopoulou et al., 1995	75 – winter 55 – summer	(Emerg Dept visits) -respiratory dis. -cardiac	1.2% (winter) 0.96% (winter)	High collinearity (values not given). No co-regressions. CO, NO_2 also significant in winter.
Barcelona, Spain	Sunyer et al., 1993	68 (IQR 45-84) winter 48 (IQR 31-63) summer	(Emerg Dept visits) -COPD	2.28% (t=5.0) (winter) 0.94% (t=2.7) + SO_2	In bivariate regr., both BS and SO_2 coeff. reduced, but BS remained signif. in winter. In summer, SO_2 sign., BS not. BS – SO_2 r = 0.7 (high)
Barcelona Spain	Castellsague et al., 1995	68 (IQR 45-84) winter 48 (IQR 31-63) summer	(Emerg Dept visits) -asthma	0.9% (-0.8 to 2.6%) winter 3.3% (lag 0 d) summer 4.6% (lag 0-3 d) summer	No co-regression. BS r=0.32 to 0.73 for O_3, NO_2, SO_2. NO_2 sign., but O_3, SO_2 not signif.

Table 12.5 Summary of Findings on Hospital Admissions and Emergency Department Visits Associated with $PM_{2.5}$

Location Reference	$PM_{2.5}$ mean (range), µg/m^3	Endpoint	% increase per 10 µg/m^3 (95% confidence limits)	Effect of other pollutants considered
Toronto, Ont. Thurston et al., 1994	18.6 (3 y, summer) (17.7, 15.8, 22.3)	respiratory asthma	9.3% (1.3-17.3%; p=0.01) 3.7% (-1.6-9.3%; p=0.08)	$PM_{2.5}$ associated in single regression, but not in bivariate regression with O_3. SO_4^{2-}-O_3 correlation coefficient high, r=0.7. Other PM also n.s. + O_3
Toronto, Ont. Burnett et al., 1996	16.8 (IQR 8-23) (3 y, summer)	respiratory cardiac	2.5% (t=3.3, significant) 2.1% (t=1.8, not significant)	$PM_{2.5}$ +O_3: 1.8% (t=2.3, significant, 28% lower) $PM_{2.5}$ +O_3: 0.9% (t=0.8, not signif., 55% lower)
Montréal, Québec Delfino et al., 1996	18.5 (90th percentile 44) 12.2 (90th percentile 22) (Summers, 1992,93)	respiratory (emergency dept., age >64 years)	9.6% (1.9 to 17.3%) (1993) (1992 results not associated)	$PM_{2.5}$ +O_3: 4.5% (not significant, but $PM_{2.5}$-O_3 correlation coefficient very high, r=0.62) PM and O_3 likely independently associated.
Southern Ont. Burnett et al., 1995	SO_4: 4.37 (95th percentile 13) [$PM_{2.5}$: 15.3 (95th percentile 31.9) – based on site-specific conversion factor from SO_4^{2-} to $PM_{2.5}$]	respiratory asthma COPD infections cardiac coronary disease dysrhythmias heart failure	[1.1% (0.7-1.4%)] [1.0% (0.4-1.8%)] [1.5% (0.7-2.2%)] [1.0% (0.5-1.5%)] [1.0% (0.5-1.5%)] [0.7% (0.2-1.5%)] [0.4% (-0.6-1.4%)] [0.9% (0.2-1.7%)] [all results based on site-specific SO_4^{2-} – $PM_{2.5}$ conversion]	Figures included adjustment for ozone. Results of single pollutant regression virtually the same as results for bivariate regression with ozone. PM and ozone independently associated.

No evidence for a threshold of effects for respiratory hospitalizations associated with particulate matter or other air pollutants was found in nonparametric concentration-response curves (in which a linear or other defined response is not assumed), or in quartile or decile plots by concentration, at the low (10 to 100 µg/m^3 PM_{10}) concentration ranges examined. Curves appeared to increase monotonically, with steep slopes at low concentrations and some suggestion of curvilinear responses (lower slope) at higher concentrations. Nonparametric concentration-response curves were shown for PM_{10} and hospitalizations due to pneumonia and COPD in the elderly in Birmingham, AB (Schwartz 1994), and for respiratory disease hospitalization in Toronto, ON associated with PM_{10}, coarse particles between 2.5 and 10 µm, $PM_{2.5}$, SO_4^{2-}, CoH and H^+ (Burnett et al., 1997).The curves were stated to be not significantly different from linear in the Toronto study, although a pronounced plateau between 19 and 35 µg/m^3 was observed for fine particles ($PM_{2.5}$), and the response appeared to be somewhat curvilinear for coarse particles and SO_4^{2-}. A decile plot for SO_4^{2-} and respiratory hospitalizations in southern Ontario showed a curvilinear response, with a steep slope from 0-6 µg/m^3, and a less steep slope between 6 and 20 µg/m^3 (Burnett et al., 1994).

Quartile analyses were undertaken in Seattle, WA for PM_{10} and asthma (Schwartz et al., 1993), Detroit, MI for PM_{10} and respiratory or cardiac hospitalizations (Schwartz 1994b; Schwartz and Morris 1995), southern Ontario for SO_4^{2-} and respiratory or cardiac hospitalizations (Burnett et al. 1995), and Barcelona, Spain for BS and COPD or asthma (Sunyer et al., 1993; Castellsague et al., 1995). In general, the respiratory responses were shown to increase monotonically with increasing concentration, despite the loss of data due to aggregation of responses into only four concentration points for each endpoint and location. The concentration-response for cardiovascular disease in the elderly in Detroit was clearly curvilinear (Schwartz and Morris 1995). The curve for COPD admissions in Detroit was the only one showing an anomalous response, since hospitalizations for quartile two (at 30 µg/m^3) were higher than for quartile three (at 50 µg/m^3). The quartile analyses were also used to determine a “Lowest-Observed-Adverse-Effect Level (LOAEL)” for respiratory hospitalizations around 20 to 30 µg/m^3 with a “best estimate” of 25 µg/m^3 for PM_{10}.

The specificity of the air pollution effect on the causes of disease was investigated by considering potential associations with cardiovascular disease as well as respiratory disease. A stronger association with air pollution was observed for respiratory diseases than for cardiovascular diseases, in most of the regressions from the four studies which examined cardiovascular diseases in addition to respiratory disease. In southern Ontario, the relative risk (RR) for cardiovascular diseases was 2.5% (95% CI 1.3 to 3.9%) for a 10 µg/m^3 increase in SO_4^{2-}, compared to 2.7% (95% CI 1.9 to 3.6%) for respiratory disease (Burnett et al., 1995). This stronger association with respiratory disease hospitalizations was also evident for SO_4^{2-} and fine particles ($PM_{2.5}$) in a much smaller study carried out in Toronto, where the risks for cardiovascular diseases hospitalizations were lower by up to one-half the RR for respiratory disease and were not significant (Burnett et al., 1997). However, the RR estimated for cardiovascular diseases using other particle metrics, PM_{10}, CP (particles between 2.5 and 10 µm), H^+ and coefficient of haze (CoH), either remained the same or were higher than those for respiratory disease. Similarly, in Detroit, MI, Schwartz (1994) and Schwartz and Morris (1995) found higher relative risks (per 10 µg/m^3 increase in PM_{10}) for respiratory disease admissions (2.0% for COPD and 1.2% for pneumonia) than for ischemic heart disease (0.56%) or heart failure (0.75%). In Athens, Greece, a 10 µg/m^3 increase in BS was associated with an 11.7% increase in respiratory hospitalizations and a smaller increase of 9.6% for cardiac hospitalizations. The RR for CO and NO_2, which were also associated with increased hospitalizations in this city, were one-half to two thirds as high for cardiac as for respiratory disease admissions (Pantazopoulou et al., 1995).

Some of the larger studies were able to examine the respiratory subcategories chronic obstructive pulmonary disease (COPD), asthma, and/or pneumonia or infectious diseases. Individuals with pre-existing COPD have been suggested as particularly susceptible to the effects of air pollution. The Burnett et al. (1995) study on the entire age range in the population of southern Ontario indicated that the increased hospitalization risk for COPD was somewhat higher than that for total respiratory admissions, approximately 3.7% per 10 µg/m^3 increase, using SO_4^{2-} as the particle metric. The European studies with BS as the particle metric did not find an association with increased hospitalizations for COPD, except for the Sunyer et al. (1993) study in Barcelona in which both BS and SO_2 were implicated. The association between PM_{10} and COPD was strong, 2.4 to 5.7% per 10 µg/m^3 increase, in a series of studies on the

elderly in four US cities (Schwartz 1994a-c, 1996). However, in these latter studies the authors did not examine and compare total respiratory admissions or any other age category.

A number of investigators examined the association between asthma and particulate matter, with mixed results. The hospitalization data provide only limited evidence for an association between particulate matter and asthma. The best evidence is provided by the southern Ontario Study, which had the most extensive database (42 asthma admissions/day over six years) (Burnett et al., 1994, 1995). While asthma showed an association with increased daily airborne sulphate concentrations, the association in the year-round analysis was about the same or slighly lower in magnitude than that for general respiratory admissions, 3.2% versus 3.5% for a 10 $\mu g/m^3$ increase in sulphate (Burnett et al., 1995). In the May-August period, the asthma rate was slightly higher, 7.1% versus 5.8% for the total respiratory admission rate (based on increases in a combination of 50 ppb ozone and 5.13 $\mu g/m^3$ SO_4) (Burnett et al., 1994). The asthma rate was highest (13%) for infants $\leq$1 year, and was also high (8.2%) for children <14 years old, and for middle-aged adults (9.8%) between 35 and 64 years. Asthma admission, doctors' visits or emergency department visits were also associated with PM_{10} increases in Montréal, Qué. (2.1%), Anchorage, AK (3.5%) and Seattle, WA (4.0%) (all per 10 $\mu g/m^3$ increase) (Delfino et al., 1994; Gordian et al., 1996; Schwartz et al., 1993). The positive association in Seattle was seen only for those less than 65 years old, and not in the elderly. In Montréal, sulphate (the only fine particle measured) showed no association (Delfino et al., 1994), while in Seattle, the PM_{10} was largely attributable to wood smoke particles in the fine fraction (Schwartz et al., 1993), and therefore the absent association between hospitalizations, doctors' visits and emergency department visits, and PM_{10} could be at least partially a fine particle effect. In univariate analysis, the association was marginal between asthma and SO_4^{2-} in Buffalo, NY (Thurston et al., 1992). In a bivariate analysis with ozone, $PM_{2.5}$ was associated marginally (3.7%; p=0.08) with asthma in Toronto, ON, while the associations with PM_{10} and SO_4^{2-} were negative (Thurston et al., 1994). PM_{10} was not associated with asthma in eastern Washington State (Hefflin et al., 1994) or in Detroit (the elderly, who appear to be less affected by asthma than the general population, were the only group included) (Schwartz 1994b). In univariate analyses, BS was not associated with asthma in Paris, France, Amsterdam and Rotterdam NL (Dab et al., 1996; Schouten et al., 1996), but a positive association was seen in Birmingham, UK, which disappeared when BS was regressed together with SO_2^{2-}, also associcated with asthma in Birmingham (Walters et al., 1994). The small number of respondents in many of these studies (e.g., 0.75/d in Detroit) could have been part of the reason for some of the lack of positive associations with respect to asthma. The size of the particle or its chemistry did not appear to play a role in determining the outcome. The southern Ontario study, with the clearest positive results for asthma, also included exposure to ozone, which has also been linked to asthma. This suggests the possibility that particulate matter might work in concert with ozone or another co-occurring air pollutant in the exacerbation of underlying asthma. It also suggests a relatively small independent role for particulate matter air pollution in exacerbation of asthma.

Laboratory studies indicating that exposure to high concentrations of airborne particles may act to compromise the immune system, have suggested that epidemiology studies should investigate the exacerbation of respiratory infections as one of their endpoints. In the southern Ontario study conducted by Burnett et al., (1994) (one of the few studies large enough to be able to subdivide data on the basis of endpoint and age without losing the power of the study to detect effects), increases in overall infection-related hospitalization rates were associated with daily increases in SO_4^{2-} and ozone combined, but the overall rate increase (4.3%) was lower than the total respiratory rate increase (5.8%), and was driven almost entirely by the infant infection-related rate (19.1%). The 1995 analysis of these data (Burnett et al., 1995) more clearly separated out the effects of SO_4^{2-} on infection rates, while retaining adjustments of the presence of ozone. The infection rate attributable to a 10 $\mu g/m^3$ increase in SO_4^{2-} was 2.5% (95% CI 1.3 to 3.7%), about the same as the asthma rate increase and slightly lower than the overall infection rate increase of 2.7% (no breakdown of age versus infection rates was presented) (Burnett et al., 1995). Two other, much smaller, studies in Utah and Anchorage, AK also recorded increases in hospitalizations due to pneumonia or upper respiratory tract infections of about 1.2% per 10 $\mu g/m^3$ increase in PM_{10}. Increases of 1.1 to 1.9% in hospitalizations for pneumonia were observed in a series of studies with the elderly ($\geq$ 65 years) in four US cities (Schwartz et al., 1994a-c, 1996). The epidemiology studies on hospitalizations thus support the conclusion that

particulate matter acts to exacerbate infections, but suggest that this effect is most marked in infants, and that it is not as important a source of increases in hospitalizations in the population at large as other pre-existing conditions.

There are some concerns as to the reliability of some of the results from hospital admissions data owing to potential confounding. The coding of the different sub-categories of respiratory disease and the differentiation between some categories of cardiac and respiratory admissions by use of International Classification of Disease (ICD) codes which may differ between hospitals or individual doctors, may cause some misclassifications. However, it should be noted that misdiagnosis does not fluctuate in concert with pollution levels and therefore will not affect the overall conclusions with respect to pollutant concentrations, but may affect the conclusions with respect to which categories of disease are most influenced by pollutants. The possibility that certain epidemics of contagious respiratory disease can occur coincidentally with particulate pollution episodes was also considered by some investigators.

The effects of age on hospitalizations or emergency department visits were examined in several locations, since historical data from episodes of high air pollution strongly suggested that it was the elderly, the young, and those with pre-existing respiratory and/or cardiovascular conditions who were responding to air pollution. While some studies (Delfino et al., 1996; Burnett et al., 1995; Schouten et al., 1996) found that the elderly were at increased risk compared to other age groups in the population, the increases observed in cardiorespiratory hospitalizations were by no means predominantly due to effects on the elderly. In the Burnett et al. (1994) study in southern Ontario, warm season sulphate and ozone air pollution was associated with smaller increases in respiratory hospitalizations in the elderly (4.3% for 50 ppb ozone and 5.1µg/m^3 SO_4^{2-} increases) than in those between age 2 and 64 years (5.5% for age 2-34 years and 7.2% for those aged 35-64 years). In a later expanded analysis of the same database, Burnett et al. (1995) reported similar increases (per 13 µg/m^3 increase in SO_4^{2-}, after taking ozone into consideration) in respiratory hospitalizations of 3.7% and 3.8% for younger adults (age 15-64 y) and the elderly (65+ y), which were higher than those seen in children (2.7% for children under 15 years), but the effects of age were evident in the data for cardiovascular hospitalizations, in which a 3.5% increase (95% CI 1.9-5.0%) was seen in the elderly compared to a 2.5% increase (95% CI 0.5-4.8%) for those less than 65 years of age. In Rotterdam, NL, the 15-64 year age group showed the strongest association between BS and all respiratory admissions, with a RR of 1.37 (95% CI 1.09-1.73) compared to a RR of 0.97 (not significantly different from 1.0) for those aged 65 or older (Schouten et al., 1996). However, for other air pollutants NO_2 and SO_2, the elderly appeared to be at greatest risk. In Amsterdam in the same study, the elderly appeared to be at greatest risk for respiratory disease associated with BS and all other included air pollutants (O_3, SO_2, and NO_2), although small numbers in subdivided groups meant that most risks were not significantly elevated (Schouten et al., 1996). In London, UK there were no consistent differences in relative risk of respiratory hospitalizations for those over age 65 compared to those between 15 and 64 y (Ponce de Leon et al., 1996). With asthma as the endpoint, the elderly were at less risk than those under age 65 years, in Seattle, WA (Schwartz et al., 1993), Anchorage AK (Gordian et al., 1996) and southern Ontario (Burnett et al., 1994). The series of studies by Schwartz (1994a-d, 1995) did demonstrate that the elderly were affected by air pollution and that elevated respiratory hospitalization rates were associated with increases in particulate air pollution, but only the elderly were studied in these cities due to limitation of the hospitalization database to this age group only.

Children were also shown to be a high-risk group for increased respiratory disease in a few studies. These included the Pope (1991) study on the Utah Valley comparing effects of respiratory hospitalizations when a steel mill (the predominant source of particulate air pollution in this area) was open as when it was closed. Bronchitis and asthma admissions were twice as high for preschool children (ages 1-5 years). By comparison, for all ages combined, the rates were only 1.4 times as high for bronchitis and 1.2 times as high for pneumonia (open mill verus closed mill). In Anchorage, AK, upper respiratory tract infections were most strongly associated with PM_{10} in children less than 10 years old and in older adults aged 45 years or more, compared to adolescents and younger adults (Gordian et al., 1996). While summertime ozone and sulphate combined appeared to have a greater effect on increasing respiratory hospitalizations in infants and children (14.8%) than on adults (4.3-7.2%) in southern Ontario (Burnett et al., 1994), all-year sulphate was associated with lower respiratory hospitalizations in children (2.7%; 95%

CI 0.8-4.7%) than in adults (3.7-3.8% for 13 μg/m^3 increases in SO_4^{2-}) after accounting for the effects of ozone (Burnett et al., 1995). The London, UK respiratory hospitalization study (Ponce de Leon et al., 1996) did not find that children were at increased risk for respiratory admissions due to BS or other air pollutants, at least not at the concentrations experienced in the 1980s and early 1990s.

Most of the studies handled potential confounding by temperature and season well, using a variety of methods, but there has been concern that the effects observed are due to the rise and fall of other unmeasured pollutants in concert with PM. In the Utah studies, most of the potential confounders were accounted for or ruled out. The studies by Schwartz et al., (1993) showed strong associations after taking factors such as weather conditions, seasonal variations and outbreak of infectious diseases into account, but not always after accounting for pollutant covariates.

Most of the hospitalization studies on particulate matter looked at at least one or two other air pollutants as potential covariates; although two (Pope et al., 1991; Hefflin et al., 1994) considered only PM_{10}.

The relationship of SO_2 to hospitalizations was examined in Detroit, MI, New Haven, CT, Tacoma, WA, Toronto, ON (two studies), and in all seven European cities (it was determined to be virtually absent in one location, Spokane, WA). In univariate regressions, SO_2 was associated with all respiratory admissions In Birmingham, UK (Walter et al., 1994), Paris, France (Dab et al., 1996), New Haven, CT and Tacoma, WA (Schwartz 1995),and in Toronto, ON (Burnett et al., 1997), with COPD in Paris (Dab et al., 1996) and Barcelona (Sunyer et al., 1993), and with asthma in Paris (Dab et al., 1996) and Birmingham, UK (Walters et al., 1996). SO_2 was also found to be asociated with cardiovascular disease in Detroit and Toronto, in univariate analysis (Schwartz and Morris 1995; Burnett et al., 1997). No associations were found with respiratory disease (also in univariate analyses) in London, UK, Amsterdam or Rotterdam, NL, Barcelona (for asthma only), Seattle, WA or Toronto, ON (Schwartz et al., 1993; Thurston et al., 1994; Castellsague et al., 1995; Ponce de Leon et al., 1996; Schouten et al., 1996).

However, in the six studies that undertook bivariate analyses with both PM and SO_2 in the regression model, SO_2 was not clearly shown to have an association that was independent of particulate matter air pollutants. In New Haven, CT, the regression coefficient for SO_2 was slightly increased when it was included with PM_{10}, but was reduced, and no longer significant, when included with ozone. This effect was even more marked in Tacoma, WA, with the RR for SO_2 declining from 1.06 in univariate regression to 0.99 with PM_{10} and 0.93 wih ozone (no correlation coefficients between these pollutants were given) (Schwartz 1995). While the bivariate analysis in Barcelona indicated that both SO_2 and BS were associated with COPD independently of each other based on similar drops in regression coefficients (with retention of statistical significance for both), the stratification by tertiles of each pollutant tested against the other indicated that BS, but not SO_2, was independently associated with COPD (Sunyer et al., 1993). In the Birmingham, UK case, BS, but not SO_2, was associated with all respiratory hospitalizations and with asthma visits in winter, in stepwise linear regressions with both pollutants incuded in the same model (Walters et al., 1994). In Toronto, Burnett et al. (1997) regressed SO_2 with each of six particle metrics in turn. For respiratory admissions, the RR for all particle metrics was significantly elevated, while the RR for SO_2 (adjusted for temperature and dew point) was reduced by about one-third, from 1.033 to 1.022, still significant or marginally so for all particle metrics except CoH and PM_{10}. For cardiac admissions, SO_2 remained significant with H^+, SO_4, and $PM_{2.5}$ (none except H^+ was significant in univariate analysis). In Detroit, MI, the relative risk for ischemic heart disease was reduced from 1.014 to 1.009 (95% CI 0.99 to 1.023) in bivariate regression with PM_{10}, while the PM_{10} RR was reduced only by about one-sixth. This indicated that SO_2 was not independently associated with cardiac hospitalizations but that PM_{10} was the best air pollution metric of those that were examined, including PM_{10}, ozone, CO, and SO_2 (Schwartz and Morris 1995).

NO_2 was examined for possible associations with respiratory disease in eight cities: London, UK, Amsterdam and Rotterdam, NL, Paris, France, Barcelona, Spain, and Athens, Greece, as well as Toronto, ON and Buffalo, NY. Correlations between NO_2 and PM were generally high, and for this reason few investigators were able to perform bivariate regressions including NO_2 with other air pollutants. NO_2 was associated with total respiratory admissions in Athens (1.4% for a 10 μg/m^3 increase), Paris (0.4%), Toronto, ON (0.44%) and Buffalo NY (approximately 0.5%) (Pantazopoulou et al., 1995; Dab et al., 1996; Burnett et al., 1997; Gwynn et al., 1996). NO_2 was also associated with COPD in Rotterdam

(2.0%; 95% CI 0.8 to 4.3% for 1 h maximum, with a cumulative lag period of 0 to 3 d), but in this city, BS was not associated with COPD. NO_2 was also associated with asthma in Paris (RR=1.175; 95% CI 1.06-1.30 for a 100 µg/m^3 increase), and in this case also, BS was not a significant predictor of asthma (Dab et al., 1996). In Barcelona, 1 h NO_2 was associated with asthma in summer with a RR of 1.8% (95% CI 0.36 to 3.24% for 10 µg/m^3 increase) and in winter (RR=2.2%; 95% CI 0.4 to 4.2%), while BS was also associated in summer (RR=3.3% (0.4 to 6.3%) but not in winter (RR=0.93%) (Castellsague et al., 1995). In London, UK, the authors of the study (Ponce de Leon et al., 1996) considered that NO_2 was not associated with respiratory admissions because the association did not appear to be robust (inconsistencies were evident in regressions categorized by age and by season), but it may have been dismissed without sufficient reason. It was associated with admissions in both the warm season and all-year regressions for all ages, and in the warm season for children, and all-year for the elderly. However its regression coefficient went down by one-third in bivariate regressions with ozone, which was the air pollutant best expressing effects on respiratory health in this city, while BS was not associated with respiratory hospitalizations (the ozone-NO_2 correlation was moderately low at 0.29 in summer, and -0.43 in winter, allowing the testing of effects with both pollutants included). In North America, Gwinn et al. (1996) found NO_2 to be associated with respiratory hospitalizations in Buffalo, NY (RR= approximately 0.5% for an IQR increase which was not given), and the association was retained when regressed together with particle acidity (H^+). Burnett et al.(1997) also found associations between NO_2 and respiratory hospitalization both singly (RR=4.4% for a 6 ppb or IQR increase), and in bivariate analyses with all six PM metrics tested (RR= 1.033-1.037 or 3.3 to 3.7%). However correlations between NO_2 and the particle metrics were high (0.45-0.61 for $PM_{2.5}$, PM_{10}, the coarse fraction between 2.5 and 10 µm, and CoH) or moderate for SO_4^{2-} (0.34) and moderately low for H^+ (0.25), which calls for the questioning of the results for the high group.

Cardiac admissions were associated with increased NO_2 in Athens (2.0% in a univariate regression; Pantazopoulou et al., 1995)) and in Toronto in a univariate analysis(0.5% for an IQR increase of 6 ppb). This association remained significant in bivariate regressions with H^+ (RR=0.38%; H^+ remained significant), SO_4^{2-}, PM_{10}, $PM_{2.5}$, and the coarse fraction between 2.5 and 10 µm, (0.39%, 0.36%, 0.38%, 0.23% respectively, with non-significant RR for all 4 particle metrics) but not with CoH (RR=-0.1%; CoH RR=0.7%). Overall, it was not possible to distinguish the effect of NO_2 from particles or other air pollutants due to high correlation coefficients between them, but there was suggestive evidence that the role of NO_2 in respiratory and/or cardiac illnesses requires further investigation.

The possibility that an association exists between CO and hospitalizations was examined in only one study for respiratory admissions in Athens Greece (Pantazopoulou et al. 1995) and in the same study, as well as in a study in Detroit MI (Schwartz and Morris 1995) for cardiovascular (CV) disease. In Athens, CO was more strongly associated with respiratory than with cardiac admissions in univariate regressions (26.5% versus 15.3% for a 6.6 µg/m^3 increase in CO). No bivariate regressions or other estimates of the potential independence of the association were undertaken, and the authors noted that the CO-PM correlation coefficient was very high. In Detroit, CO was found to have a strong association with increased risk for congestive heart failure (RR=1.02; 95% CI 1.01-1.03) which was unchanged in bivariate regressions with PM_{10} (Schwartz and Morris 1995). PM_{10} was also shown to be independently associated, although its relative risk fell by about 25% in the bivariate analysis (RR=1.024; 95% CI 1.004-1.044 in bivariate analysis, versus RR=1.032 in single analysis). The relatively low correlation between CO and PM_{10} in this location supports the independent role of both pollutants in exacerbation of cardiovascular diseases.

Ozone in addition to particulate matter was examined in most locations for possible associations with respiratory hospitalizations. In single regressions, after adjustment for weather, season, year and day of the week effects, an association was found between ozone and respiratory hospitalizations in 12 locations (but marginally in three of these). The relative risk for a 10 ppb increase in ozone varied from 1.012 (southern Ontario) to 1.098 (Spokane, WA) with a median of 1.026 (Burnett et al., 1994; Schwartz 1996). In three locations (Seattle, Birmingham, AB, Paris, France), no association was found between ozone and respiratory admissions when ozone was regressed singly. There was also no association between increased ozone and cardiovascular disease in Detroit MI (Schwartz and Morris 1995). In bivariate regressions with particulate matter in nine locations (5- PM_{10}, 3- SO_4^{2-}, 2- $PM_{2.5}$ with overlap),

ozone retained its association with respiratory hospitalizations in all nine locations, and its regression coefficient and relative risk was relatively unchanged or even greater than in the single regressions. Particulate matter was also associated in addition to ozone in all cases except Montréal, in which $PM_{2.5}$ was no longer significant in the bivariate regression with ozone, and in London, UK, in which BS was not significantly associated in either single or bivariate regressions. This association with respiratory hospitalizations was strongest for PM_{10} in three locations (Detroit, MI, Minneapolis, MN, New Haven, CT) and for ozone in the other six locations. In the bivariate regressions with ozone, SO_4^{2-} remained associated in Toronto (Thurston et al., 1994; Burnett et al., 1997) and southern Ontario (Burnett et al., 1994), as did $PM_{2.5}$ in Toronto, both with reduced regression coefficients. In a further study in Toronto, ozone was tested against six particulate matter metrics, all of which remained associated independently of ozone except SO_4^{2-}, for which the correlation coefficient with ozone was higher (0.53) than the other particulate matter metrics (0.20-0.34 for $PM_{2.5}$, PM_{10}, coarse particles between 2.5 and 10 µm, particle strong acidity, or CoH) (Burnett et al., 1997). Thus, the evidence is considered to point to the independent association of both particulate matter and ozone with respiratory hospitalizations.

Thus, of the five different air pollutants considered in single and multiple analyses in various locations, particulate matter was the air pollutant with the most consistent and stable association with increases in hospitalizations. Ozone was also shown to be associated independently of PM in some analyses, in six locations with a greater magnitude of association than PM itself. Indications that CO was also associated with cardiorespiratory hospitalizations were observed in two studies, and this finding deserves to be followed up. SO_2 was not clearly shown to have an association independent of particulate matter in locations where bivariate regressions could be undertaken. While NO_2 was found to be associated with respiratory hospitalizations in several univariate analyses, its independence from PM could not be properly evaluated because of the high correlation between NO_2 and PM in most or all locations.

12.4 ACUTE EFFECTS – RESPIRATORY HEALTH

A number of studies have examined the effects of short-term variations in particulate pollution on pulmonary function and/or respiratory health, including measures such as absences from school or work due to respiratory illnesses. Both cross-sectional and time-series methods of analyzing data were used in these studies. The geographical areas range greatly, as do the sources of the particulates. Most of the studies have been done on panels of children.

Some concern has been expressed that the evaluation of respiratory symptoms is too subjective, but these studies provide valuable information on adverse health effects less severe than those requiring hospitalization or resulting in premature mortality, and they potentially affect many more individuals in the population than the more severe effects. In addition, most studies used well standardized and validated methods for determining adverse respiratory effects. The significance of slight changes in pulmonary function has also been questioned, but these tests are objective; moreover they have been shown to be predictive of future respiratory health status.

12.4.1 Acute Effects – Lung Function and Respiratory Symptoms

Studies on PM_{10}

Pope et al. (1991) conducted a study evaluating respiratory health and PM_{10} in the Utah Valley in the winter of 1989-1990. The principal source of PM_{10} in the study area was an integrated steel mill built during World War II. Respiratory symptoms (trouble breathing, runny or stuffy nose, wet or dry cough, wheezing, fever, rash, burning, aching or red eyes, upset stomach) and peak expiratory flow (PEF) measurements were recorded daily over the winter of 1989-90 in 55 participants (34 school children aged 9-11 years with respiratory symptoms, based on questionnaire responses, and 21 asthma patients aged 8-72 years). During the study period, PM_{10} levels ranged from 11 to 195 µg/m^3, with a mean of 46 µg/m^3. Limited monitoring conducted for SO_2, NO_2 and O_3 showed that concentrations of all were considerably lower than the then-current standards; NO_2 averaged 0.03 ppm (annual standard 0.05 ppm), mean SO_2 was <0.01 ppm (24 h standard 0.14 ppm) and ozone was virtually absent in wintertime in Utah. Strong particle acidity never reached the detection limit of 8 nmol/m^3. An increase in PM_{10} of 150 µg/m^3 was associated with a 3 to 6% decline in peak expiratory flow rate (PEF) in both groups. The current-day level had the largest effect, but effects were noted for up to three days later. Results from the regression analysis indicated that a 10 µg/m^3 increase in PM_{10}

was associated with a decline of 0.66 L/min in PEF rate. The mean percentage reporting symptoms of respiratory disease also increased with increasing PM_{10} pollution in the school-based sample, but not in the asthma patient sample. In the schoolchildren, the estimated probabilities of reported symptoms of upper and lower respiratory disease were found to be 1.5 and 2.1 times higher when 24 h PM_{10} levels were at the highest level (195 µg/m^3) compared with when levels were at their lowest level (11 µg/m^3). The odds ratio for lower respiratory tract symptoms was 1.25 (95% CI 1.06-1.55) for a 50 µg/m^3 increase in $PM_{10,}$ and for upper respiratory tract symptoms, it was 1.18 (95% CI 1.03-1.33). Extra medication use increased by two to three times in both groups as PM_{10} levels rose from less than 50 µg/m^3 to 100 or more µg/m^3. This study provides some evidence that the impacts of PM_{10} on children with pre-existing respiratory symptoms, (a potentially susceptible subgroup) may be more severe than for a randomly-selected group of children, since comparison of an earlier study showed that 74% of the Utah children had negative responses to air pollution, compared to 59% in a similar study in Steubenville, Ohio (Dockery et al., 1982, in Pope et al., 1991). The lower associations between PM_{10} and both PEF and respiratory symptoms in the asthma patient-based sample may not imply that asthmatics are less susceptible to the effects of air pollution, but may indicate that the asthmatic subjects were managing their symptoms with medication.

Pope and Dockery (1992) expanded the above study in the winter of the following year (100 days from December 6, 1990 to March 15, 1991), examining the association between daily changes in respiratory health and PM_{10} pollution in 39 symptomatic and 40 asymptomatic fifth- and sixth-grade children selected from the same population as previously. As previously, other air pollutant concentrations were very low. Peak flow measurements were recorded by the participants three times a day, and the following respiratory symptoms were reported in a daily diary: trouble breathing, runny or stuffy nose, wet cough, dry cough, wheezing, fever, rash, burning, aching, red eyes or upset stomach. During the study period, 24 h PM_{10} levels averaged 76 µg/m^3 and ranged from a minimum of 7 µg/m^3 to a maximum of 251 µg/m^3. Several pollution episodes occurred during the study period, during which the 24 h US national standard of 150 µg/m^3 was exceeded up to 14 times. A negative association was found between peak flow measurements and PM_{10} pollution levels in both groups, a 10 µg/m^3 increase being associated with a PEF decrease of 0.36 L/min in the symptomatic children and 0.26 L/min in the asymptomatic children. The mean PEF of the symptomatic children was also 11 L/min (3.6%) lower than the asymptomatic children, which indicates that this group is not only more affected by PM_{10} increases, but also starts with a slightly compromised lung function. Five-day moving-average PM_{10} levels were more strongly associated with peak flow than were concurrent-day PM_{10} levels, suggesting that response and recovery may last several days and that the timing of response and recovery varies between children. The PM_{10} data were divided into quartiles, with means of 25, 55, 89, and 141 µg/m^3, and the changes in PEF showed a good dose-response for both groups that was not significantly different from linear. The mean percentage of children reporting symptoms of respiratory disease increased with PM_{10} pollution. Symptomatic children reported higher upper respiratory symptoms (57%), lower respiratory symptoms (82%) and cough (100%), during days when PM_{10} levels were in the highest quartiles than during days when PM_{10} levels were in the lowest quartile. Although no association between pollution and upper respiratory symptoms was found in asymptomatic children, there was approximately a 40% and 78% increase in lower respiratory symptoms and cough during days with pollution levels in the highest quartile compared with days with pollution levels in the lowest quartile, respectively (Pope and Dockery 1992).

Again, as indicated in the previous study, the researchers identified a sensitive subgroup, symptomatic children. The positive results observed in the asymptomatic children indicate that PM_{10} pollution could potentially affect a wide range of children, giving rise to transient changes in pulmonary health (Pope and Dockery, 1992).

Children were again subjects of a study examining respiratory symptoms through a diary in the Gardanne coal basin, near Marseille, France (Charpin et al., 1988). The study was conducted between December 1983 and March 1984 using 450 schoolchildren in the third, fourth and fifth grades. Health effects were evaluated before and after an extension of the power plant was implemented. Pollution data were recorded for respirable particles and SO_2. No size range was given for what was included in respirable particles; it could be assumed that this represents either PM_{10} or PM_{15}. Monthly means ranged from 46 to 92 µg/m^3, with a

minimum and a maximum of 21 μg/m^3 and 262 μg/m^3, respectively, for the four-month study period. The questionnaire obtained information on symptoms such as morning cough, eye irritation, runny nose, sneezing, sore throat and wheezing. Researchers found no correlation between daily prevalence of symptoms and daily respirable particle levels. Smoking in the home, a common potential confounder in this type of study, was not mentioned and therefore probably not controlled for (Charpin et al., 1988).

Associations between respiratory function in children and heavy industrial pollution were examined in Cubatao, Brazil, during the 1988 school year (March-June, August-November) (Spektor et al., 1991). Six hundred six-year-old children, attending six different kindergarten schools, were tested monthly for standard spirometry measures. Pollution in the area was primarily of industrial origin: iron and steel mills, fertilizer, cement and gypsum production and coke kilns, as well as chemical, paint and many other secondary plants. In addition, the city is located on the coast and surrounded by mountains, which leads to frequent trapping of air pollutants. Measurements recorded included PM_{10}, SO_2 and O_3 levels, as well as $PM_{2.0}$ and coarse particles, as PM_{10-2}, (these were not further considered in this preliminary analysis). Yearly average PM_{10} concentrations ranged from 59 μg/m^3 to 110 μg/m^3 in the six school areas (with children participating in the study living within 500 metres of the schools). Lung function data were regressed against mean monthly PM_{10} levels, and significant associations were found with reductions in FEV_1 (-0.3 to -0.6 ml/μg/m^3), PEF (-1.2 to -2.6 ml/sec/μg/m^3), and FEF_{25-75} (-1.1 to -3.1 ml/sec/μg/m^3) for the month prior to measurement. The reporting of pollution data for the six school sites was inexact. However, this study area does appear to be an ideal area for future studies because of the wide range of pollution levels and sources in the different regions of the valley (Spektor et al., 1991).

Studies with various measures of fine particles:

Perry et al. (1983) studied the effects of particulate air pollution in adult asthmatics as measured by PEF, symptoms of airway obstruction and aerosolized bronchodilator use. The study was conducted in Denver, Colorado, from January through March 1979, during which time measurements were recorded for both fine (<2.5 μm) and coarse (2 μm to 15 μm) particulates, SO_4^{2-}, NO_3, SO_2, CO and O_3. No relationship was found between most of the air pollution variables measured and peak expiratory flow, symptoms of exacerbation of asthma, or medication use. Fine sulphates had a borderline effect on increases in medication use ($p=0.065$), and fine nitrates were associated with increased symptoms ($p=0.02$) and increased medications both in the morning ($p=0.04$) and evening ($p=0.02$). Pollutant levels were not reported, making it difficult to interpret the data. It was also mentioned that there were very few days of high pollution during the study period.

A daily air monitoring program was conducted in Denver, Colorado, between November 1987 and February 1988 (Ostro et al., 1991), in which 207 asthmatics between the ages of 18 and 70 years were asked to provide daily diary information on asthma symptoms, medication use, utilization of medical services, indoor exposures as well as other variables related to measured pollutants in the area. The pollutants measured twice daily included $PM_{2.5}$, sulphates, nitrates, acidity and SO_2. Mean, minimum and maximum levels of $PM_{2.5}$ were reported as 22, 0.5 and 73 μg/m^3, respectively. $PM_{2.5}$ concentrations were only mildly associated with overall asthma ratings ($p<0.1$), but not with indicators of respiratory health such as cough or shortness of breath. Acidity, as hydrogen ion, was associated marginally with asthma exacerbations, and with significant increases in cough and shortness of breath ($p<0.05$). These effects were more marked after adjustment for time spent indoors. Sulphate was associated with symptoms of shortness of breath. The strengths of this study were good reporting of pollution measurements and screening of potential study candidates. However, the selection of all participants from a single clinic, a majority of whom were white females, employed and well educated, with an average age of 46, formed a sample that is clearly not representative of the general population, thus limiting the validity of the results with respect to the general population (Ostro et al., 1991).

A panel study with 155 asthmatic children and 102 asthmatic adults was recently carried out over two winters in three neighbouring cities, Erfurt and Weimar in former East Germany, and Sokolov, Czech Republic (Peters et al., 1996a). Possible associations were investigated between the air pollutants SO_2, TSP, PM_{10}, SO_4^{2-}, particle strong acidity, and the health indicators of respiratory symptoms and lung function as peak expiratory flow rate (PEF). Children's PEF was significantly reduced by increases in the 5 d means of all the pollutants. SO_4^{2-} and SO_2 provided the strongest reductions (1.1 and 0.9%

respectively), for their interquartile ranges (t=4.0 for both). The fine particle measures were more strongly associated with these reductions than the particle measures PM_{10} or TSP, which both included coarser fractions. For example, the PEF reduction associated with SO_4^{2-} (interquartile range) was twice as great as that with particle strong acidity, while it was 2.6 and 3.2 times greater than the reductions associated with PM_{10} and TSP. A 15% increase in adverse respiratory symptoms was significantly associated only with the gaseous pollutant SO_2 for an interquartile range increase of 128 µg/m^3 in the 5 d mean. Concurrent day air pollution was generally not associated with any endpoints, except for a 0.43% decrease in PEF associated with PM_{10} (52 µg/m^3 interquartile range), about the same magnitude as the decrease for the 5 d mean (48 µg/m^3 range). On the basis of a 10 µg/m^3 increase in pollution for each of the particulate pollutant metrics, the percentage decreases in PEF were 1.2% for SO_4^{2-}, 0.14% for PSA, 0.09% for PM_{10} and 0.05% for TSP (Peters et al., 1996a).

The results for the adults in the same study are as follows. In adults, effects on PEF were smaller and less consistent; a 0.4% decrement in PEF was significantly associated only with 5 d average TSP (interquartile range increase of 71 µg/m^3), equivalent to 0.06% for a 10 µg/m^3 increase. Symptom responses were more marked in adults than in children. Five-day average SO_2, PM_{10} and PSA were all significantly associated with symptom increases (18%, 15%, and 11% for respective interquartile range increases), while TSP and SO_4^{2-} were not. Concurrent day pollutant indices were not associated with any endpoints in adults. Thus, in this study, asthmatic children were found to be more responsive than asthmatic adults in the same communities, but less responsive regarding symptoms. It was noted that medication use was frequent in both children and adults, which could have modified effects differentially among people with pre-existing respiratory conditions (Peters et al., 1996a). This study, although small and with some monitoring data gaps, was carefully conducted. It also gave indication that the fine fraction ≤2.5 µm, as SO_4^{2-} or H^+ (PSA), had a greater effect on children's PEF (but not on symptoms) than other larger particle measures. However, the results in this regard were inconsistent for adults. The authors did not co-regress SO_2 with any of the particle measures. TSP and PM_{10} were highly correlated (r=0.63-0.88), and PSA was moderately correlated (r=0.43) to the other particle measures. About 15% of PM_{10} was composed of SO_4^{2-}.

Peters et al. (1996b) investigated the relevance of numbers of fine particles compared to their mass, during the winter 1991-92 (145 days), in Erfurt, former East Germany. A mobile opticle particle counter and a differential mobility analyzer gave number and mass concentrations of particles less than or equal to 2.5 µm in diameter. Seventy-nine percent of the particles were smaller than 0.1 µm in diameter, while 82% of the mass concentration was associated with particles in the size range 0.1 to 0.5 µm. The evening mean PEF of a panel of 27 non-smoking asthmatic adults (44-80 years old) were regressed against the 5 d mean (lag 0-4 d) of number counts and equivalent particle mass concentrations, after adjustments for weekends, 24 h mean temperature, and a linear trend. While declines in PEF for the interquartile ranges of all measured fractions were significant, the decline in PEF was more pronounced for the number concentrations than for the equivalent mass concentrations. An interquartile range (IQR) increase in number concentration (PM<0.1 µm) of 9200/cm^3 (79% of all particles) was associated with a decline of 4.04 L/min (95% CI -2.0 to -6.1), while an IQR mass concentration ($PM_{0.1-0.5}$) of 28.8 µg/m^3 (82% of all mass) was associated with a smaller decline of 2.1 L/min. (95% CI -0.6 to -3.7) (p=0.04). Similarly the IQR for the number concentration of the entire $PM_{2.5}$ sample, 9950/cm^3, was associated with a decline of 3.8 L/min (95% CI -2.0 to -5.6), while a smaller decline of 2.3 L/min (95% CI -0.5 to -4.1) was associated with the IQR of 36.0 µg/m^3 for the $PM_{2.5}$ mass concentration (Peters et al., 1996b). This is perhaps the first epidemiology study which has attempted to examine the role of the submicron fraction of particulate matter in respiratory function. Although a very small study, requiring confirmation in other work on larger populations and on other endpoints, it provides supporting human data for the animal toxicology work which has suggested that ultrafine particles are the most important fraction with respect to cardiorespiratory toxicity.

Dassen et al. (1986) measured the effect of exposure to $PM_{2.5}$ during an air pollution episode on the pulmonary function of 163 primary schoolchildren in the Ijmond area, The Netherlands. From January to February 1985, mean levels of respirable suspended particulate (RSP) (≤3.5 µm in size) remained well below 100 µg/m^3, whereas maxima reached 200-250 µg/m^3 during a five-day pollution episode. Measurements were represented by 24 h averages taken once every three days. Other pollutants measured were TSP and SO_2. The source of the particles was

generally wind-blown iron ore, coal sand and vehicle exhaust from a nearby industrial area. Researchers recorded five parameters of pulmonary function, including FVC, $FEV_{0.5}$ (forced expiratory volume in 0.5 seconds), FEV_1, PEF (peak expiratory flow), MMEF (maximum mid-expiratory flow), $MEF_{25\%}$, $MEF_{50\%}$ and $MEF_{75\%}$ (maximum flow at 25, 50 or 75% of vital capacity). The periods of high pollution (200-250 µg/m^3 over five days) for all three pollutants were associated with a transient decline in pulmonary function (percentage not specified). This decline appears to have persisted for at least two weeks, but not longer than 3.5-4 weeks after the episode. The authors suggest that effects are dependent on the duration of the polluting episode. A two-day increase in 24 h average levels of all three pollutants (RSP, TSP and SO_2) in the range of 100-150 µg/m^3 was not associated with a decline in pulmonary function, suggesting that the episode was not long enough to cause changes in pulmonary function lasting more than one day (Dassen et al., 1986).

In a study by Hoek et al. (1990), pulmonary function was measured in 630 primary schoolchildren living in the Ijmond region, near Amsterdam, The Netherlands. In January 1985, an air pollution episode occurred during which levels of respirable suspended particulates (< 3.5 µm), TSP and SO_2 were recorded in the range of 200-250 µg/m^3 (24 h averages). Pulmonary function (FVC, FEV_1, PEF, MMEF) was measured during the episode as well as two weeks and 3.5 weeks after the episode. These data were compared with baseline measurements taken when pollution levels were much lower. Most lung function variables were significantly decreased during and, to a lesser extent, two weeks after the episode. There were no significant differences from baseline levels in observations made 3.5 weeks after the episode. Lack of detailed pollution levels and short study duration make it difficult to interpret these data.

Another study by some of the same researchers was conducted involving 112 children, 7-12 years of age, in Wageningen, a small non-industrial town in the eastern part of The Netherlands (Hoek and Brunekreef 1993). Pulmonary testing (FVC, FEV_1, PEF) as well as respiratory symptoms (throat irritation, cough, cough with phlegm, wheeze, runny/stuffed nose, aching throat, shortness of breath, chest tightness, eye irritation, sneezing) were matched against measured levels of PM_{10}, SO_2, NO_2 and black smoke (BS). PM_{10} was measured by daily 24 h measurements. No average PM_{10} level was reported for the study period, but monitoring data did appear to show that the range of PM_{10} levels was ~10-174 µg/m^3. Results showed that during a winter episode of moderately elevated concentrations of PM_{10}, SO_2 and Black Smoke, pulmonary function of the schoolchildren was significantly lowered. There was no association between the prevalence of respiratory symptoms and air pollution concentrations. It was calculated that FVC, FEV_1 and MMEF decreased by ~2.5% when same-day PM_{10} levels increased by 100 µg/m^3. It was also pointed out that the magnitude of the response would be considered small (Hoek and Brunekreef, 1993).

Between December 1990 and March 1991, acute respiratory effects as measured by PEF were studied in 73 children aged 6-12 with chronic respiratory symptoms in two small non-industrial towns, Wageningen and Bennekom, The Netherlands (Roemer et al., 1993). Children were screened through a questionnaire, and 74 participants were chosen from 131 available children. No major sources of pollution exist in either of the towns or in their vicinities, thus implying that pollution levels are mainly due to long-range transport. Ambient concentrations of PM_{10}, SO_2, NO_2 and BS were recorded. Maximum, minimum and mean PM_{10} levels were moderate, at approximately 180, 15 and 55 µg/m^3, respectively. In addition to peak flow measurements, participants were asked to register the occurrence of acute respiratory symptoms (cough, phlegm, runny or stuffed nose, shortness of breath, etc.) and medication use. Small but statistically significant associations were observed between moderately high levels of PM_{10} and decreases in peak flow. Daily prevalence of wheeze and bronchodilator use also had a positive correlation with PM_{10} levels. Other respiratory symptoms were also associated with PM_{10}, but only in a weak positive correlation. Reporting of pollution levels in this study was not clear, and therefore rough estimates were calculated from the data. It is also difficult to determine which pollutant was responsible for the effects observed, as almost all of them were equally associated with the measured health effects (Roemer et al., 1993).

Another study was conducted by Hoek and Brunekreef (1994) on the respiratory health of Dutch children over three consecutive winters (1987-1988, 1988-1989 and 1989-1990) in three non-industrial commmunities and one non-industrial city in the Netherlands. Pulmonary function testing (between 6 and 10 manoeuvres) was performed on more than

1000 children (546 male, 532 female) between the ages of 7 and 11. The occurrence of acute respiratory symptoms (hoarseness, cough, cough with phlegm, wheeze, runny/stuffed nose, aching throat, shortness of breath, chest tightness, eye irritation and sneezing) was registered by the parents in a diary. Information on ambient levels of PM_{10}, fine particle sulphate, fine particle nitrate and nitrous acid was collected. No separation of fine and coarse particles could be accomplished with the sampler used. The 24 h mean PM_{10} level for the study was 44.9 µg/m^3, with a minimum and a maximum of 14.1 and 126.1 µg/m^3, respectively. A weak negative association was found between lung function and PM_{10}, as well as most of the other air pollution measurements. Daily prevalences and incidences of symptoms were not clearly associated with any of the air pollutants measured in this study.

Two studies (acute and chronic) were conducted in cities in Montana in the 1978-1979 and 1979-1980 school years (Johnson et al., 1990). The acute study in 1978-79 consisted of a comparison of schoolchildren's (8-10 years) lung function as a function of air pollution levels in one community. Approximately 375 third- and fourth-grade children in the town of Missoula were tested. Measurements were conducted for both TSP and respirable particles (coarse and fine) every three days. Coarse particles included those with aerodynamic equivalent diameters greater than 2.5 µm and less than 15 µm, and fine particles included those less than or equal to 2.5 µm. The sources of the particulates were identified as wood smoke and entrained dust. Results for fine and coarse particulates (24 h sampling) were grouped into categories of 0-30 µg/m^3, 31-60 µg/m^3 and >60 µg/m^3 and results for TSP were grouped into categories of 0-100, 101-150, and 151-200 µg/m^3. Pulmonary function measurements recorded were FVC, $FEV_{0.75}$ (forced expiratory volume in 0.75 seconds), FEV_1, FEF_{25-75} (mean forced expiratory flow during the middle half of FVC) and PEF. Fine particles showed a trend toward association with small concentration-dependent declines in lung function of 0.65% to 0.75% for FVC (p=0.04-0.08) and 0.47 to 0.5% for FEV_1 (not significant) for the highest category, 61+ µg/m^3, compared to the lowest category, 0-30 µg/m^3. The coarse fraction between 2.5 and 15 microns in size was not consistently associated with any lung function endpoint. An increase from the first to the third category of TSP was marginally associated with a decline of 1.0% in FEV_1 (p=0.07). This was confirmed in a followup test program the next year, in which an average decline of 1.65% in FEV_1 was associated with a rise from the winter average of 119 µg/m^3 to 440 µg/m^3 in a pollution episode. Declines were also noted in FVC and FEF_{25-75}, but were significant only in females. Thus, fine particles appeared to affect the overall pulmonary volume (FVC), whereas the larger particles affected pulmonary rate (FEV_1), supporting the theory that smaller particles are able to penetrate deeper into the human pulmonary system.

Respiratory health was measured in 2199 schoolchildren in the community of Port Alberni, located at the head of an inlet on the west coast of Vancouver Island (Vedal et al., 1991). The primary sources of pollution in the area are pulp mill boilers and residential wood-burning. The site is bounded on one side by high mountains and is often subject to temperature inversions, which contribute to air pollution problems. In a pilot study in 1986, it was determined that reduced sulphur compounds, SO_2 and methyl mercaptan levels were low in the area. Particulate matter monitoring was conducted between 1989 and 1990, during which TSP was measured for 24 hours every six days at 13 sites. Two sets of rotating monitors were also used to measure PM_{10}, changing sites every six days. From these data, PM_{10} values were predicted for all the sites. A health questionnaire was administered, and spirometry was performed measuring forced expiratory parameters. Two sites had 24 h PM_{10} concentrations that exceeded 150 µg/m^3. This occurred 2% of the time. Eleven of the 13 sites had 24 h PM_{10} concentrations that exceeded 50 µg/m^3, occurring 32% and 21% of the time. Estimated PM_{10} and submicrometre particle concentrations were associated with increased chronic cough, chronic phlegm production, congestion, wheezing symptoms and hospitalization for a chest illness before age 2. Threshold concentrations were observed at 35-40 µg/m^3 for PM_{10} and 20 µg/m^3 for submicrometre particles. Asthma prevalence was not associated with any of the particle measurements, nor was there an association found between particle exposure and changes in lung function measurement (Vedal et al., 1991).

Respiratory health, measured as the incidence of cough, lower respiratory symptoms and upper respiratory symptoms, was studied in a randomly selected cohort of 1844 schoolchildren in six US cities or approximately 300 children per city (Schwartz et al., 1994). A daily diary of respiratory symptoms was kept by the parents of each child for a period of a

year, beginning in 1984. Each home was also visited, and socioeconomic status, home characteristics, and parental smoking were recorded. Community measures for daily PM_{10}, $PM_{2.5}$, $PM_{2.5}$ sulphur (as a measure for sulphate), and acidity (H^+) were recorded, as well as the gaseous air pollutants ozone, SO_2, and NO_2, along with temperature. For the non-winter months of April to August (chosen because ozone was relatively high at this time and the incidence of infectious diseases, which could act as a confounder, was low) the median and maximum PM_{10} (combined for the six cities) were 30 µg/m^3 and 117 µg/m^3 respectively, with the interquartile range being 20.0 to 41.0 µg/m^3. For $PM_{2.5}$, median and maximum values were 18.0 and 86 µg/m^3 respectively, and for $PM_{2.5}$ sulphate, 2.5 and 15.1 µg/m^3 respectively (n=657-660 days). An increase of 30 µg/m^3 in daily PM_{10} was associated with an odds ratio of 1.22 (95% CI 1.03-1.45) for incidence of cough, 1.53 (95% CI 1.20-1.95) for incidence of lower respiratory symptoms, and 1.22 (95% CI 0.98-1.52) for incidence of upper respiratory symptoms. These increases were similar to those seen in the two Utah valley studies on schoolchildren (Pope et al., 1991; Pope and Dockery 1992). Concentration-response curves for PM_{10} and each of the three endpoints, controlled for temperature, city, and day of the week, were monotonically increasing, and were not significantly different from linear. A 20 µg/m^3 increase in $PM_{2.5}$ was also associated with increased incidence of cough (OR 1.19; 95% CI 1.01-1.42) and lower respiratory symptoms (OR 1.44; 95% CI 1.15-1.82), while a 5 µg/m^3 increase in $PM_{2.5}$ sulphate was associated only with increased incidence of lower respiratory symptoms (OR 1.82; 95% CI 1.28-2.59), and not with increased incidence of cough (OR 1.23; 95% CI 0.95-1.59). Hydrogen ion acidity was not associated with any of the three endpoints. PM_{10} was thus considered to be the best predictor of the particle metrics for increases in adverse respiratory symptoms due to particulate air pollution. In bivariate co-regressions with ozone, SO_2 and NO_2, the association with PM_{10} remained strong and relatively unchanged, while the associations for SO_2 and NO_2 were reduced and no longer significant. Ozone was associated with cough incidence, in the single analysis, and its coefficient remained almost the same, but with a loss of significance in the bivariate analysis, which is interpreted to mean that ozone had some effect on the incidence of cough which was independent of the PM_{10} effect.

12.4.2 Days of Work or School Absences, and Restricted Activity Days

One study attempted to associate PM_{10} with school absenteeism in 6700-6900 elementary schoolchildren from Utah Valley (Ransom and Pope, 1992). A daily time-series was conducted for the school years from 1985 to 1990. The main source of the PM_{10} in this study is a steel mill that was cited for multiple violations of the US EPA particulate standard of 150 µg/m^3 throughout the monitoring period. Mean levels of PM_{10} recorded were 50.9, 50.4 and 40.9 µg/m^3, with maximums of 243, 251 and 234 µg/m^3 for the Lindon, Orem and Provo school districts, respectively. Other pollutants measured included O_3 and SO_2, which were both very low in this area during the school year. Average absenteeism was found to be higher during periods of relatively high PM_{10} pollution than during periods with low PM_{10} pollution. Because of the potential lagged effects of particulates, moving averages of 7, 14, 21, 28 and 35 days were calculated, and the best fit was selected. Absenteeism was approximately 54% and 77% higher on days with a 28-day average above 100 µg/m^3 relative to those days with an average below 50 µg/m^3. However, caution was advised when interpreting the data, owing to the many and varied components that could not be controlled for and which may have influenced absenteeism. Although results from this study show high correlations between absenteeism and elevated levels of PM_{10}, this type of measured effect is more useful as a qualitative indicator of effects rather than in evaluating a dose-response relationship.

The relationship of airborne particulate matter to morbidity, measured as days of work lost, or days of restricted activity, was investigated in a cross-sectional analysis of 68 metropolitan areas in the US (Ostro 1987). A sample of adults, ages 18-65, was taken from metropolitan areas of all sizes and regions of the United States. These cities were part of the Health Interview Survey (HIS) conducted by the National Center for Health Statistics. The HIS is an annual multistage probability survey of individuals in which data on social, economic, demographic and health status are collected. The author used available data for 1976-1981 and a Poisson distribution to model the following health endpoints: days of work loss (WDL), days of restricted activity (RAD) and days of respiratory effects-related restricted activity. Days of restricted activity are defined as days when a respondent was forced to alter his/her normal

activity and indicates the most generalized health outcome. The respondents' responses to questionnaires on WDL and RAD in the previous two weeks were correlated to the previous two-week pollutant levels. Data on fine particulates (<2.5 µm) were based on airport visibility data. Particle light scattering, a primary factor in the development of regional hazes, is dominated by particles ranging from 0.1 to 1.0 µm in size (Chapter 7). The PM mass measured by particle light scattering is roughly equivalent to fine particulates, because nearly all of the fine particle mass is from particles less than 1 µm in size. A mean particulate concentration of 24 µg/m^3 was calculated based on the arithmetic mean of four daytime three-hour readings. The airborne particulates came from a wide variety of urban sources, such as vehicle exhaust and industrial emissions. Regression analysis demonstrated a consistent association between fine particulates and the health endpoints measured. For days of respiratory symptoms-related restricted activity, the estimated coefficient for fine particulates was positive and significant in all six years. A 10 µg/m^3 increase in estimated fine particles resulted in an estimated 2.8 to 9.0% increase in restricted activity days (RAD) (n=10 900-12 800). For days of work loss, the estimated coefficient of fine particulates was positive and significant in four of the six years and negative in two years; this measure was therefore unstable. The authors noted, however, that the years with the lowest RAD coefficients were also the two that were not significant for working days lost. The health variables in this study may be attributable to a variety of factors. Measurement of fine particulates by airport visibility is a relatively crude means of estimating actual fine particulate levels. Maximum and minimum levels of particulates, which are good relative indicators of air pollution episodes, were not reported (Ostro, 1987).

Another study by Ostro and Rothschild (1989) again used HIS data from the years 1976-1981 for acute respiratory morbidity (respiratory symptoms-related restricted activity days (RRAD)and minor restricted activity days). Two pollutants were analyzed: fine particulates (<2.5 µm, estimated from daily airport visibility data) and ozone. The mean concentrations of fine particulates for each year ranged from 20.7 to 22.3 µg/m^3. A consistent positive relationship was found between fine particulates and RRAD. The relationship is statistically significant in all six years, with an estimated coefficient ranging from 1.02 to 1.81 in the regressions in which both fine particulates and ozone were included. The association of fine particles with minor restricted activity days was weaker than with RRAD. A 1 µg/m^3 change in concentration was associated with a 1.58% increase in respiratory symptoms-related activity days, or an excess of 4800 days per 100 000 population.

In an expansion of the data on fine particles, Ostro (1990) repeated the methodology of the previous two surveys, using HIS data from 1979-81, on acute respiratory morbidity, measured as the number of days of RRAD in the two weeks prior to the day of the survey. Health outcomes were compared for TSP (<30 µm), inhalable particulates (IP, <15 µm), fine particles (FP, <2.5 µm) and sulphates (SO_4^{2-}). The total data set included 25 metropolitan areas throughout the United States, concentrated mostly in the south. Data for the 24 h mass of the particles were collected every six days. The mean concentration for fine particulates was 23.5 µg/m^3, and the correlation between the different measures ranged from 0.81 between FP and IP to 0.35 between TSP and SO_4^{2-}. No maximums and minimums were reported. Results showed that among the particulate measurements used, only the sulphate measurement was positively and significantly associated with respiratory health status, with an 8.3% increase in RRAD per 10 µg/m^3 increase in SO_4^{2-}. Inclusion of a two week lag period (in addition to a two week mean) increased the RRAD by 17.4% for SO_4^{2-}, 12.9% for FP, 9.0% for IP, and 6.4% for TSP (all significant at p=0.01) (Ostro, 1990). This study provides good support for the effect of fine particles compared to IP or TSP, the relative strength of association being SO_4^{2-} >FP >PM_{10} >TSP. The results were not robust for winter, when ozone levels were low, suggesting that at least part of the effect could have been due to an independent or combined effect of ozone, an unmeasured confounder.

12.5 LONG-TERM AND CHRONIC EFFECTS

The effect of longer term exposure (i.e., greater than daily or weekly variations) or chronic exposure has been examined by means of cross-sectional studies that compare populations in different geographic regions with different pollutant mixes, and cohort studies on a defined group of individuals followed through time. Most of these studies, including some with the cohort design, have had to rely on grouped community exposures rather than individual exposures, although they may have data on other individual risk factors such as smoking or occupational history. Studies have been grouped according to

endpoint, on mortality, long-term effects on the respiratory system, and cancer.

12.5.1 Cross-Sectional and Prospective Studies on Mortality

A number of cross-sectional studies, most carried out prior to 1990, have been reviewed by Lipfert and Wyzga (1995b), Pope et al. (1995a-c), and the US EPA (1996). The general conclusions were that although mortality rates were associated with air pollution, most strongly with fine particles or sulphate, the study limitations were sufficiently great (limited air quality data, subject to confounding by smoking, lifestyle factors, and choice of model), that the studies were in fact of limited value in the elucidation of the mortality – air pollution/particulate matter association. Only one of these population-based cross-sectional studies (Ozkaynak and Thurston 1987) is considered here, because it investigated several fine particle associations which are potentially of greater concern than larger particle size fractions. Two large cohort studies have also recently been completed. Since these were able to include individual risk factors known to affect mortality and they followed individuals through time, they are considered to provide better and more reliable evidence than the cross-sectional studies on the pollution – mortality association. One study (Pope et al., 1995a) was based on a large sample of participants in the American Cancer Society's cohort study covering 150 US communities while the other (Dockery et al., 1993) was based on a more limited sample from six US cities. Both studies considered at least two measures of fine particles, as well as larger particle sizes including PM_{10} and TSP.

In the cross-sectional mortality study by Özkaynak and Thurston (1987), fine particles (FP or $PM_{2.5}$) and inhalable particles (IP or PM_{15}) were estimated for 60 of the 98 US Standard Metropolitan Statistical Areas (SMSAs) which did not have measured values. The estimating techniques gave $\pm$ 30% error for IP and $\pm$ 13% error for FP. TSP and SO_4^{2-} measurements were also collected, but no gaseous pollutants were considered. Mortality rates from the year 1980 were extracted for 98 areas from the 117 SMSA data set, and a regression analysis was conducted on the association between the annual averages of various particle measures and total mortality, including terms for median age, the proportion of population over age 65, proportion of non-whites, population density, proportion with a college education, and proportion below the poverty line. No correction for temperature was employed.

Of the particle measurements examined in the study, SO_4^{2-} showed the strongest and most consistent association with increased mortality, followed by fine particulate matter. Estimates for various regression models ranged from 6.1 to 7.5 deaths per 10^5 per $\mu g/m^3$ for SO_4^{2-}, and 2.1-3.7 deaths per 10^5 per $\mu g/m^3$ for FP (both measured and estimated). This was equivalent to an 8.2% increase in deaths per year per 10 $\mu g/m^3$ for SO_4^{2-} (95% CI 5.0-11.4%), and a 4.3% increase for FP (95% CI 0.4-8.2%) (single regression). The estimated mean concentrations of sulphates and fine particulate matter were 11 and 23 $\mu g/m^3$ respectively, and estimated total mortality effects of air pollution ranged from approximately 4 to 9% for SO_4^{2-} and 3 to 8% for $PM_{2.5}$. The association between mortality and inhalable particles (IP or PM_{15} and TSP) was of lower magnitude, at 0.8% (95% CI 0.14-1.5%) and was not a significant predictor of mortality. In a model with both estimated and measured values for FP and IP, the regression coefficients were strengthened for the measured versions of both FP and IP, but IP remained below the level of statistical significance. The measurement error noted above could have been responsible at least in part for the non-significance of IP. Overall, the pollution coefficients had the ranking SO_4^{2-} > FP > PM_{10} > TSP. Simultaneous regression including all four particulate metrics indicated that only SO_4^{2-} was significantly associated with mortality, but the high correlations between SO_4^{2-} and FP casts some doubt on the lack of positive results with respect to FP. Correlations between SO_4^{2-} and TSP or IP were low, -0.06 and 0.14 respectively. The analysis was sensitive to the results from the Ohio Valley, where sulphates are high; removal of the Ohio Valley results lowered the SO_4^{2-} regression coefficient by 40-50%.

The nature of the study did not allow for consideration of confounding factors such as smoking. However, sensitivity analyses showed that the overall statistical trend and conclusions were relatively robust to model adjustments. An interesting analysis of particle sources was carried out for 36 of the SMSA areas (Ozkaynak and Thurston 1987). Small particles from the iron/steel industry and coal combustion appeared to be relatively greater contributors to mortality (regression coeff. 10.0 and 5.7 deaths/10^5/ $\mu g/m^3$ respectively) than the larger soil-derived particles (regr. coeff. 0.7, not significant).

Mortality risks associated with air pollution were studied in a prospective cohort study beginning in 1974 (Dockery et al., 1993). Data were obtained from a 14- to 16-year mortality follow-up of a random sample of 8111 adults (1430 deaths) from the Harvard Six Cities Study (Watertown, Massachusetts; St. Louis, Missouri; Portage, Wisconsin; Kingston-Harriman, Tennessee; Steubenville, Ohio; Topeka, Kansas). Measurements were taken for five classes of particles: TSP, fine particles (<2.5 µm), inhalable particles (<15 µm before 1984 and <10 µm starting in 1984), SO_4^{2-}, and H^+. Other pollutants included were NO_2, SO_2 and O_3. At the beginning of the study, spirometric tests were administered, and information was collected by questionnaire on age, sex, weight, height, education level, complete smoking history, possible occupational exposures, and medical history. After adjustment for age (5 y categories), body-mass index, current and former smoking, number of pack-years of smoking, and an indicator for less than a high-school education (as a surrogate for socioeconomic status), significant and robust associations were observed between air pollution and mortality, as assessed by comparison of the range of pollutants in the most polluted versus the least polluted city. Based on the authors' graph (figure 2 of Dockery et al., 1993), the probability of survival over a 14-year period was reduced from 88% in the least polluted city to 79% in the most polluted city, and represented an average life-shortening of about four years (the mean for all six cities thus being two years). This strongly suggests that the effect on mortality is not just a phenomenon of "harvesting" or hastening the deaths of seriously ill people by a few days or weeks.

Mortality risk was most strongly associated with mean concentrations of inhalable particles ($PM_{10/15}$) (mean concentration range 18.2-46.5 µg/m^3), fine particles ($PM_{2.5}$) (mean concentration range 11.0-29.6 µg/m^3), and sulphate particles (4.8-12.8 µg/m^3) (Dockery et al., 1993). The adjusted rate ratios (RR) for these ranges were virtually the same at 1.27 (95% CI 1.08-1.48) for $PM_{10/15}$, 1.26 (95% CI 1.08-1.47) for $PM_{2.5}$, and 1.26 (95% CI 1.08-1.47) for SO_4^{2-}. This was equivalent to 10%, 14% and 32% increases in the chances of dying for each 10 µg/m^3 increase in PM_{15}, $PM_{2.5}$, and SO_4^{2-} respectively. Ratios were smaller for TSP, SO_2, and NO_2. These associations persisted after stratification by the individual city. In an additional analysis of these data (US EPA 1996), the RR for TSP was 1.22 and was marginally significant (lower confidence limit (LCL) =0.99), but when TSP data from 1970, prior to the beginning of the study, was regressed, the RR increased to 1.25 and was significant (95% CI 1.03-1.50). This, taken with the information that TSP pollutant levels had decreased over the years, suggests the importance of previous exposure. The EPA re-analysis also investigated the importance of coarse particles, as PM_{15}-$PM_{2.5}$, and the sulphate portion of the fine fraction, as $PM_{2.5}$-SO_4^{2-}. The coarse fraction was not significant (RR 1.19; 95% CI 0.91-1.55), but the non-sulphate fraction of $PM_{2.5}$ retained significance (RR=1.24; 95% CI 1.16-1.32), and the regression co-efficient doubled from the $PM_{2.5}$ value and dropped about 14% from the SO_4^{2-} value. The lack of significance of acidity (H^+) is to be noted, since Kingston-Harriman, TN was selected for the study on the basis of its high acidity levels. However, only one year of measurements were available. Ozone was not significant, but 24 h measurements were used instead of peak daytime levels, and ozone levels did not differ much between cities; either or both of these factors could have been responsible for the lack of association with ozone. Although a supplementary analysis of these data by the US EPA (1996), showed that SO_2 and NO_2 were associated with premature mortality at least as strongly as TSP in single pollutant regressions (rate ratios 1.20 with 95% CI 1.01-1.43 for SO_2 and 1.22 with 95% CI 1.00-1.49 for NO_2, these associations were of smaller magnitude and were less robust than the associations with PM_{15}, $PM_{2.5}$, SO_4^{2-}, and the non-sulphate fraction of $PM_{2.5}$. Thus SO_2 and NO_2 were unlikely to act as confounders in the particulate matter associations despite the lack of testing in bivariate regressions.

A strong linear concentration-response was shown in the US EPA reanalysis (1996) of the Dockery et al. (1993) data for sulphate and non-sulphate fine particles and for fine particles combined. The linear association was a little weaker for inhalable particles (PM_{15}) and the coarse particle fraction of inhalable particles (PM_{15}-$PM_{2.5}$). TSP or total particles and the non-inhalable fraction (TSP-PM_{15}) showed only a weak linear trend. However, it is noted that this is based on only six observations (cities). Exposure misclassification could have accounted for the reduced significance of TSP and coarse particles, since they are less homogeneous over the six areas, which were represented by only one monitoring location each. Additionally, these do not penetrate as readily indoors (where most people spend most of their time) as the finer particles and sulphates.

The mortality effect of individual risk factors including current or former smoking, 10 or 25 pack-years of smoking, less than a high school education in men, body-mass index in women, and living in the most polluted city (Steubenville), was analyzed in a combined Cox proportional hazards model. The largest RR was observed for current smokers (RR= 1.59; 95% CI 1.3-1.9). The estimated risk ratio between the most and least polluted city using $PM_{2.5}$ as an indicator was 1.26, with a 95% confidence interval of 1.08-1.47. The rate ratios for the effect of $PM_{2.5}$ on mortality among former and current smokers, and for men with occupational exposure, were slightly increased to 1.32-1.35, indicating that these factors may have had some influence on the increase in risk. By category of cause of death, risks in the most polluted versus the least polluted city were increased for cardiopulmonary disease (RR=1.37) and lung cancer (RR=1.36), but the latter was not statistically significant. Exclusion of persons with pre-existing hypertension or diabetes did not lower the RR. Overall, this study found a strong and consistent relationship between increased mortality and particulate matter. This relationship was robust to various model specifications and to the inclusion of several possible confounders (Dockery et al., 1993). Because of the lack of long-term monitoring for most of the pollutants prior to the start of the study, the potential effect of chronic non-concurrent exposure could not be investigated.

A second large prospective cohort mortality study has been carried out on a much larger (non-random and not entirely representative) sample of the US population (Pope et al. 1995a). This study used data on individual risk factors from a cohort of 552 000 adults aged 30 or older (the ACS or American Cancer Society Cohort) who resided in 1980 in 151 US metropolitan areas. Deaths (38 000+) were recorded for 7.3 years from September 1982 to December 1989. Death certificates were obtained for 96% of all deaths and coded to ICD-9 by a specialist. A subcohort (295 000 subjects; 20 765 deaths) was also selected from 50 cities which had available fine particle data in addition to the SO_4^{2-} data for the main cohort. Pollutant concentrations for the year 1980 were used as the index of exposure for sulphate (mean 11.0 $\mu g/m^3$; range 3.6-23.5 $\mu g/m^3$), and the median fine particle concentration for 1979-1983 from a previous cross-sectional study (Lipfert et al., 1988) was used for the subcohort (median average $PM_{2.5}$ = 18.2 $\mu g/m^3$; range 9.0-33.5 $\mu g/m^3$). Relative risk ratios, stratified by age (5 y intervals), sex, race, and gender, and adjusted for smoking status, passive smoke exposure, duration of exposure, body-mass index, alcoholic drinks, educational attainment, and occupational exposure, were calculated based on the Cox proportional hazards model using survival time as the variable. All information had been collected by interview prior to the starting date.

For individuals residing in the city with the highest mean pollutant levels compared to those with the lowest levels, the risk ratio of dying over the 7+ year period was 1.15 (95% CI 1.09-1.22) for an increased sulphate level of 19.9 $\mu g/m^3$ (its range over all cities), and 1.17 (95% CI 1.09-1.26) for increased $PM_{2.5}$ were of 24.5 $\mu g/m^3$ (also its range). Per 10 $\mu g/m^3$ increase, this was equivalent to a 7.5% increase in the chance of dying in the high sulphate area or to a 6.9% increase in the high $PM_{2.5}$ area. The risk ratio was increased for both sulphates (RR =1.26; CI 1.16-1.37) and $PM_{2.5}$ (RR=1.31; 95% CI 1.17-1.46) for cardiopulmonary deaths. Increased lung cancer deaths (RR=1.36; 95% CI 1.11-1.66) were associated with sulphates but not with $PM_{2.5}$ (RR=1.03; n.s.-LCL 0.80). These RRs were internally consistent with the null results for all other causes of death (RR= 1.01 for SO_4^{2-} and 1.07 for $PM_{2.5}$, neither significant), and with the greatly increased RR observed in all four categories for current smokers who smoked one pack of cigarettes per day for 25 years or more (e.g., the lung cancer RR associated with smoking was 9.73 for a person who smoked one pack per day for 25 years. A broader range of individual risk factors, especially those having to do with smoking status, was included in this study than in the Dockery et al. (1993) cohort study. The associations between mortality and particulate air pollution were not sensitive to the inclusion of body-mass index (BMI), alcohol consumption, education or occupational exposures. Temperature effects could not explain these increases in risk ratio, since temperature highs, means or lows were not correlated with sulphates or fine particles ($r<0.1$) and analyses including variables for "hot" (mean >60°F) and "cold" cities (<50°F) had little impact on the results. No other air pollutants were considered in the analysis, but the wide geographic range of cities covered in the analysis would include a broad range of air pollutant mixes, making less likely the possibility that the effects were due entirely to confounding.

A population-based cross-sectional ecological analysis was also carried out for the same cities or metropolitan areas, for comparison with the cohort study

(Pope et al., 1995a). Age-, sex-, and race-adjusted regression coefficients for total mortality were 10.5 $\pm$ 1.3 deaths/year/100 000 people per µg/m^3 SO_4, and 8.0 $\pm$ 1.4 deaths/year/100 000 people per µg/m^3 $PM_{2.5}$ ($p<0.001$). No other lifestyle confounders (e.g., smoking status) were included. Using the mean age-sex-race adjusted mortality rate as the baseline risk, the estimated risk ratios for the most polluted city versus the least polluted city were 1.25 using sulphate and 1.24 using $PM_{2.5}$. These were somewhat higher than the RR found in the prospective cohort study, of 1.15 for SO_4^{2-} and 1.17 for $PM_{2.5}$. Thus the inclusion of likely demographic and lifestyle confounders in the cohort study reduced the RR due to pollution but did not eliminate it. The coefficents were also almost twice as high for SO_4^{2-} and two to four times higher for fine particle coefficients as the coefficents found in the cross-sectional ecological analysis by Ozkaynak and Thurston (1987). The risk ratios in the main cohort study were consistent with, but somewhat lower than those seen in the six-city study. This was probably due to the much larger geographic and population coverage of 151 cities versus six cities, as well as to inclusion of a broader range of potential confounders in the regressions. These risk ratios (Pope et al., 1995a) are therefore considered to be a more accurate expression of the relationships of mortality to sulphate and fine particles, as combustion-source air pollutants. It is noted that the observed risk ratios may also be a consequence of higher pollutant concentration in earlier years, prior to the 1980 determination of exposure levels, a hypothesis supported by the higher risk ratios associated with 1973 TSP levels.

12.5.2 Long-Term Effects on Respiratory Health and Pulmonary Function

This section considers cohort and cross-sectional analytical studies that have considered a range of particle metrics in examining the relationship of seasonal or annual variations in air pollution to worsening of respiratory symptoms and/or lung function. Included are two recent and two older cross-sectional studies on children, as well as a British study on a birth cohort of young adults and a prospective cohort study on older adults in California in which individual exposure estimates could be made.

In a cross-sectional study carried out in the 1978-79 school year, pulmonary function and respiratory symptoms in children aged 8 to 10 years (n=300 to 400 for each community and season) from five Montana communities were examined for possible associations with seasonal variations in TSP, and in fine and coarse particles (Johnson et al., 1990). Air pollution, which was highest in winter, arose from industrial sources (mining, smelting, pulp and paper mill, sawmill, coal-fired power plant) and both industrial and residential wood-burning. The three-month seasonal averages for TSP in the five cities ranged from 27 to 128 µg/m^3, for coarse particles ($PM_{15-2.5}$) from 11 to 56 µg/m^3, and for fine particles ($PM_{2.5}$) from 8 to 46 µg/m^3 . Differences between cities were more striking with TSP than with fine or coarse particles. TSP was measured daily, while fine and coarse particles were measured only every third day and the remaining two days estimated. Correlation coefficients for TSP – coarse particles, TSP – fine particles, and TSP – fine plus coarse particles (PM_{15}) were 0.82, 0.55, and 0.32 respectively (the latter being unexpectedly low). Pulmonary function tests (FEV_1, FVC, FEF_{25-75}) were carried out in each of the cities three times over the study period, once each season, and the results were analyzed by season. Great Falls children showed the highest pulmonary function values, and these were used as controls for the other four cities. Results for FEV_1/FVC and for FEF_{25-75} were the lowest in Anaconda and Butte, followed by Missoula. FEV_1 and FVC were consistently lowest in Missoula. Researchers observed the greatest negative correlations between TSP and PM_{15} and pulmonary variables in simple linear regression analysis, but the detailed results were not presented. The slope for FVC for all females was -0.39 ml/µg/m^3 and for males it was -0.65 ml/µg/m^3, roughly similar to the results of other researchers, but the authors noted that the significance level was low for girls. The effects observed also appeared to be transient: children's pulmonary function rose significantly after two months of clean spring air. (Johnson et al., 1990). The analysis and reporting of the pollution-response data was vague and inadequate in this study. Although this study does not support a greater role for fine particles than for coarse particles, this could be a function of the unsophisticated analysis as well as inaccurate measurement and estimation.

Dockery et al. (1989) conducted a cross-sectional study of air pollution and health using a health questionnaire and spirometric measurements. The subjects were 5422 children aged 10-12 years in six cities (Watertown, Massachusetts; St. Louis, Missouri; Portage, Wisconsin; Kingston-Harriman, Tennessee; Steubenville, Ohio; and Topeka, Kansas)

in the eastern United States. The sources of pollution again included vehicle exhaust and industrial emissions. Pollutants measured were $PM_{2.5}$, PM_{15}, TSP, SO_4^{2-}, SO_2, NO_2 and O_3. Mean levels reported for $PM_{2.5}$ ranged from 11.8 to 36.7 $\mu g/m^3$. Health data collected during the 1980-1981 school year included the following five respiratory illness and symptom responses: bronchitis, cough, chest illness, wheeze and asthma. Pulmonary measurements recorded were FVC, FEV_1, $FEV_{0.75}$ and MMEF.

The only significant associations found between measures of particulate matter and measures of illness and symptoms were with bronchitis, and possibly chronic cough. The odds of contracting bronchitis over the range of PM_{15} observed (38.7 $\mu g/m^3$) were increased by a factor of 2.5 (with a 95% confidence interval of 1.1-6.1 $\mu g/m^3$). Although the odds ratios were in the same range for the other particle metrics, they were not significant; for example, the OR for $PM_{2.5}$ (range 24 $\mu g/m^3$) was increased by a factor of 2.1 with a 95% confidence interval of 0.8-5.9. These non-significant results appeared to be due to the low power of the study to detect effects of this size, given that there were only six units of observation (i.e., the pollution level in each of six cities). It was also observed that among the 571 children with asthma or persistent wheeze, the prevalence of bronchitis, and to a more limited extent, chest illnesses and chronic cough, was much higher than in children without these symptoms. When the prevalence of bronchitis was plotted against the city-specific mean concentrations of PM_{15}, it became clear that children with asthma were reporting most of the excess cases of bronchitis in the more polluted communities, since the slope of the regression curve was close to zero for the non-asthmatics. This association was found for all four particle measurements, but was strongest for PM_{15}. There was no evidence of adverse effects on pulmonary function associated with any measure of particulate air pollution as experienced over a period of one year, although this could have been due to the low power of this study to detect such effects (Dockery et al., 1989).

The same research group has recently completed a much larger cross sectional analytical study to investigate the relationship of fine particles, ozone, and acidity with both lung function and respiratory symptoms in children of 24 communities in the US and Canada (Dockery et al., 1996a; Raizenne et al., 1996). Communities were selected on the basis of provision of a wide variety of demographic and atmospheric conditions, and were largely suburban or rural, without significant industrial sources of pollution. Eleven communities (all US) were in the “sulphate belt”, six were in the “transport region” for sulphates and photochemical smog (four in southern Ontario), three were west coast (California) and four were “background” (including Yorkton, Sask. and Penticton, B.C.). For the respiratory symptoms study, 13 369 nine- and ten-year old (white) school children in 24 communities participated, with the median being 581 per community (range 329-676) (Dockery et al., 1996). One-hour maximum ozone (mean 46.5 ppb), SO_2 (mean 4.8 ppb), ammonia (mean 1.3 ppb), and gaseous acids (nitric and nitrous acid, mean 59 $nmol/m^3$) were monitored in addition to PM_{10} (mean 23.8 $\mu g/m^3$), $PM_{2.1}$ (mean 14.5 $\mu g/m^3$), SO_4^{2-} (mean 4.7 $\mu g/m^3$) and H^+ (mean 31.1 $nmol/m^3$). Monitoring began for this study in the spring of the preceeding school year and continued for at least one year (study was carried out in the different communities over three years, 1988-1990). This one year of monitoring was shown to be representative of a lifetime of exposure for most pollutants, and for a majority of the children, based on at least four years of monitoring results, available for PM_{10}, $PM_{2.1}$, and SO_4^{2-}, but only one year for particle strong acidity (PSA or H^+); a detailed exposure assessment and discussion of the monitoring results was reported by Spengler et al. (1996). A standard respiratory symptom questionnaire on symptoms in the past 12 months was filled out by the parent(s) in the fall (average response rate 91%) and lung function tests were administered at the school later in the year.

After adjustments on a city-specific basis for sex, child’s history of diagnosed allergies, parental history of diagnosed asthma, parental (either parent’s) post-high school education, and current smoking in the home, the odds ratio for developing bronchitis in the past year were elevated for communities with high acidity and high sulphate levels, the OR for a PSA range of 52 $nmol/m^3$ from the lowest to the highest community being 1.66 (95% CI 1.11-2.48), and the OR for a sulphate range of 7 $\mu g/m^3$ being 1.65 (95% CI 1.12-2.42). Respirable particulates ($PM_{2.5}$; range 14.9 $\mu g/m^3$) and inhalable particulates (PM_{10}; range 17.3 $\mu g/m^3$) were associated with increased bronchitis (OR=1.50) but the association was not significant. Gaseous acids (nitrous and nitric acid) were associated with a higher risk of asthma (OR =2.00; 95% CI 1.14-3.53), as well as marginally elevated ORs for other asthmatic symptoms and chronic phlegm. However, this association was driven by one community

with unusually high levels, and the association was no longer significant if this community was removed from the analysis. SO_2 (12.7 ppb range) was associated with increased odds for chronic phlegm (OR= 1.55; 95% CI 1.01-2.37) and marginally associated with bronchitis and other bronchitic symptoms. The maximum 1 h ozone average was not associated with increased odds for any symptoms.

Stratification of the results was carried out by sex, history of a severe chest illness before the age of 2, use of a humidifier in the home, lung function in the lowest quartile of FVC, current exposure to environmental tobacco smoke, prenatal exposure to maternal smoking, year of study, country, and eastern versus western cities. Reporting of chest illness before age 2 years, asthma symptoms, and use of home humidifiers were associated with slight increases (not statistically significant) in the OR for bronchitis associated with acidity, while parental asthma, maternal smoking during pregnancy, and environmental tobacco smoke in the home lowered the OR and reduced its significance. There was no evidence that the prevalence of asthma or asthmatic symptoms in children was associated with air pollution. The strong correlations between particle strong acidity and other particle measures make it difficult to ascribe the effects with certainty to any one of these (PSA-SO_4^{2-} r=0.90; PSA-$PM_{2.1}$ r=0.82). The correlation with ozone was relatively low by study design (r= 0.37). Thus the negative results for ozone can not be ascribed to allocation to particulate measures. The finding that bronchitis was most strongly affected by air pollution is consistent with the previous findings from the six-city study (Dockery et al., 1989), but the agent most closely associated with this was acidity in this study (Dockery et al., 1996a) instead of PM_{10} as in the smaller six-city study.

Lung function testing, including forced vital capacity (FVC), forced expiratory volume (FEV) in 1 and 0.75 sec., forced expiratory flow rate between 25 and 75% of FVC (FEF_{25-75}), and peak expiratory flow rate (PEFR), was carried out in 22 of the 24 communities with a total of 10 251 children providing at least two acceptable tests (Raizenne et al., 1996). After adjustment for height, weight, age and sex, 2 to 3.5% decrements in FVC, FEV_1 and $FEV_{.75}$ were associated with all the particle measurements, with the most marked effects for particle strong acidity (PSA), followed by $PM_{2.1}$, SO_4^{2-}, and PM_{10} in that order. FVC was most strongly affected, and PSA was associated with a 3.5% decrement (95% CI -4.9 to -2.0%) for a range increase of 52 nmol/m^3. Sulphate, $PM_{2.1}$, and PM_{10} were associated with decrements in FVC of 3.1%, 3.2% and 2.4% respectively, for range increases of 6.8 µg/m^3 (SO_4^{2-}), 14.9 µg/m^3 ($PM_{2.1}$), and 23.8 µg/m^3 (PM_{10}). When converted to a standard range increase of 10 µg/m^3 , FVC was reduced 4.5% (SO_4^{2-}), 2.2% ($PM_{2.1}$), and 1.4% (PM_{10}) respectively. The association of lung function decrements with particle strong acidity was consistent throughout the results. Only particle strong acidity was associated with decrements in FEF_{25-75} and PEFR, the associations with the other particle metrics being non-significant. However, the strong correlations between particle strong acidity and other particle metrics (e.g., PSA/SO_4^{2-} r=0.83-0.95 in east and central North America) limits our ability to distinguish which of these, if any, was independently responsible for the observed effect.

Ozone (all three measurements, 24 h, daytime, and 1 h max.) was also associated with decrements in FVC and FEV_1 (Raizenne et al., 1996). A range of 39.4 ppb daytime ozone resulted in a 3.74% decrease in FVC (95% CI -6.45 to -0.94%). Bivariate regression with PSA reduced this association to -2.2%, but significance was retained. The PSA association remained unchanged in the co-regression. This indicates that ozone has some independent association with decrements in lung function, additional to the association with PSA, but it was noted that the PSA-ozone correlation was moderate to high (r=0.45-0.61 for 1 h max., average of all communities except four Prairie communities).

No potentially sensitive subgroups in the population were identified when regressions were carried out with subgroups of children who were asthmatic, wheezy, who had had severe chest illnesses before age two, whose parent(s) had asthma (although the association here was slightly stronger), or who lived in homes with smokers. This was based on lack of appreciable differences in decrements in FVC between any subgroups and the overall mean, although all were significantly different from null. Air pollution was associated with low lung function in some children, whose measured FVC was <85% of predicted for their age, sex, and size. PSA across the 52 nmol/m^3 range of exposures was associated with a 2.5 times increase in the proportion of children whose FVC was <85% (95% CI 1.8-3.6%). This proportion was not altered by bivariate regression with ozone, but the odds of having a FVC <85% associated with the range of 38.4 ppb daytime ozone were reduced from

2.9% (95% CI 1.4-5.8) with ozone alone, to 2.0% (95% CI 1.6-2.5%) for ozone with PSA included in the regression. This represents a significant decrement in lung capacity and lung growth, development, and function in children, associated with chronic exposure to the air pollutants ozone and PSA (and probably also with several of the other particle metrics) (Raizenne et al., 1996). The data analysis carried out for this study tended to emphasize the results for particle strong acidity, without presenting the same depth of analysis for $PM_{2.5}$ or SO_4^{2-}, each of which had almost as strong an association with decreases in FVC, FEV_1 and $FEV_{0.75}$ as particle strong acidity.

A possible explanation for the lung function decrements is that air quality on the day of testing or on the several previous days was poor, and was the cause of the observed decrements. Since so many tests were conducted in a broad range of geographic locations on many different days, this is not a likely explanation for the majority of observations. However, the year of testing could also have had unusually high air pollution, which would have affected the results for some communities compared to others, since about one-third of the testing was carried out in each of the three different years in the various communities. The chronic nature of the effects was explored in several ways. The annual averages for the communities were closely comparable to regional results for 4-13 years of monitoring data for all particle metrics (except H^+, for which only one year was available). This indicates that they did represent chronic exposures (Spengler et al., 1996). Within the study itself, stratification by residence in the community since age 6 and residency since before age 2 showed that lifelong residency provided stronger links with FVC decrements (4.2%; 95% CI 2.5-5.8%) than the shorter residency of children who had moved into the community more recently, within the past three to four years (FVC -2.4%; 95% CI 1.0-4.0%).

A British cross-sectional study investigated the effect of current annual levels of air pollution, as BS and SO_2 on the prevalence of respiratory symptoms in a birth cohort of 11 552 23-year old young adults who had been born in March 1958 and interviewed in 1981 (Scarlett et al., 1995). Exposure status was by population only, on a county-wide basis (n=53). Counties were further grouped, roughly into quintiles for both measurements. Mean BS was 17.9 $\mu g/m^3$ (range 2.0-55.1 $\mu g/m^3$) , and the medians of the quintiles were 11.0, 16.4, 20.5, 22.3, and 30.2 $\mu g/m^3$. Mean SO_2 was 42.6 $\mu g/m^3$ (range 7.0-87.7 $\mu g/m^3$), and medians of the quintiles ranges from 43.0 to 50.5 $\mu g/m^3$. After adjustment for sex, social class, and smoking status, the odds ratio for prevalence of chronic phlegm was increased in all four groups (ORs = 1.36, 1.34, 1.48, 1.20) relative to the lowest group for which the median was 11.0 $\mu g/m^3$ ($p<0.01$), and the test for trend was significant. The relationship was, however, somewhat non-linear, with the OR (1.20) for the highest group lower than expected, indicating some offsetting factor in this group, and/or the possibility of a flattening of the concentration-response curve. BS had no effect on the prevalence of wheeze or cough symptoms, nor on asthma prevalence either at age 16 or at age 23. There was no evidence that SO_2 independently influenced the prevalence of any of the symptoms, but BS and SO_2 were highly correlated (r=0.61), which makes separation of their effects difficult. Smoking exerted a much greater effect on cough and phlegm prevalence and on asthma at age 16 than the air pollution indices. This study indicates that chronic or long-term exposure to particulate air pollution, as measured over the preceding year, increases the prevalence of some respiratory symptoms (not including asthma) in young adults, but that the air pollution effect was considerably less than the effect of smoking. The study could neither confirm nor refute the hypothesis that the observed effects were a residual of exposure in childhood, since few ambient measurements were available for that early period.

A longitudinal study on respiratory symptoms and lung function changes over a 12-year period was carried out with a random sample of 3948 adults aged 25 to 74 years in 1974, from the six US cities cited in other analyses (Sherman et al., 1992). At the initial and followup visits after three, six, and 12 years, subjects completed a respiratory symptom questionnaire and lung function tests (forced expiratory volume in one second – FEV_1). Sex-specific linear regression models were developed to investigate the relationship between symptoms and lung function. After adjustment for height, age and smoking status, those who reported chronic symptoms of cough and/or phlegm on the inital visit showed both a slight reduction in initial lung function and an accelerated decline in lung function. The difference between observed and predicted slope for subjects with any critical respiratory symptoms was -4.0 ml/y for males and -2.5 ml/y for females ($p>0.05$), and for cough, the decline was 5.6 ml/y for males and 4.4 ml/y for females ($p<0.001$). The effect was likely to be highly

underestimated because of the high attrition in the original cohort (52% of cohort not included) and the pronounced "survivor" effect in those who could be included. While this study does not deal directly with particulate matter-lung function associations, it sheds some light on the relationship between the prevalence of chronic symptoms and acceleration in lung function decline over time.

The effect of air pollution over a 10- to 20-year period on non-smoking adults has been examined prospectively in a cohort of non-smoking adults in California (Abbey et al., 1995a). A subcohort of 1868 individuals from the AHSMOG cohort (Adventist Health and Smog Study) who had resided since 1966 within a few miles of nine California airports were selected, and their individual cumulative exposure to $PM_{2.5}$ was calculated, based on site and season-specific estimates of $PM_{2.5}$ from airport visibility data (r=0.82), and adjusted individually by taking into account their duration of exposure, and monthly residence histories. TSP, PM_{10} estimated from TSP, SO_4^{2-}, O_3, SO_2, and NO_2 data were also estimated for each individual. A standardized respiratory questionnaire was given in 1977, and again in 1987, to all participants who had resided in their area for the past 10 years since 1966. The questionnaire also ascertained household and lifestyle characteristics (gender, age, educational status as a surrogate for socioeconomic status, occupational exposure, any previous smoking history (Adventists are non-smokers), passive smoking exposure, and history of childhood colds and/or childhood airway obstructive disease (AOD). The development between 1977 and 1987 of new cases of respiratory symptoms of AOD, chronic bronchitis, and asthma was followed in those without possible symptoms in 1977, and correlated with their previous chronic exposure in the 10 years preceding the start of the study, as well as their "current" 10 year average exposure from 1977 to 1987. The relative risk (RR) of developing new cases of chronic bronchitis was elevated at 1.81 (95% CI 0.98-3.25; p=0.058) for an increment of 45 $\mu g/m^3$ in average $PM_{2.5}$ in the years 1966-March 1977. This is equivalent to an 18% increase per 10 $\mu g/m^3$. Slight enlargement of the cohort to 1940 subjects who had resided only 80% of time instead of 100% in the same location in the 1966-77 period resulted in statistical significance being reached. An increased relative risk was also associated with an exceedance cutoff of 20 $\mu g/m^3$, a RR of 1.41 being associated with 4000 h/y (167 d/y) at or above 20 $\mu g/m^3$. A dose-response relationship was observed for new cases of chronic bronchitis, with a 53% increase in new cases for a $PM_{2.5}$ cutoff of <30 $\mu g/m^3$ versus <20 $\mu g/m^3$, and 64% for a 40 $\mu g/m^3$ cutoff versus a 20 $\mu g/m^3$ cutoff (Abbey et al., 1995a). No associations were observed between past $PM_{2.5}$ concentrations and incidence of new cases of asthma or airway obstructive disease (including emphysema, asthma and bronchitis).

The association of new cases of chronic bronchitis with past exposure was stronger than the association with the average 10-year current exposure (1977-87); the RR for the latter was not given but the t=statistic was reduced from 1.90 to 1.68. Current exposure (1977-87) to sulphate was associated with development of new cases of AOD, but not bronchitis or asthma (no measurements were available for past exposure to sulphate, 1966-1977). The development of airway obstructive disease (AOD) and/or asthma was not significantly associated with current exposure to $PM_{2.5}$, but AOD development was significantly associated with past exposure (1966-77) to TSP and PM_{10} (t=2.81 for TSP and 2.09 for PM_{10}).

The presence of possible symptoms in 1977 was highly predictive of increased RR for new cases between 1977 and 1987 of all three conditions, particularly for asthma, in which the RR was almost 26 times higher than unity. A history of childhood colds and childhood AOD also was associated with significant increases in risk for AOD and chronic bronchitis, but not for asthma.

The possibility that $PM_{2.5}$ was acting as a surrogate for one or more other air pollutants was investigated by substituting TSP, PM_{10}, SO_4^{2-}, O_3, and visibility (an indirect measure of fine particles which was used to estimate $PM_{2.5}$) into the regression analyses in place of $PM_{2.5}$ (Abbey et al., 1995a). While "current" 1977-87 SO_4 showed an association with new cases of AOD (t=2.09), and with exacerbations in symptoms of AOD and bronchitis, it was not associated with new cases of bronchitis, thus indicating that it was not a surrogate in the $PM_{2.5}$-bronchitis association ($PM_{2.5}/SO_4^{2-}$ correlation coefficient r=0.35, low-moderate). Past exposure (1973-1977) to PM_{10} and TSP gave stronger associations than $PM_{2.5}$ with development of new cases of AOD (t=2.09 and 2.81 vs. 1.37 for $PM_{2.5}$) and chronic bronchitis (t=2.08, 2.24 vs. 1.90 for $PM_{2.5}$). High correlations between these three metrics (r=0.91-0.92) made it impossible to distinguish between their effects. Ozone exposure (1977-87) was not associated with development of new cases of AOD, bronchitis or asthma, although it was strongly associated, along with all the particle

metrics, in exacerbation of asthma symptoms. Its high correlation coefficients with all the PM metrics (r=0.67-0.77) except SO_4^{2-} (r=0.38) makes it difficult to distinguish an independent effect for ozone.

Significant increases in the severity of respiratory symptoms over the 10-year 1977-87 period were also recorded for all three endpoints, in association with past 1966-77 PM_{10} exposure, except for asthma for which present 10-year exposure was more highly associated than past exposure. A number of other factors including the presence of possible symptoms in 1977, AOD in childhood, larger number of childhood colds than average, and past smoking history, were more important than air pollution in exacerbation of symptoms, however. An extensive discussion of the study limitations and sensitivity analyses to address some of these were presented. The authors' conclusions were that previous exposure to $PM_{2.5}$ >20 µg/m^3 was associated with development of new cases of chronic bronchitis, but that the associations with increasing severity of disease could have been due to surrogate relationships with TSP and PM_{10} (Abbey et al., 1995a).

12.5.3 Cancer Incidence

There are few data correlating the occurrence of cancer with chronically high air pollution, specifically with high levels of particulates. Some of the key early studies from the 1950s and 1960s were identified in a review paper by Speizer (1983). The author found that in most of these studies, potential confounders such as smoking and occupational exposure (radiation and asbestos) were not adequately controlled for. These factors were found to have a far greater impact than air pollution on lung cancer rates. The author concluded that the likely effect of air pollution on lung cancer was something greater than zero, but that the estimate was unlikely to exceed 2% of all lung cancers, or 5/100 000 cases in urban males. Thus, the effect on all cancers was considered likely to be less than 1% of all cases. The cancer risk related to general air pollution has been considered to be so low relative to other risks that the time and expense involved in conducting studies large enough to demonstrate the possible low relative risk have not been warranted. In addition to this, levels of pollution have declined significantly over the past 25 years in most parts of the industrial world (Speizer, 1983).

The correlation between air pollution and lung cancer mortality in Harris County (includes Houston), Texas, between 1979 and 1981 was re-examined by Buffler et al. (1988) in an cross-sectional analysis. Previous reports had been published asserting that the high incidence of respiratory cancer among white males in Houston, Texas, provided evidence that exposure to air pollution increased the risk of respiratory cancer. These reports had provided no actual air pollution data or any proper controls for potentially confounding variables, such as smoking, occupation or socio-economic status. After controlling to an extent for smoking status, socioeconomic status and migration for each census tract division (n=249), and including available air pollution data on TSP (but no other air pollutants), the estimated increase in lung cancer deaths for the TSP range of 16 µg/m^3 between the median of the lowest to the median of the highest quartile was 1.9 per 100 000 white males (the total range for TSP was 58.8 to 83.6 µg/m^3). However only 3% of the total variation in lung cancer mortality was explained by TSP. The authors concluded that air pollution in the study area was not a strong determinant of lung cancer mortality and that, unless other risk factors for lung cancer such as smoking could be better controlled for, the hypothesis of an association between air pollution and lung cancer could not be tested.

Lung cancer mortality has occasionally been reported as elevated in daily time-series analyses, a somewhat unexpected association in view of the long latency period required for development of most cancers. For example, in Philadelphia, the RR for dying of lung cancer on the 10% of days with the highest TSP values (mean 141 µg/m^3) was elevated to 1.19 compared to the 10% of days when TSP was lowest (mean 47 µg/m^3) (Schwartz 1994d). This is likely a manifestation of the enhanced effect of particulate and other air pollution on those with pre-existing respiratory conditions, rather than any chronic effect.

Mills et al. (1991) examined cancer incidence and mortality in a cohort of 6300 Seventh-Day Adventist non-smokers in California (the AHSMOG cohort) over a six-year period (1977-1982) in relation to concentrations of TSP and ozone. Residence history since 1960, percentage of time spent outdoors and indoors, commuting time, history of exposure to passive smoking, past smoking history, occupational exposure, and history of respiratory disease were determined individually by questionnaire. After adjustment for age, sex, and past smoking history, increased frequencies of exceedance of various cutoffs of TSP from prior exposure (1973-1977) were

most closely associated with increases in the risk of all cancer incidences combined among females, for whom the largest increases in risk estimates were observed to occur in the smoking-related respiratory cancers (larynx, lung, pleura). The coefficient associated with mean concentration of TSP (99.7 μg/m^3) increased three-fold from 0.0053 to 0.016 after adjustment for indoor exposure (mean TSP 44.1 μg/m^3). An increased risk was not observed in males. Elevations in cancer risk were observed at TSP concentrations of 100 μg/m^3 for 1000, 2500, or 5000 h/y exposure (42,104, or 208 days) but not at 75 μg/m^3 or 60 μg/m^3 cutoffs. Analysis of cancer mortality (180 deaths in the 10-year mortality follow-up period, 1977-86) revealed somewhat stronger associations in males compared with females. This was somewhat inconsistent with the results for incidence, in which females showed associations while males did not. It was also suggested that TSP may not be the best measure of particulates in determining health effects, and $PM_{2.5}$ was recommended as a possible alternative.

In an updated report (Abbey et al., 1995b) which included TSP, PM_{10}, and $PM_{2.5}$ measurements from 1973 to 1987, the relative risk for incidence of all cancers in females was increased to 1.37 (95% CI 1.05-1.80) for TSP with 42 days/yr>200 μg/m^3. For PM_{10} at 42 days/yr >100 μg/m^3, the RR was marginally increased (RR=1.15; 95% CI 0.97-1.38) This reduced strength of association for PM_{10} could have been due to measurement error, since PM_{10} was estimated from TSP for a portion of that time. Although the RR was doubled for females in association with an average annual increase of 45 μg/m^3 $PM_{2.5}$, the result should be viewed with caution due to the small size of the subcohort for which $PM_{2.5}$ data were available (n=1800), and the consequent wide confidence intervals (RR=2.01; 95% CI 1.05-3.86). The RR for respiratory cancer incidence was also increased for exposure to TSP, PM_{10}, and $PM_{2.5}$, but the increases all included a RR of 1 (Abbey et al., 1995b). These results were based on relatively few cases of newly diagnosed cancers (n=301) and respiratory cancers (n=17) which contributed to the weakness of the findings, especially when subsets were examined.

In a study by Dockery et al. (1993), already reviewed in section 12.5.1 above, the authors examined the association between air pollution and cancer mortality over a 14- to 16-year period in six US cities. After adjustment for age (5 y age groups), sex, education as a surrogate for socioeconomic status, occupational exposure, and smoking status both present and past, the Relative Risks (RRs) for the association between mortality due to lung cancer and particles (fine and inhalable), as well as the other pollutants were slightly elevated, but the confidence intervals were broad. The RR for the association with fine particles was 1.37 (95% CI 0.81-2.31) for a range of 18.6 μg/m^3 , or 19.9% for a 10 μg/m^3 increase in $PM_{2.5}$). Smoking was found to be the factor most strongly associated with mortality due to lung cancer; the RR for current smokers was 8.4 (95% CI 3.0-21.6), six times the overall RR, and the RR for former smokers was 1.9 times the RR for the most versus the least polluted city. Only 8.4% of the total of 143 deaths were due to lung cancer. This probably contributed to the high variance and lack of statistical significance for the increased RR for lung cancer.

The 151-city ACS cohort study (Pope et al., 1995a) also reported an association between sulphates and lung cancer mortality, but not with the more general index of fine particles ($PM_{2.5}$). The total adjusted mortality risk ratio for a range of 19.9 μg/m^3 SO_4^{2-}, adjusted for age,sex, race, cigarette smoke, occupational exposure, education as a surrogate for socioeconomic status, body-mass index, and alcohol use, was 1.36 (95% CI 1.11-1.66), or 18.1% for an increase of 10 μg/m^3 SO_4^{2-}. When the cohort was subdivided by sex and by smoking history, a part of the increase in risk was seen to be due to increases in males, and in never-smokers, although the RR was elevated but non-significant in women and in never-smokers. The results of this study agreed broadly with the results in the much smaller cohort study of Dockery et al. (1993), that increases in fine particle pollution lead to increases in mortality due to lung cancer, but this study found no effect of $PM_{2.5}$ itself, only of the SO_4^{2-} fraction of fine particles. The magnitude of the effect was virtually the same in the Pope analysis for SO_4^{2-} (18.1%) as that in the Dockery analysis for $PM_{2.5}$ (19.9% for an increase of 10 μg/m^3).

12.5.4 Summary of Long-Term or Chronic Exposure Effects on Mortality and Morbidity

In contrast to the large number of studies on daily variations in pollution associated with mortality and morbidity, relatively few studies are available that examine the effects of long-term or chronic exposure on health endpoints. Such exposures, varying between one and 16-20 years duration, were demonstrated to be associated with increases in mortality,

lung function, respiratory disease symptoms, and lung cancer in both cross-sectional and prospective cohort studies, which are considered to provide greater weight of evidence than cross-sectional studies. Drawing conclusions regarding community effects from the population-based cross-sectional studies generally has been difficult due to the inability to account for personal demographic and socio-economic factors, all contributing to the probability of confounding of the results. However, several new prospective cohort studies, in each of the three endpoints examined (mortality, respiratory health and lung function, and cancer), have been able to include some of these factors, thus avoiding to some extent at least, the probability of confounding. They have thus been able to shed some additional light on the effects of longer term and/or chronic exposure on health. With respect to exposure, however, all studies (with the partial exception of the Abbey et al. studies (1995a,b)) were still reliant on population-based exposure calculations.

In both of the prospective cohort mortality studies, the probability of survival over a 7 to 16-year period was reduced for people living in the most polluted city compared to the least polluted city, based on the Cox proportional hazards model (Dockery et al., 1993; Pope et al., 1995a). In the six-city study by Dockery and colleagues (1993), the probability of survival over a 14-year period was reduced from approximately 88 to 79%, and represented a four-year shortening of lifespan between the most and the least polluted city, or about two years for the mean pollutant level, based on the graphical presentation of survivorship curves for each of the six cities. An important point illustrated by this analysis is that mortality is not only a matter of "harvesting" or shortening by a few day or weeks the lives of those who are already ill, but that the lifespan is significantly shortened, and moreover, by several years.

In the six-city study, average mortality was increased by 10%, 14% and 32% for each 10 $\mu g/m^3$ increase in PM_{15}, $PM_{2.5}$ or SO_4^{2-}, while the mortality increases were much smaller, 6.9% for $PM_{2.5}$ and 7.5% for SO_4^{2-} (10 $\mu g/m^3$ increase) in the much larger (Pope et al., 1995a) study. In addition to its much greater geographic coverage (151 cities instead of six cities) and inclusion of many more individuals (552 000 versus 8100), more potentially confounding factors were included. The lower risks calculated in this study are therefore considered to be the more accurate of the two. The two cross-sectional studies also support the particulate-mortality association with a relative risk for increased mortality (10 $\mu g/m^3$ increase) of 4.3% for $PM_{2.5}$ and 8.2% for SO_4^{2-} in Ozkaynak and Thurston (1987), and 9.8% for $PM_{2.5}$ and 12.6% for SO_4^{2-} in the cross-sectional study reported in Pope et al. (1995a) which was the companion to the latter authors' cohort study.

Annual variations in particulate air pollution and ozone were associated with reduced lung function in children in a large cohort study in 22 communities in the US and Canada (Raizenne et al., 1996). The annual values were also shown in an accompanying exposure analysis to be representative of the children's chronic exposures over most of their lives (Speizer et al., 1996). Decrements in FVC ranged from 2.4% to 3.5% for the four particle metrics, with particle strong acidity showing the strongest associations. Moreover, acidity was associated with a 2.5 times increase in the proportion of children whose FVC was less than 85% of the predicted value for their age, sex and height. Co-regression with ozone did not alter this proportion, but ozone was shown to have an independent, if smaller association. Other lung function parameters were also affected, but to a lesser extent than FVC. The study results indicate that significant decrements in lung capacity, lung growth, development, and function result from chronic exposure of children to air pollutants. These results contrasted with the results of an earlier cross-sectional study by the same research group on 5400 children in only six cities, in which no effects on lung function were found in association with particulate air pollution (Dockery et al., 1989), probably due to the low power of the earlier study to detect an effects-on-lung-function-as-result of the numbers of observation (six cities).

Respiratory health was also found to be adversely impacted by particulate air pollution in several studies, in both children and adults. The cohort study on over 13 000 children in 24 US and Canadian communities in whom lung function decrements had been demonstrated, also showed that the odds ratio for developing bronchitis in the past year was elevated for communities with high acidity (OR=1.66 for a range of 52 $nmol/m^3$) and high sulphate levels (OR=1.65 for a range of 7 $\mu g/m^3$) (Dockery et al., 1996a). Asthma, wheeze and other asthmatic symptoms, chronic cough and phlegm production were not significantly affected by high particulate levels. There was a suggestion that asthma and prior respiratory disease, as chest illnesses before age 2, may have

played some role in elevation of the bronchitis OR, since they were also associated with non-significant increased OR for bronchitis. The findings of increased OR for bronchitis associated with particles were consistent with the previous findings from a smaller cross-sectional study on six cities by the same authors (Dockery et al., 1989), but in that study, PM_{15} was the particle most closely associated with effects on health (no fine particle metrics were available), while in the newer cohort study, acidity, and to a lesser extent, SO_4^{2-} gave the strongest associations. The "asthma effect" was also much more marked in the earlier study, and it was clear that most of the excess bronchitis in the most polluted cities was being reported by children with asthma.

Annual exposure to BS increased the OR for prevalence of phlegm, but not of asthma, wheeze or cough symptoms, in a cross-sectional analysis of a British birth cohort of young adults, aged 23 years (Scarlett et al., 1995). The effect of asthma or other respiratory diseases in childhood on prevalence of symptoms in adulthood was not investigated, although it was apparent that asthma at age 16 had no effect on asthma prevalence seven years later.

The development of new cases of chronic bronchitis was shown to be associated with 10- to 20-year (chronic) exposures to estimated $PM_{2.5}$ in excess of 20 $\mu g/m^3$ in a cohort of 1863 non-smoking older adults (average age 48 y) in California who were followed prospectively for 10 years from 1977 to 1987 (Abbey et al., 1995a). Exposures in this cohort were calculated individually, taking into account lifestyles, time-activity, indoor exposure and history of residence and occupation. For a 45 $\mu g/m^3$ increase above the mean, the RR for development of chronic bronchitis was 1.8, which is equivalent to a 17.7% increase in incidence per 10 $\mu g/m^3$. Relative risks for new cases of airway obstructive disease (AOD) and asthma, although elevated, were not significant because the number of new cases was small. Those who gave some indication of possible pre-existing disease or susceptibility in the first survey were three times as likely to have developed new cases of chronic bronchitis or AOD, and 15 times more likely to have developed asthma. A previous high incidence of childhood respiratory disease was also linked to increased risk of new cases of AOD or chronic bronchitis in these older adults, similar to the findings of Dockery et al. (1989, 1996a) in children. Significant increases over the 10-year period were also recorded in the severity of the symptoms for all three endpoints in association with PM.

Lung cancer appeared also to be associated with increased exposure over long periods to some component(s) of the fine fraction of particulate matter in the two cohort mortality studies previously examined. In the six-city study (Dockery et al., 1993) the mortality incidence of lung cancer over a 16-year period was increased 19.9% for each 10 $\mu g/m^3$ increase in $PM_{2.5}$, but the increase was not statistically significant, probably due to the few units of observation in this study. PM_{10} and sulphate results for lung cancer mortality were not presented. The larger cohort study of Pope et al. (1995a) found a similar increase of 18.1% in lung cancer (statistically significant in this case) over a seven year period for each 10 $\mu g/m^3$ increase in SO_4^{2-}, but $PM_{2.5}$ was not a significant predictor of cancer mortality in this cohort, in contrast to the six-city results. The remaining cohort, the AHSMOG cohort of Seventh Day Adventists (Mills et al., 1991), gave inconsistent results with respect to lung cancer as related to TSP, possibly because of the use of this coarse particle measurement, and possibly also because of the relatively small size of the cohort combined with the short followup period of six years. Although smoking, past and present, was taken into consideration in all three studies, it exerts such a strong influence on lung cancer rates (for example a relative risk of 8.0 for current smokers in the six-city study) that the possibility of residual confounding cannot be dismissed with respect to the associations seen between particles and lung cancer.

Cross-sectional or prospective cohort studies that examine annual or longer averages in exposure are usually interpreted as indicating the chronic or cumulative effects of exposure. The health consequences of chronic exposure to air pollution, whether the effect is due to cumulative exposures, to some time-window of past exposure, or to residual damage caused by a large number of individual events, have not been as easy to distinguish as acute adverse effects from single day or short-term exposures. It is clear that exposure to air pollution over a period of years results in a substantial reduction of survival, in the order of several years. This reduction cannot be merely a "harvesting" of persons who would have died anyway within a few days or weeks, since the survivorship data are incompatible with such an interpretation. It also seems reasonable that, if highly susceptible persons die on days with elevated

pollution levels, there could also be induction of some residual chronic health effect(s) in the survivors. However, the cohort mortality studies do not provide information on this aspect, since either long-term (low) exposure or a long series of acute exposures would be expected to result in the same observed effects on mortality in these studies (Vedal 1996). However, a few additional endpoints strongly suggest chronic toxicity effects. These include the development of new cases (increased incidence) of chronic disease, increasing severity of an adverse effect over time, more rapid loss of function in adults than is the expected case, reduced pulmonary growth rates in children, and lung cancer. Results from studies that have investigated these effects are discussed below.

The development of new symptoms of chronic respiratory disease (such as chronic bronchitis), as noted above, suggests the results of chronic exposure. Many of the time-series studies on acute effects have inferred that symptoms of respiratory disease are manifested entirely in those with pre-existing conditions. Development of new disease in older (mean age 48 y) adults without pre-existing symptoms in response to past chronic exposure was clearly shown in the AHSMOG cohort study (Abbey et al., 1995a). An 18% increase was observed in new cases of chronic bronchitis per 10 $\mu g/m^3$ increment in average $PM_{2.5}$ measured for the 10-year period before the study began. The development of airway obstructive disease was also linked to past exposure to TSP and PM_{10} in the four years preceeding the start of the study. Development of chronic bronchitis has also been observed in children, in association with long term exposure to increases in PM_{15} (Dockery et al., 1989), SO_4^{2-}, and particle strong acidity, the latter providing the strongest association (Dockery et al. 1996a). Although measurements were taken for only the year preceding the study, these were shown to be representative of concentrations for the past four to 13 years in the 24-city study (except for PSA, for which only the one year of measurements were available), and thus could be considered to be representative of the children's entire lifetime exposure. Moreover, stratification of the samples by length of residency in the communities showed that life-long reidence was associated with a greater decrement (4.2%) in forced ventilatory capacity (FVC) than residency for only the past three to four years (2.4% decline). It is possible that part or all of the new development of disease was due to pre-existing genetic susceptibility, but the lack of association with parental asthma does not support this hypothesis well. The increased incidence of disease in childhood appears to have additional chronic effects due to carryover of increased susceptibility into adulthood, as observed in the association of increased respiratory illnesses and/or airway obstructive disease as a child with increased odds for development of chronic bronchitis or airway obstructive disease in adulthood (Abbey et al., 1995a).

Over a period of 10 years, increases in severity of respiratory symptoms for airway obstructive disease, chronic bronchitis, and asthma was shown in the Adventists' prospective cohort to be associated with both past and concurrent 10-year average particle concentrations (TSP, PM_{10}, $PM_{2.5}$, and SO_4^{2-}) ; increases in severity of asthma were additionally associated with ozone and visibility (Abbey et al., 1995a).

Decrements in lung function were observed in children in the 24-city study, and increased odds of having a forced vital capacity (FVC) less than 85% of normal were associated with particle strong acidity and ozone (results were not reported for other particle metrics), and the odds were increased by 2.5 times in the most, compared to the least polluted city (Raizenne et al. 1996). This represents a significant decrement in lung growth and capacity, development, and function in children associated with chronic exposure to air pollution. The longitudinal study on lung function declines in adults from one of the six-city analyses demonstrated that age-related lung function declines were accelerated in those who had reported symptoms of chronic cough 12 years previously (Sherman et al., 1982). The Abbey et al. (1995a) results from the Adventist cohort provide a link between these accelerated lung function declines in adults and the occurrence of symptoms of chronic respiratory disease associated with chronic exposure to particles.

Lung cancer is manifested only after a long latency period, and is generally considered to be a multi-step process leading to a chronic condition. In both the prospective cohort mortality studies (six-city and ACS), lung cancer rates in cities with more air pollution were higher than rates in less polluted cities, and were about the same, per 10 $\mu g/m^3$ increase, for $PM_{2.5}$ in the six-city study as for SO_4^{2-} in the 151 city ACS study (Dockery et al., 1993; Pope et al., 1995a). Thus the lung cancer results give limited support for a role for particulate matter air pollution in elicitation of chronic effects.

12.6 REVIEW STUDIES, PRIMARILY ON PM_{10}

Because of the large number of recently published studies linking particulate matter concentrations in the environment to observed health effects in the general population, several review papers evaluating the data have been published.

A review of the health effects of particulates was carried out by Withey (1989). The author stated that numerous confounding variables, such as personal habits, weather, climate and lack of definite thresholds, have made correlations between exposure and response, as well as selection of protective or acceptable levels of particulate pollution, very difficult to determine. Recognizing this, the author also recommended that further research should use modern multivariate statistical methods and improved analysis of data to refine and improve the definition of the dose-respose relationship. It was also acknowledged that there existed special sensitive subgroups, such as young children, the elderly and those with COPD. Furthermore, based on some of the data reviewed, it could be concluded that long-term exposure to high levels of particles has been shown to induce or accentuate heart and lung disease (Withey, 1989).

Pope et al. (1995b,c) reviewed approximately 70 references published since 1985, which focussed not only on the health effects of PM_{10}, but also on all measurements of particulates. These consisted of acute and chronic morbidity and mortality studies evaluating particulate levels commonly observed in cities across a wide geographical spectrum and were considered by the author to be competently carried out. Based on evaluation of the data, it is evident that there exists a wide variety of health endpoints associated with particulate levels, including decreased lung function, increased hospitalizations, health care visits for cardiopulmonary disease, increased respiratory morbidity (as measured by absenteeism from work or school or other restrictions in activity) and increased cardiopulmonary disease mortality. Health effects were reported at levels common to a number of both US and Canadian cities, where no threshold could be identified. There appears to be evidence to support a linear dose-response relationship. Future research was recommended, to be directed at finding a biological mechanism to help answer why particles have been so closely linked to these measures of morbidity and mortality.

A review and meta-analysis of 13 studies reporting associations between particle exposure and mortality were carried out by Schwartz (1994e). These studies associated short-term changes in particulate air pollution with short-term changes in daily mortality in their respective study locations. A meta-analysis was conducted by analyzing the measure of the effect and computing an average coefficient, an estimated standard error for that coefficient and often a weighted average. Several criteria were taken into account in assessing these time-series studies, such as potential for confounding by other pollutants, quality of exposure assessment (measurement size and location of monitoring) and quality and quantity of levels of temperature and humidity (weather data) in the cities under study. Results showed that the unweighted meta-analysis of all the studies resulted in a relative risk of 1.06 (95% CI=1.05-1.07) for a 100 $\mu g/m^3$ increase in TSP mass. The most likely sources of potential confounding, such as infectious diseases, weather and other pollutants, were discussed at length with respect to the specific studies. The evidence suggested that it is unlikely that the observed associations resulted from any of the confounders.

A review and analysis of several cross-sectional and time-series studies examining the occurrence of daily fluctuations in air pollution and mortality were conducted by Ostro (1993). For inclusion in the meta-analysis, certain criteria had to be met, such as proper study design and methodology, minimal confounding and omitted variables, concern for the effects of seasonality and weather and acceptably complete analysis of the data. Because of varying measures of particulate matter used in the different studies, general estimates of the relationships between the measurements were used. The authors concluded that the studies generated consistent results. The means of the estimated effect on mortality of a 10 $\mu g/m^3$ change in PM_{10} implied by these studies ranged between increases of 0.31 and 1.49%, with a mean of 0.96%. The means of the lower and upper bound estimates were 0.63% and 1.30%, respectively. Evidence for specificity of effects was also demonstrated, as most of the studies demonstrated an association with disease-specific mortality, such as respiratory or cardiovascular diseases.

Wood smoke has been associated with adverse effects on health and is made up of inhalable particles as well as PAHs, CO and a large group of other compounds, including hydrocarbons and NO_2. Vedal

(1993) and Larson and Koenig (1995) reviewed and summarized evidence relevant to an assessment of the human health effects of wood smoke. The component of wood smoke that is of most significance in causing adverse health effects is fine particulate matter. Exposure to wood smoke has been shown to increase the risk of serious respiratory illness in children and to cause decreases in children's lung function, with asthmatic children probably being more susceptible. Mutagenicity studies such as the Ames bioassay and sister chromatid exchange have identified wood smoke as a mutagen. In the case of combustion emissions, mutagenicity and carcinogenicity seem to be highly correlated, inferring that the carcinogenicity of wood smoke particles is due to their ability to cause mutations. Inhalable particles such as those contained in wood smoke have been associated with a number of health effects, ranging from reduced pulmonary function in children to increased mortality. Levels of particles found in regions of British Columbia that have been attributed to wood smoke may be high enough to cause adverse respiratory health effects. Exposure to wood smoke is estimated to cause substantial morbidity in terms of increased respiratory symptoms and functional limitations. Wood smoke is also thought to cause increases in emergency room visits for asthma, increases in respiratory hospitalizations and excess mortality, although the extent of the impact of these effects on the general population is estimated to be relatively small.

12.7 REVIEW OF FINE PARTICLE EFFECTS

Ambient particulate matter is composed of a heterogeneous mixture of particles varying in size and chemical composition. The attributes that determine the toxicity of particles are very little known. The size distribution of particles is a very important determinant of inhalability and eventual deposition within the respiratory tract. It has been recognized that in order to be inhalable and to reach the tracheobronchial area of the respiratory tract, particles must be smaller than about 10 µm in diameter. Particles 2 to 3 µm and smaller are able to reach the alveoli in the distal parts of the lung, and have been termed "respirable". It thus seems reasonable to assume that these and smaller particles may be more pathogenic than larger particles. Also, particles generated by combustion processes appear to be more pathogenic than airborne dust from crustal origins. The former are mostly in the smaller size fractions, while the latter are generally larger. The chemical composition of particulate matter (for example, sulphates, nitrates, or acids) which varies greatly according to source, has also been hypothesized to play an important role in its toxicity. The number of particles, rather than their mass, has also been suggested as an important determinant of toxicity, since large numbers of very small particles have a very high surface to volume ratio. They therefore present greater opportunities for surface adsorption of toxic substances such as heavy metals or PAHs, and subsequent deposition deep in the lung. Regulatory agencies have therefore begun to turn their attention to the finer inhalable particles, at or below about 2.5 µm in diameter, since strategies to reduce or prevent adverse impacts of air pollution on public health are more likely to be successful if focussed on fine particles of some kind.

A review of the evidence that the fine particle fraction is the critical size range determining the adverse health effects that have been associated in epidemiological studies with increases in airborne particles was commissioned by Health Canada in 1996, and prepared by Dr. S. Vedal, of the University of British Columbia. This section is based partly on that review (Vedal 1996).

The most valuable health studies for the purpose of attributing effects to a specific particle size and composition are those studies in which several particle measures were employed, and particularly if these were not too highly correlated with each other. Typically, when PM_{10} and $PM_{2.5}$ concentrations are both measured, it is often not possible to distinguish the effects of one from another, because $PM_{2.5}$ is a part of $PM_{10,}$ and is usually highly correlated ($r \geq 0.6$). However, the coarse fraction of PM_{10} larger than 2.5 µm is often not highly correlated to $PM_{2.5}$ because it stems from different sources than the finer fraction. A few recent carefully conducted studies that included large data sets, have directly compared the coarse fraction of PM_{10} and fine inhalable particles.

Table 12.6 presents data on recent studies on acute and long-term effects on mortality of both fine and coarse particle measures. Because sulphates, which are secondary products of combustion processes, have consistently shown correlation with adverse health endpoints, they have been included in the table along with $PM_{2.5}$. Particle strong acidity, as H^+, has also been suggested, partly on the basis of evidence from animal toxicity studies, as a good candidate agent for the observed health decrements during air pollution episodes.

Table 12.6 Comparison of Fine Particle Effects with Coarse Particle Effects – Mortality

Location (reference)	Study Type Duration	Fine Particles mean (µg/m^3)	% Change/10 µg/m^3 increase (95% CI)	CP ($PM_{2.5-10}$) (PM_{10}) (µg/m^3)	% Change/10 µg/m^3 increase (95% CI)	other pollutants, correlations PM interactions
Effects of acute exposures (daily, several days, or weekly) on mortality						
St Louis, MO, US (Dockery et al., 1992)	time series 1 yr. 1985-86	$PM_{2.5}$ 17.7 SO_4^{2-} 8.0 H^+ 9.7 nmol/m^3	1.5% (0.0 to 3.7%) 6.3% (n.s. t=1.05) 0.9% (n.s. t=0.73)	$PM_{2.5-15}$ (not given) (PM_{10} 27.6)	"effects no different than $PM_{2.5}$" (1.5%, t=2.17) +ve	SO_2 - n.s. NO_2 - n.s. O_3 - n.s. order of significance: $PM_{2.5} \approx PM_{15-2.5} \approx PM_{10} > SO_4^{2-} > H^+$
Kingston-Harriman, TN (Dockery et al., 1992)	time series 1 yr. 1985-86	$PM_{2.5}$ 21.0 SO_4^{2-} 8.7 H^+ 36.1 nmol/m^3	2.3% (n.s. t=1.23) 8.3% (n.s. t=0.67) 0.2% (n.s. t=0.31)	$PM_{2.5-15}$ (not given) (PM_{10} 30)	effects same as $PM_{2.5}$, i.e. n.s. (1.6% , n.s., T=1.07) n.s.	SO_2 - n.s. NO_2 - n.s. O_3 - n.s.
Philadelphia, PA (Dockery et al., 1996b)	time series summers, 1991-92	$PM_{2.5}$ (mean not given) H^+ (mean not given)	2.0% (0.4 to 1.35%) n.s. (p=0.57)	$PM_{2.5-10}$ (not given) (PM_{10} not given)	(p=0.85) n.s. 1.2% (p=0.06) marginal	order of significance: $PM_{2.5} > SO_4^{2-} > PM_{10} > H^+ > PM_{10-2.5}$
6 US cities – overall (Schwartz et al., 1996a; US EPA 1996)	time series 8 yrs., 1979-87	$PM_{2.5}$ 14.7 SO_4^{2-} 5.8 H^+ 10 nmol/m^3	1.5% (1.0 to 1.9%) 2.2% (1.3 to 3.2%) n.s.	$PM_{2.5-10}$ 9.0 (PM_{10} 25.0)	0.4% (-1.0 to +1.0%) n.s. 0.8% (0.5 to 1.0%) +ve	PM correl. high; no coregressions Order of significance (by RR for IQR): $PM_{2.5} > PM_{10} > SO_4^{2-} > PM_{10-2.5} \approx H^+$
(6-city) Portage, WI	(see above)	$PM_{2.5}$ 11.2	0.5% (-1.2 to 2.3%)	$PM_{2.5-10}$ 6.6 (PM_{10} 17.8)	0.5% (-1.2 to 2.3%) n.s. -0.7% (-0.4 to 1.7%) n.s.	r=0.32, $PM_{2.5}$-CP
(6-city) Topeka, KN	(see above)	$PM_{2.5}$ 12.2	-1.3% (-3.3 to 0.6%)	$PM_{2.5-10}$ 14.5 (PM_{10} 26.7)	-1.3% (-3.3 to 0.6%) n.s. -0.5% (-2.0 to 0.9%) n.s.	r=0.29, $PM_{2.5}$-CP
(6-city) Boston, MA	(see above)	$PM_{2.5}$ 15.7	2.2% (1.5 to 2.9%)	$PM_{2.5-10}$ 8.8 (PM_{10} 24.5)	0.2% (-0.6 to 1.2%) n.s. 1.2% (0.7 to 1.7%) +ve	r=0.23, $PM_{2.5}$-CP
(6-city) St. Louis, MO	(see above)	$PM_{2.5}$ 18.7	1.1% (0.4 to 1.7%)	$PM_{2.5-10}$ 11.9 (PM_{10} 30.6)	0.2% (-0.7 to 1.1%) n.s. 0.6% (0.1 to 1.0%) +ve	r=0.45, $PM_{2.5}$-CP
(6-city) Knoxville, TN	(see above)	$PM_{2.5}$ 20.8	1.4% (0.2 to 2.6%)	$PM_{2.5-10}$ 11.2 (PM_{10} 32.0)	1.0% (-0.6 to 2.6%) n.s. 0.9% (0.1 to 1.8%) +ve	r=0.44, $PM_{2.5}$-CP
(6-city) Steubenville, OH	(see above)	$PM_{2.5}$ 29.6	1.0% (-0.1 to 2.1%)	$PM_{2.5-10}$ 16.1 (PM_{10} 45.6)	2.4% (0.5 to 4.3%) ve 0.9% (0.1 to 1.6%) +ve	r=0.69, $PM_{2.5}$-CP
Buffalo, NY (Gwynn et al., 1996)	time series 2.5 yrs, May 1988-October 1990	SO_4^{2-} (not given) H^+ (not given)	(~12% for max-mean) (~22% for max-mean)	CP not separated (PM_{10} est. from 6-d monitoring)	— (~12% for max-mean)	O_3, NO_2 ,CO also sign for total mortality, SO_2. n.s. None signif. for resp. mort. Both H^+ and gases associated in multiple regression. Order $H^+ > SO_4^{2-} > PM_{10} >$ CoH

Table 12.6 Comparison of Fine Particle Effects with Coarse Particle Effects – Mortality *(continued)*

Location (reference)	Study Type Duration	Fine Particles mean (μg/m^3)	% Change/10 μg/m^3 increase (95% CI)	CP ($PM_{2.5-10}$) (PM_{10}) (μg/m^3)	% Change/10 μg/m^3 increase (95% CI)	other pollutants, correlations PM interactions
Amsterdam, NL (Verhoeff et al., 1996)	time series 7 yrs, 1986-92	BS 12 (BS are FP, size to 7μ but underest. SO_4^{2-}, NO_3 etc.)	1.9% (0.2 to 3.8%) +ve (1.8% +O3 ; 2.7% +SO^2; 2.0% +CO)	— (PM_{10} 38)	— 0.6% (-0.1 to 1.4%) marg	O_3 (lag 2d) 0.5% (.0 to 1%) O_3 RR reduced to 0.3% +BS; O_3RR same + PM_{10}, but both n.s. SO_2, CO n.s. alone or with BS, PM_{10} Order of significance: BS >PM_{10}
Paris, France (Dab et al., 1996)	time series 6 yrs, 1987-92	BS 31.9	0.7% (-0.25 to 1.8%) n.s.	(PM_{13} 50.8)	1.7% (0.4 to 3.1%) +ve	SO_2 (1 h) 0.85% (0.1 - 1.6%) singly O_3 (1 h, 24 h), NO_2 (1 h, 24 h) n.s. no correl. Coeff., no coregressions Order of significance: PM_{10} >BS
Effects of longer term or subchronic exposure on mortality						
6 cities, US (Dockery et al., 1993)	prospective cohort 14-16 yrs follow-up, 1974-91	$PM_{2.5}$ 16.8 (median) SO_4^{2-} 7.3 (") H^+ 15 (") (nmol/m^3) non-SO_4^{2-}- $PM_{2.5}$ (n.g.)	(rate ratio incr., low-high) 14% (3-27%) 35% (7-66%) n.s. 29% (19-38%)	$PM_{15-2.5}$ n.g. (PM_{15} 28.9) TSP 53 (TSP 1970>100)	(increase in rate ratio, low-high cities) 19% (-9 to +57%) n.s. 9% (3 to 17%) +ve 4% (-0.001 to 9%) n.s. 1% (0 to 3%) weak+ve	no co-regressions. Correlation coefficients not shown, but generally high (reason for no coregression) O_3 (24 h) n.s. SO_2, NO_2 significant,; rate ratios (10ppb) =1.10, 1.13 resp. and lower conf. limits 1.00 (both) Order of significance: $PM_{2.5}$-SO_4^{2-} > $PM_{2.5}$>SO_4^{2-}>PM_{15}>TSP >$PM_{10-2.5}$> H^+
151 metro areas, US (50 for $PM_{2.5}$, 151 for SO_4^{2-}) (Pope et al., 1995a)	prospective cohort 7.3 yrs follow-up, Sept 1982-end 1989	$PM_{2.5}$ 18.2 SO_4^{2-} 11.0	6.6% (3.6 -9.9%) 7.2% (4.4-10.5%)	no other PM measures	—	no consideration of any other PM or gaseous air pollutants Order of significance: SO_4^{2-} >$PM_{2.5}$
50 and 151 metro areas as above, US (Pope et al., 1995a)	cross-sectional 1980 data	$PM_{2.5}$ 18.2 SO_4^{2-} 11.0	9.2% (CI not given) (8.0+1.4 deaths/y/10^5) 11.9% (CI n. given) (10.5+1.3 deaths/y /10^5 per μg/m^3)	no other PM measures	—	no consideration of any other PM or gaseous air pollutants Order of significance: SO_4^{2-} >$PM_{2.5}$
98 metro areas, US (38 areas with FP, IP) Ozkaynak and Thurston (1987)	cross-sectional 1980 data	$PM_{2.5}$ 19.9 (meas.) 23.1 (est.) SO_4^{2-} 11.1	4.3% (on meas. $PM_{2.5}$) (3.7+1.7 deaths/y/10^5) (3.0+1.3 deaths/y/10^5) 8.2% (7.0+1.4 deaths/y/10^5)	no CP separately PM_{15} 37.8(meas.) 47.6 (est.) TSP 77.6	— 1.9% (meas. PM_{15}) (1.6±0.8 deaths/y/10^5) marg (0.7±0.4 deaths/y/10^5) marg 0.35% (0.4±0.3 deaths/y/10^5) ns	When SO4co-regr. with all others, β increased to 7.5 deaths/y/10^5, others n.s. Correl. coeff., SO_4^{2-}-$PM_{2.5}$ high: r=0.65. r<0.14 for PM_{10}, TSP Order of significance of regre. coeff. SO_4^{2-} >$PM_{2.5}$ >PM_{15} >TSP

One of the most interesting reports on the relative effects of a wide range of particle metrics comes from the recent extension and re-analysis of the six-city acute mortality data (Schwartz et al., 1996a; US EPA 1996). Coarse particles (CP), as the fraction between $PM_{2.5}$ and PM_{10} in size, were measured and compared directly to PM_{10}, $PM_{2.5}$, SO_4^{2-}, and H^+. While $PM_{2.5}$ (median 14.7 µg/m^3) was associated in the overall results for all six cities with a 1.5% increase (95% CI 1.1 to 1.9%) in total mortality per 10 µg/m^3, coarse particles ($PM_{10-2.5}$) were associated only with a 0.4% increase (95% CI -0.1 to 1.0%). Moreover, when the pattern was examined for each of the six cities individually, CP were significantly associated only in one city, in which a 2.4% increase in mortality per 10 µg/m^3 was predicted. This occurred in the only city in which the correlation coefficient between $PM_{2.5}$ and CP was high, strongly suggesting attribution of the effect from $PM_{2.5}$ to CP. In the other five cities, a -1.3 to a 1.0% increase (Lower CI -0.6 to -3.3%) was predicted per 10 µg/m^3 increase in CP. In contrast, the predicted increases for $PM_{2.5}$ were between -1.3 and 2.2% for the six cities individually, with the results not significant in the two cities having the lowest $PM_{2.5}$ values (11.2 and 12.2 µg/m^3). The order of significance (based on RR for the equivalent interquartile ranges) for all the particle metrics in this study was: $PM_{2.5}$ (2.1%) >PM_{10} (1.8%) >SO_4^{2-} (1.5%) > $PM_{10-2.5}$ (0.4%) ~ H^+ (0.4%).

The three other individual cities (St. Louis, MO, Kingston, TN, Philadelphia, PA) in other studies for which a direct comparison of $PM_{2.5}$ and coarse particles was possible, also indicated that $PM_{2.5}$ was associated with a 1.5 to 2.3% increase in mortality per 10 µg/m^3 increase, while CP was not significantly associated (Dockery et al., 1992, 1996b). The order of significance in the more recent study in Philadelphia was: $PM_{2.5}$ >SO_4^{2-}>PM_{10} >H^+ = CP (Dockery et al., 1996). A similar pattern was shown in a long-term prospective cohort study in the same six cities, in which a 14% rate ratio increase in all-cause mortality was shown to be associated with a 10 µg/m^3 increase in $PM_{2.5}$ (Dockery et al., 1993). The increases in mortality for larger particles (10 µg/m^3 increases) were reduced, at 9% for PM_{15}, 4% for TSP (marginally significant), and a non-significant increase of 19% (95% CI -9 to + 57.%) for CP ($PM_{15-2.5}$). The order of significance of the particle metrics examined in this study was: non-sulphate $PM_{2.5}$ >$PM_{2.5}$ >SO_4^{2-} >PM_{15} >TSP>H^+.

In a cross-sectional study on 98 metropolitan areas in the US, annual variations in two fine ($PM_{2.5}$ and sulphate) and two coarse particle metrics (PM_{15} and TSP), were examined (Ozkaynak et al., 1987). Unfortunately this study did not examine the coarse particles reaction of PM_{15} (i.e., PM_{15}-$PM_{2.5}$). An increase of 4.3% in total mortality per 10 µg/m^3 was associated with $PM_{2.5}$, while the increase associated with PM_{15} was 1.9% and with TSP was 0.35%, both only marginally significant.

In summary, the rate ratio increases for all four of the subchronic exposure studies (Table 12.7) were significant, and varied between 4.3% and 14% for a 10 µg/m^3 increase in $PM_{2.5}$. The highest value was obtained for the six-city cohort study (Dockery et al., 1993), while the remaining cohort study (Pope et al., 1995) and the two cross-sectional studies (Pope et al., 1995a; Ozkaynak and Thurston,1987) gave values that were 34 to 69% below that in the six-city study. This is likely to be due at least in part to the much broader number of cities in different geographic areas with different climatic and socioeconomic regimes that were included in these studies, compared to the six carefully chosen northeastern and central cities in the study by Dockery et al. (1993).

Thus, in almost all cases in both the acute and subchronic mortality studies, fine particles, as $PM_{2.5}$, had a stronger and more significant association with mortality than more coarse particles, as either the particle fraction between $PM_{2.5}$ and $PM_{10/15}$, or PM_{10} and/or TSP. In only two cases was there an association between coarse particles (CP), as $PM_{10/15-2.5}$, and mortality. In the early analysis of the St. Louis data the effects of CP were stated to be "no different than $PM_{2.5}$" but exact figures were not presented (Dockery et al., 1992). The only city of the six-city study in which a positive association was found for CP showed a high correlation coefficient between CP and $PM_{2.5}$ (r=0.69), and in this case the $PM_{2.5}$ regression coefficient was not significant, making it likely that the effect was ascribed in the regression analysis to CP rather than $PM_{2.5}$ (Schwartz et al., 1996a). The strength of the association of mortality with PM_{10} was notably lower than that for $PM_{2.5}$ in both the acute and subchronic studies in all cases except the aforementioned St. Louis results. In both the acute and subchronic six-city studies and in four individual cities (six if the cities comparing BS are included), results were positive, while in Philadelphia (Dockery et al., 1996b), Amsterdam (compared here with BS) and in 38 cities of the

98 city cross-sectional subchronic study (Ozkaknak and Thurston, 1987) results were marginal. The associations for PM_{10} were negative in the first analysis of eastern Tennessee (Dockery et al., 1992) in which a smaller data set was available than in the later six-city study (where it was small but positive), and in Portage and Topeka in the same study (Schwartz et al., 1996a).

Sulphate, which is a part of the fine fraction of particulate matter, was compared with $PM_{2.5}$ in both the acute and subchronic six-city studies (Dockery et al., 1993; Schwartz et al., 1996a), the earlier St. Louis and eastern Tennessee study (Dockery et al., 1992), the prospective cohort study and accompanying cross sectional study on 151 metro areas in the US (Pope et al., 1995a), and the cross-sectional subchronic study on 98 metro areas in the US (Ozkaynak and Thurston, 1987). In the acute six-city study, the association between mortality and SO_4^{2-} was of a lesser magnitude than that for $PM_{2.5}$ for the equivalent IQR. The increase in mortality per IQR increase was estimated to be 1.5 % (95% Cl 0.9 to 2.2%) for SO_4^{2-} and 2.1% (95% Cl 1.5 to 2.7%) for $PM_{2.5}$ in the acute study (Schwartz et al., 1996a). The increase in the mortality rate ratio in the longer term six-city study (also for a 10 µg/m^3 increase) was 35% for SO_4^{2-} (95% CI 7 to 66%) compared to 14% for $PM_{2.5}$ (95% CI 3 to 27%); Dockery et al., 1993) . In the two cities in the earlier acute study (Dockery and Thurston,1992), the increases for SO_4^{2-} were 6.3% and 8.3%, but they were not significant (t=0.1.05 and t=0.67), probably due to the small number of measurements available (Table 12.7). In the remaining three long-term analyses, SO_4^{2-} was a stronger predictor of mortality than $PM_{2.5}$, and the mortality rate ratio per 10 µg/m^3 increase was 7.2 to 11.9% (Table 12.7), or 9% and 29% higher than $PM_{2.5}$ in the ACS cohort and concurrent cross-sectional analysis (Pope et al., 1995a) and almost twice as high as $PM_{2.5}$ in the cross sectional study on 38 of 98 metro US areas (Ozkaynak et al., 1987). No correlation analyses between PM metrics were presented for any of these studies, but they were likely high (Dockery et al., 1993). Thus, sulphate appears to be in the middle in any of the orders of significance found for the studies in which it was included, unless it was the only fine particle metric, in which case it was at the top.

The question then arises, whether SO_4^{2-} is itself toxic, or whether it is merely a good fine particle surrogate. The only study in this mortality series which provided some information on this question was the long-term cohort study on six cities (Dockery et al., 1993). In the US EPA analysis of this study for the particulate matter criteria document (US EPA 1996), the rate ratio (RR) given for non-sulphate $PM_{2.5}$ was greater than the RR for either $PM_{2.5}$ or SO_4^{2-} alone, the latter being lower than $PM_{2.5}$. This indicates that, under the conditions occurring in this study, the association of the non-sulphate portion of $PM_{2.5}$ with mortality is as strong or stronger than the association of the sulphate fraction, although both show independent associations.

The role of acidity, as hydrogen ion (H^+), was examined in both six-city studies and in four individual cities (Dockery et al., 1992, 1996b; Schwartz et al., 1996a; Gwynn et al., 1996). Acidity was not found to be significantly associated with mortality in five of the six locales and was at or close to the end of the order of significance for the various particle metrics in most of the studies. It was noted that acidity was not significant in eastern Tennessee, which was specifically chosen for inclusion in the study because its average acidity concentration was 36 nmol/m^3, much higher than the average of 10 to 15 nmol/m^3 in the other five cities (Dockery et al., 1992). However, Gwynn et al. (1996, preliminary report) showed that, in Buffalo, NY, an increase from the mean to the maximum acidity was associated with an approximate 22% increase in total mortality, almost twice as much as SO_4^{2-} for its increase from mean to maximum. Respiratory mortality was also significantly increased for H^+, but the results were less robust for respiratory mortality than for total mortality. H^+ had the strongest association of the four particle metrics examined in this study, and was closely followed by SO_4^{2-}, then PM_{10}. CoH, which was also analyzed, was far from significance. Correlation coefficients between SO_4^{2-}, PM_{10}, CoH, and H^+ were noted to be high, but were not presented. The results for H^+ on mortality were coherent with results on total and respiratory hospital admissions, in which paired regressions with the four air pollutant gases were carried out, showing that the association with H^+ was robust to inclusion of these (multiple-pollutant regressions were not conducted for the mortality data). The duration of the study was 2.5 years, and included three summers, during which H^+, O_3, and PM_{10} reach their highest annual levels. No data were available for $PM_{2.5}$, and all comparisons with fine particles were based on SO_4^{2-}.

Tables 12.7 and 12.8 present data on recent studies, mostly time-series analyses, comparing the acute effects of fine and larger particle sizes on hospitalizations and emergency visits to the hospital or to doctors' offices. Two studies examined the effects of a broad range of PM metrics on respiratory admissions in Toronto. Thurston and colleagues (1994) regressed seven PM metrics singly and with O_3, but were unable to co-regress them together because of strong correlations between them. This probably contributed to the mixed picture with respect to the order of significance of the various measurements. Based on p-values, the fine particle metrics $PM_{2.5}$, SO_4^{2-}, and H^+ were more significant predictors of respiratory disease than the coarse particle metrics except PM_{10}, which ranked between $PM_{2.5}$ and H^+. However, when each was co-regressed with O_3, only H^+ remained marginally significant.

Burnett and colleagues, in a very recent study, have again examined the association of respiratory and cardiac disease in Toronto with four fine particle metrics ($PM_{2.5}$, SO_4^{2-}, H^+, and CoH) and two coarse particle metrics ($PM_{15-2.5}$ and PM_{10}), co-regressing each with four gaseous air pollutants individually and together (Burnett et al., 1997). The most robust individual association with increases in both cardiac and respiratory hospital admissions was found with CoH. Individually, the relative risks for respiratory hospitalizations, for an increase equal to the concentration range measured for each pollutant, varied from 1.024 to 1.037 (all significant) (Table 12.8). The association with CoH remained significant after coregression with the gases O_3, NO_2, SO_2, and CO, while the other PM metrics became non-significant. For cardiac disease, the order of significance in individual regressions was CoH >CP >PM_{10} >H^+, with SO_4^{2-} and $PM_{2.5}$ not significantly associated. This suggests that coarse particles may play some role in cardiac disease, if not in respiratory disease. This work also showed the importance of considering the effects of the gaseous pollutants in any conclusions based on regressions with particles. Taken together with what is known of the precursors of PM and the formation of CoH, it also suggests that CoH is acting as a surrogate for air pollution from combustion gases.

All three hospitalization studies (Thurston et al., 1994; Burnett et al., 1997; Delfino et al., 1997) which included $PM_{2.5}$ as one of the fine particles examined, found it to be either first or second in order of significance within the fine particle group, which in general was more significant as a predictor of increases in respiratory hospitalization than the coarse particle group including $PM_{10-2.5}$ (two Toronto studies), PM_{10} (all three studies), TSP and TSP-PM_{10} (Thurston et al., 1994). In the only two studies which included a direct measurement of CP ($PM_{10-2.5}$), CP was last, or second to last in order of significance. Only the even coarser fraction TSP-PM_{10} was less significant in the Thurston et al. (1994) study in Toronto.

Sulphate was examined as one of several fine particle metrics in the three previously cited studies in Toronto and Montréal, and in two studies in Buffalo area (Thurston et al., 1992: Gwynn et al., 1996). In Montréal, SO_4^{2-} was the strongest predictor of hospitalizations compared to $PM_{2.5}$ and H^+, while in the two Toronto studies, it ranked below CoH and $PM_{2.5}$ (Burnett et al., 1997), or below H^+, $PM_{2.5}$, and even PM_{10} in the earlier study by Thurston and colleagues. In the two Buffalo studies, which were both also carried out by this research group, H^+ was more consistently associated with increased hospitalizations than SO_4^{2-}, but the correlation coefficients were very high (r=0.77; Thurston et al., 1992), making it difficult or impossible to distinguish the effects of one from another. These same five studies also allow a comparison of the relative strength of the SO_4^{2-} association compared to coarse particle metrics. In the five comparisons of SO_4^{2-} with $PM_{10-2.5}$ and/or PM_{10}, SO_4^{2-} was clearly the better predictor except in the Montréal study (Delfino et al., 1994). In this case, however, the correlation coefficient between PM_{10} and SO_4^{2-} was 0.90, which suggests that the PM_{10} effect was really due to the fine SO_4^{2-} fraction.

BS had higher risk (with marginal significance) than the larger particle size PM_{13} in Paris (Dab et al., 1996), the only hospitalization study which examined a coarse particle fraction as well as BS. The two studies which examined only PM_{10} largely composed of a coarse fraction have been included in Table 12.9, since they shed some light on the relative non-toxicity of large quantities of the coarse fraction of PM composed of crustal materials (Gordian et al., 1996: Hefflin et al., 1994). This suggests that efforts to control larger particle sizes such as those arising from road dust will be ineffective, or at least much less effective than control efforts directed to smaller, combustion-derived particles.

Table 12.7 Comparison of Fine Particle Effects with Coarse Particle Effects – Hospitalizations and Emergency Department Visits

Location Study Type Period of Study (Reference)	Endpoints	Fine Particles (mean, µg/m^3)	% Change/10 µg/m^3 increase (95% CI)	Coarse particles CP $PM_{2.5-10}$ (& PM_{10}) mean, (µg/m^3)	% Change/10 µg/m^3 increase (95% CI)	Other pollutants, correlations, PM interactions
Toronto, Ontario daily time-series 3 summers, July-August 1986-88 (123 d) (Thurston et al., 1994)	Respiratory admissions Asthma admissions	(1986, 1987, 1988) $PM_{2.5}$ (17.7,15.8, 22.3) SO_4^{2-} (74.4, 38.0, 123.6 nmol/m^3) H^+ (21., 13, 52 nmol/ m^3)	single pollutant model : respir.(p) asthma (p) 6.5% (0.01) 3.7% (0.08) 0.8% (0.03) 0.7% (0.04) 1.65% (0.01) 2.1% (0.01)	CP (12.7, 13.9, 16.5) PM_{10} (30.4,29.5,38.8) TSP (62, 66, 87) TSP- PM_{10} (32, 35, 47)	single pollutant model respir.(p) asthma (p) 8.9% (0.09) 7.5% (0.12) 4.7% (0.01) 0.4% (0.43) 1.8% (0.07) 0.8% (0.30) 1.3% (0.18) 2.7% (0.07)	Most robust assoc. with O_3- sign. with all PM. H^+ sign. alone, marg with O_3. All other PM fell 50-66% when co-reg + O_3 O_3 r =0.7 FP; 0.8 SO_4^{2-}; 0.5 H^+; 0.65 CP; 0.7 IP; 0.6 TSP. Order of sign. (% + p): (resp.) FP> PM_{10}> H^+> SO_4^{2-}>TSP >CP>TSP- PM_{10}. (asthma) TSP> H^+>TSP- PM_{10} >FP> PM_{10} >CP
Toronto, Ontario daily time-series 3 summers, June-September 1992-94 (388 d) (Burnett et al., 1997)	respiratory admissions cardiac admissions	$PM_{2.5}$ (14; 4-40) SO_4^{2-} (33; 5-229 nmol/m H^+ (1; 0-23 nmol/ m^3 CoH (0.8 x103 ft) $PM_{2.5}$ (see above) SO_4^{2-} H^+ CoH	RR for range, single regr. respiratory (t); cardiac (t) 1.037 (3.29) 1.031 (1.80) 1.029 (4.07) 1.017 (1.56) 1.024 (3.48) 1.024 (2.30) 1.037 (5.36) 1.062 (5.63) RR, regr. with all gases 0.999 (0.10) 0.993 (0.33) 1.000 (0.02) 0.984 (1.06) 1.006 (0.76) 1.005 (0.46) 1.023 (2.44) 1.059 (3.75)	CP (10; 4-23) PM_{10} (25; 10-58) CP PM_{10}	RR for range, single regr. Respiratory (t) cardiac (t) 1.023 (3.41) 1.036 (3.41) 1.030 (3.42) 1.033 (2.24) RR, regr. With all gases 1.007 (0.82) 1.022 (1.68) 1.004 (0.36) 0.996 (0.23)	Order (Single regr., resp) CoH>FP > SO_4> PM_{10}> H^+ ~ CP. (Cardiac):COH >CP > PM_{10} ~ H^+>FP(ns)> SO_4^{2-} (n.s.) Order (multiple regr., resp) CoH> all rest (n.s.) (Cardiac) CoH>CP n.s.> all rest n.s. CoH r<0.5 for all exc NO_2 O_3 signif. In all single and multiple regressions. O_3 r< 0.34 for all PM exc. SO_4^{2-} (r=0.53)
Southern, Ontario (incl. Algoma, Sudbury) daily time-series, 6 yrs., 1983-88 (2192 d) (Burnett et al., 1994)	respiratory admissions (May-August calculated)	SO_4^{2-} (5.3) (Toronto 6.7; 95th percentile 20.1)	4.15% (single regr.) 2.08% (Model + O_3) 2.05% (model + O_3 lag 1, 3 + SO_4^{2-} lag 1 d)	—	—	O_3 was more important predictor of resp. admissions than SO_4^{2-} but SO_4^{2-} independently assoc. (P<0.0001) O_3- SO_4^{2-} r=0.38-0.65, var. monitors
Southern Ontario (incl. Algoma, Sudbury) daily time-series, 6 yrs., 1983-88 (Burnett et al., 1995)	respiratory admissions cardiac admissions	($PM_{2.5}$ site-spec. Conversion Factor:15=4.13 SO_4^{2-}) SO_4^{2-} (4.37; max 33)	(Adjusted for O_3, temp) resp: 0.74% (0.49-0.99%) cardiac: 0.70% (0.36-1.02) resp: 2.7% (1.8-3.6%) Cardiac: 2.5% (1.3-3.7%)	—	—	Site-specific conversion factor available, SO_4^{2-} - $PM_{2.5}$ O_3 stronger RR for resp than SO_4^{2-}. Correl coeff. O_3 – SO_4^{2-} R=0.53 (summer), -0.04 (winter)
Buffalo, NY daily time-series June-August, 2 yrs, 1988-89 (Thurston et al., 1992)	respiratory admissions	— SO_4^{2-} (9.0; max 37.4) H^+ (2.2; max 18.7)	9.0% (p<0.01) 28% (p<0.01)	—	—	O_3 had highest mean effect. O_3 correl. coeff r=0.51, (H^+); 0.67 (SO_4^{2-}) H^+- SO_4^{2-} r=0.77 (can't be disting.)

Table 12.7 Comparison of Fine Particle Effects with Coarse Particle Effects – Hospitalizations and Emergency Department Visits *(continued)*

Location Study Type Period of Study (Reference)	Endpoints	Fine Particles (mean, μg/m^3)	% Change/10 μg/m^3 increase (95% CI)	Coarse particles CP $PM_{2.5-10}$ (& PM_{10}) mean, (μg/m^3)	% Change/10 μg/m^3 increase (95% CI)	Other pollutants, correlations, PM interactions
Buffalo, NY daily time-series 3 years, 1988-90 (Gwynn et al., 1996)	total admissions respiratory admissions	— SO_4 (not given) H^+ (" ") CoH (" ")	Total: all sign., RR ≈ 1.02 except CoH (marginal) Resp: (range, mean-max) 20% (14 – 26%) 38% (27 – 51%) 1-2% (not signif.)	— PM_{10} (Not given)	Total: 1-2%(significant) Resp: 18% (12 to 24%)	All gases signif. correlated with resp hospital admiss (t=4 to 7.5 exc CO, t=2) RR reduced only slightly when H^+ coregressed with gases. H^+ most consistent.
Montréal, Québec daily time-series 5 years, 1984-88 (May-Oct, 911 days) (July-Aug, 310 days) (Delfino et al., 1994)	respiratory admissions, asthma and non-asthma	— (May-Oct) (July-Aug) SO_4^{2-} 4.2 4.9 (90th percentile 8.2; 9.7)	— 9.6% for days >8.2 μg/m^3, for respiratory non-asthma admissions. (no continuous data given)	— PM_{10} (29.5; May-Oct) (31.5; July-Aug)	2.1% (0.6 to 4.0%) (Asthma)	O_3, temp included in model Correlations high between PM_{10}, SO_4^{2-} (r=0.90); O_3- SO_4^{2-} (r=0.59); PM_{10}- O_3 (r=0.63) Suggested that PM_{10} effect was really FP.
Montréal, Québec daily time-series 2 summers, June-Sept 1992, (66 d) 1993 (98 d) (Delfino et al., 1997)	emergency room visits for respiratory disease	(1992) (1993) $PM_{2.5}$ 18.5 12.2 SO_4^{2-} 51.7 34.8 H^+ 11.3 4.0 (SO_4^{2-}, H^+ in nmol/ m^3)	Results for 1992 not sign. single regr. results, 1993 (elderly, > 65 y) 9.6% (1.9 – 17.3%) 18.2% (2.4 -34.3%) (infants, < 2 y) 12.6% (1.0-24%)	— (1992) (1993) PM_{10} 30.1 21.7	(elderly, > 65 y) 7.3% (1.9 to 12.7%)	H^+ signif. only in infants In adults, PM order of signif.: SO_4^{2-} > $PM_{2.5}$> PM_{10} All n.s. when coregr. + O_3.(e.g. 4.5% (n.s.)/10 μg/ m^3 for $PM_{2.5}$). (correl. coeffic. v. high; $PM_{2.5}$- SO_4^{2-}- PM_{10} 0.87-0.96; O_3-PM .46-.63 O_3 7.2% for 10 ppb, signif. coregr. with all PM
Anchorage, Alaska daily time-series 22 mo., May 1992-March 1994 (Gordian et al., 1996)	outpatient visits to emergency rooms or doctors' offices, for respiratory disease	— ($PM_{2.5}$ was unusually low fraction of PM_{10}. limited monitoring gave av. ratio 0.26, as low as 0.14	—	— (CP av. 74% of PM_{10},, up to 86%) PM_{10} 48 (37- wkend) (PM_{10} max 600;>100 months after volcano erupt.	— (Results n.s. for 4-mo. period of volcano, 100-600 3.5% (p<0.01) (lag 1d)	CO also examined. Coarse fraction of PM larger than usual; PM sign., but high PM during eruption n.s. for asthma, resp. infections (CP not as important as fine fraction PM_{10}
Eastern Washington St. 3 towns. Daily time-series Oct 1990, all of 1991 (Hefflin et al., 1994)	Emergency Dept. visits for respiratory diseases (various)	— (area subject to blowing dust, therefore $PM_{2.5}$ smaller than average fraction of PM_{10})	—	— (CP high fraction of PM_{10}, due to dust storms) PM_{10} 40; max 1689)	— (bronchitis) 0.35% (p=0.03) OR 1.2 for resp., Oct 1991 (2 dust storms, PM_{10}>1000, vs. Oct 1990)	Although the OR for ER visits was raised slightly in dust storms, this was less than expected on basis of high PM_{10} levels. Concl. that crustal dust n.s.
Paris, France daily time-series 6 y, 1987-92 (Dab et al., 1996)	hospital admissions, respiratory disease COPD, Asthma	BS 31.9; max 268 (39.9 – winter) (24.6 – summer)	0.41% (0.07 – 0.75%)-all -0.05% (n.s.) – COPD 0.43% (n.s.) – asthma	— PM_{13} (50.8; max 138) (54.4 – winter) (47.6 – summer)	— 0.45% (0.04-0.87%) all -0.05% (n.s.) – COPD -0.025% (n.s.) – asthma	No correlations or coregre. BS ≈ PM_{13} (BS CI slightly narrower) O_3 n.s. for any endpoint. SO_2 sign. for all, COPD, asthma. NO_2 sign. for asthma.

Table 12.7 Comparison of Fine Particle Effects with Coarse Particle Effects – Hospitalizations and Emergency Department Visits *(continued)*

Location Study Type Period of Study (Reference)	Endpoints	Fine Particles (mean, μg/m^3)	% Change/10 μg/m^3 increase (95% CI)	Coarse particles CP $PM_{2.5-10}$ (& PM_{10}) mean, (μg/m^3)	% Change/10 μg/m^3 increase (95% CI)	Other pollutants, correlations, PM interactions
London, England daily time-series 5 yrs, Apr.1987-Feb 1992 (Ponce de Leon et al., 1996)	hospital admissions, respiratory disease	BS 14.6 (6-27)	RR ≈ 1,0 (n.s. year, both seasons)	—	—	O_3 most signif. assoc. with resp. illness, singly or coregr. with BS, NO_2, SO_2 BS n.s. for all 3 ages, single or double regression
Birmingham, England daily time-series 3 years, 1988-1990 (Walters et al., 1994)	hospital admissions - respiratory - asthma	BS 12.7 (max. 188)	24.6% – resp (lag 2d) 20.9% – asthma (lag 2d)	—	—	SO_2 also assoc. with 17% incr. in asthma (marg.) and 20% incr. in resp.adm., summer + winter (signif. less than BS) No co-regres. No data for other pollutants.
Amsterdam, NL Rotterdam, NL daily time-series 4 years, 1986-89 (Schouten et al., 1996)	hospital admissions - respiratory (all) - COPD - asthma	BS (Amst.) 11 (1-37) BS (Rot.) 26 (6-61)	(A)-RR n.s., any endpoint (R)-3.7% (0.9-1.7%) resp. - n.s. COPD, - n.s. asthma	—	—	(Amst.) O_3 -resp dis positive, marg. (Rot.) O_3 -resp. dis. sign., age 65+ NO_2 sign., resp dis., age 15-64; COPD All ages SO_2 n.s., both cities, all ages
Athens, Greece daily time-series 1 year, 1988 (Pantazopoulou et al., 1995)	emergency visits, - respiratory - cardiac disease	BS 135, 112,75 (winter) 106, 89,55 (summer) (3 monitoring locs.)	respiratory (summer n.s.) 1.6%, 1.1%, 4.1% -winter Cardiac (summer n.s.) 0.8%, 0.9%, 1.5% – winter	—	—-	CO also significant, also in winter 1 of 3 monitors, NO_2 in city centre, also signif. in winter. concentration-response poor, possibly because of low no. of events.High collinearity noted (no values given)
Barcelona, Spain daily time-series 5 years, 1985-89 (Sunyer et al., 1993) (Castellsague et al., 1995)	emergency visits for - COPD (Sunyer et al.) - asthma (Castellsague et al.)	BS ~68 (winter) 48 (summer)	COPD: n.s. in summer 2.3% (t=5.0) winter 0.9% (t=2.7) +SO_2 winter asthma: 4.6% single regr., (Lag 0-3d) summer	—	—	SO_2 gave similar increases in winter, also sign., summer. but reduced in coregres. +BS. No other pollutants given SO_4^{2-} was 38% of BS in summer., 23% in winter. RR, SO_2 same + SO_4^{2-}

Table 12.8 Summary of Comparison of Fine and Coarse Particle Effects in Hospitalization Studies

Location	Reference	Fine particles	Coarse particles	Other pollutants	Order of significance
Toronto, ON	Thurston et al., 1994	$PM_{2.5}$, SO_4^{2-}, H^+	CP, PM_{10}, TSP, TSP-PM_{10}	O_3 (significant with all PM in co-regression) Correl. coeff. with PM high, 0.5-0.8.	H^+ most robust (but marginal with O_3). FP>PM_{10}>H^+>SO_4^{2-} >TSP>CP>TSP-PM_{10} For asthma, mixed results
Toronto, ON	Burnett et al., 1997	$PM_{2.5}$, SO_4^{2-}, H^+, COH	CP, PM_{10}	O_3, SO_2, NO_2, CO (O_3 signif. with all PM in pairwise regression; PM n.s. except CoH)	single regression order (respir): CoH>FP>SO_4^{2-}>PM_{10}>H^+≈CP multiple+ gases: CoH>all others Entire effect can be explained by gases without any PM.
Montréal, Qué.	Delfino et al., 1996	$PM_{2.5}$, SO_4^{2-}, H^+	PM_{10}	O_3 (significant in co-regression)	adults: SO_4^{2-}>$PM_{2.5}$>PM_{10}>H^+ infants: H^+> all others (n.s.)
Montréal, Qué.	Delfino et al., 1994	SO_4^{2-}	PM_{10}	O_3 (n.s., + temp included)	PM_{10} > SO_4^{2-} (but r=0.90)
Buffalo, NY	Gwynn et al., 1996	SO_4^{2-}, H^+, CoH	PM_{10}	O_3, SO_2, NO_2, CO	H+>SO_4^{2-}>CoH (marg) PM_{10} µ SO_4^{2-} H^+ gases sign., consistent
Paris, France	Dab et al., 1996	BS	PM_{13}	O_3 (n.s.), SO_2, NO_2 (signif.)	BS ≈ or > PM_{13}
Buffalo, NY	Thurston et al., 1992	SO_4^{2-}, H^+	—	O_3 (more signif. than PM)	H^+ – SO_4^{2-} r=0.77 (can't distinguish apart)
S. Ontario	Burnett et al., 1994	SO_4^{2-}	—	O_3 (>SO_4^{2-})	—
S. Ontario	Burnett et al., 1995	SO_4^{2-}	—	O_3 (>SO_4^{2-})	—
Anchorage, AK	Gordian et al., 1996	—	PM_{10} (74-86% CP)	CO	PM_{10} > CP (CP marginally significant)
E. Washington	Hefflin et al., 1994	—	PM_{10} (high CP from dust)	—	PM_{10} > CP (CP not significant)

Overall, these studies thus support the hypothesis very well that the fine particle fraction is more important as a predictor of toxicity than the coarse fraction. While we do not yet know which components of the air pollution mix are responsible for the toxic effects observed, nor do we know the precise mechanisms by which they act, the consistency of the associations of excess mortality and morbidity with the fine fraction of particulate matter in well-conducted studies supports the need for objectives and other control measures for the fine fraction.

12.8 SUMMARY OF EPIDEMIOLOGY RESULTS

12.8.1 Acute Mortality

Daily or short-term variations in particulate matter, as PM_{10}, BS, $PM_{2.5}$, or sulphate, were significantly associated with increases in all-cause mortality in 43 regressions carried out in 20 cities across North and South America, England, and Europe (18 studies). The magnitude of the relative risk for PM_{10} was small, varying between 0.4% and 1.7% per 10 $\mu g/m^3$ increase, with an unweighted mean of 0.8% and a weighted mean of 0.5% per 10 $\mu g/m^3$ increase. While these increases seem small in terms of relative risk, they signify substantial numbers of avoidable deaths, due to the very large size of the population that is impacted by air pollution.

The magnitude of the increase in relative risk for BS was about the same as that for PM_{10} , and remained the same or slightly higher in two of the three co-regressions with ozone and/or SO_2. In the best-conducted study which examined $PM_{2.5}$, a mean increase in mortality for six US cities of 1.5% per 10 $\mu g/m^3$ was observed; this increase ranged from 0.8 to 2.2% for the six individual cities (Schwartz et al., 1996). The association with $PM_{2.5}$ was stronger than that with PM_{10} in the same study, 1.5% for $PM_{2.5}$ compared to the 0.8% for PM_{10} (per 10 $\mu g/m^3$) (combined results for all six cities). By comparison to other particles, sulphate was also strongly associated with mortality. Although the magnitude of the mortality risk was greater in the six-city study for SO_4^{2-} compared to $PM_{2.5}$, (2.2% compared to 1.5% per 10 $\mu g/m^3$, all cities combined), the strength and robustness of the association was greater for $PM_{2.5}$ than for SO_4^{2-}.

These increases in relative risk were observed at ambient concentrations that were usually well below current standards and objectives; the median concentration for PM_{10} in 16 studies from North America in which significant PM_{10}-mortality associations were found was 38 $\mu g/m^3$ (range 24.5-51.0 $\mu g/m^3$). The results were highly consistent under the widely varying climatic exposure conditions and pollutant mixtures encountered in the different locations.

In all of the analyses that examined one (or more) gasous air pollutants together in the same model with particulate matter or which corrected for them in some other way, the association of particulate matter with daily mortality was remarkably robust, despite the problems of disentangling the effects of PM from other air pollutants. Sulphur dioxide was not itself predictive of mortality in most of the analyses in which it was co-regressed with BS or PM_{10}. Both ozone and particulate matter appeared to act as independent factors in the association of air pollution with daily mortality, since their respective regression coefficients were relatively unchanged in bivariate regressions in seven locations. Some evidence was also found for an independent association between CO and mortality, but further studies are required to confirm this. The evidence for an association of NO_2 with mortality was weak in bivariate regressions, but high correlation coefficients between NO_2 and particulate matter could serve to hide any association. The magnitude, robustness and consistency of the PM association across so many locations with differing air pollutant mixtures strongly suggests that PM is the best indicator of the air pollution effect on mortality, and is considered to give some support to PM of some kind as a causal agent in adverse health responses in the community.

12.8.2 Daily Hospitalizations and Emergency Department Visits

All of the 16 studies that examined PM_{10} and one or more respiratory endpoints requiring hospitalization showed significant associations, varying between 0.45% and 4.7% per 10 $\mu g/m^3$ increase in PM_{10} at mean concentrations varying between 25 and 53 $\mu g/m^3$. When regressed together with ozone, PM_{10} remained significant in three locations but became marginal or non-significant in three others in which the correlations between these pollutants was high. In a preliminary study in Toronto (Burnett et al., 1997), five of six particle metrics tested in bivariate regressions with ozone retained their association with increases in respiratory hospitalizations, the exception being SO_4^{2-}, the only measurement which had a high correlation coefficient (r=0.53) with ozone.

In the six studies that undertook bivariate analyses with both PM and SO_2 , SO_2 was not clearly shown to have associations that were independent of PM_{10}. While NO_2 was found to be associated with respiratory hospitalizations in several univariate analyses, its independence from PM could not be properly evaluated because of the high correlations between NO_2 and PM in all locations. CO was found to have an independent association with cardiac-related admissions when co-regressed with PM_{10}, (suggesting the possibility that some of the positive PM-total mortality results discussed above could have been due to this seldom-regressed pollutant). Thus, of the five different air pollutants considered in single and bivariate or multiple analyses, particulate matter was the air pollutant with the most consistent and stable association with increases in hospitalizations. Ozone and CO were judged to have independent associations as well as PM.

The respiratory sub-categories chronic obstructive pulmonary disease (COPD) and pneumonia hospitalizations for the elderly ($\geq$ 65 y) were also significantly associated with PM_{10} (2 to 5.7% for COPD and 1.1 to 1.9% for pneumonia were found, both per 10 $\mu g/m^3$ increase in PM_{10}). The increased risk for hospitalizations due to COPD was higher (4.1%) than the overall increase in risk (3.7%) for all respiratory diseases in all age groups, thus confirming that those with pre-existing COPD are a susceptible subgroup. The hospitalization data provided only limited evidence for an association between particulate matter and exacerbations of asthma, although the small number of respondents in many of the studies limited their power to detect an effect. The southern Ontario study (Burnett et al., 1994), with the clearest positive results for asthma, also included exposure to ozone, which has also been linked to asthma. This suggests the possibility that particulate matter might have a relatively small role, if any, in exacerbation of asthma.

Particulate matter was shown to have associations with cardiovascular disease in addition to its associations with respiratory disease, but the magnitude of the cardiovascular associations were generally smaller than those for respiratory disease.

In six of the eight studies which employed BS as the particle metric, the relative risk for respiratory hospitalizations was increased, providing some evidence for an association between increases in BS and hospitalizations for respiratory disease, despite variations observed in strength and significance of the associations and lack of data on its significance when included in regressions with the range of gaseous air pollutants known to occur with it.

Sulphate has a strong association with respiratory hospitalizations, and appears to act as a good surrogate for fine particles in locations where fine particle measurements are not available. This does not mean that sulphate is itself directly toxic. All eight studies which examined SO_4^{2-} found positive associations in univariate regressions, but significance was lost in three of these when SO_4^{2-} was co-regressed with ozone, due to high correlations between them. In the largest and best-conducted study available on SO_4^{2-} (Burnett et al., 1995), a 2.0 to 2.7% increase in respiratory hospitalizations per 10 $\mu g/m^3$ increase in SO_4^{2-} was indicated in regressions which included adjustments for ozone. This was calculated to be equivalent to a 1.1% increase in relative risk per 10 $\mu g/m^3$ increase in $PM_{2.5}$, based on site-specific monitoring and conversion factors.

Particle strong acidity (PSA or H^+) was associated with respiratory hospitalizations in five studies, two in Buffalo, two in Toronto and one in Montréal (Table 12.8). In the Montréal study PSA was associated with respiratory hospitalizations only in infants and not in adults, a finding considered to be spurious by the authors, because of inconsistencies in the association. The association was strong (38% per 10 $nmol/m^3$) in the studies by Thurston and colleagues in Buffalo and Toronto, but high correlations between H^+ and ozone or sulphate meant that the associations could not be attributed to any one of them specifically. When H^+ was regressed with each of the gaseous air pollutants in Toronto in the Burnett et al. (1997) report, significance was lost for H^+.

Although ozone appears to be independently associated with hospitalizations for respiratory disease in analyses of summertime results, adequate studies confirm that the association for particulate matter remains strong, based on bivariate regression results in addition to single regressions. The equivocal results with respect to particulate matter obtained from some co-regressions of the hospitalization data generally reflected high correlations between ozone and particulate matter, making it difficult or impossible to separate out their effects. An alternative explanation is that ozone, and possibly other gases as well, act synergistically with particulate matter to produce adverse effects.

12.8.3 Effects on Respiratory Health

In addition to its effects on increases in mortality and hospitalizations, increases in particulate matter have been shown to cause small reversible decrements in lung function in normal asymptomatic children, and in both adults and children who have some form of pre-existing respiratory condition, particularly asthma. These changes were often accompanied, especially in adults, by increases in symptoms such as chronic cough or bronchitis. Respiratory-related restrictions in activity severe enough to result in an increased number of days lost to work in adult workers and in school absences in children were also demonstrated to be associated with increased concentrations of ambient particulate matter, in some cases PM_{10}, and in others, $PM_{2.5}$ or other fine particles such as SO_4^{2-}.

12.8.4 Long-Term or Chronic Effects

Longer term, subchronic or chronic exposures, varying in duration between one and 16-20 years' exposure, were associated with increases in mortality, respiratory disease symptoms, decrements in lung function and, possibly, with increases in lung cancer in both cross-sectional and more powerful prospective cohort studies. In one of the cohort mortality studies, lifespan was reduced due to increases in particulate matter by an average of two years over a 14-year period (Dockery et al., 1993), an observation incompatible with suggestions that most or all the observed deaths were due to "harvesting", or accelerating death of persons already ill by a few days or a few weeks. Mortality increases associated with a 10 $\mu g/m^3$ annual increase in fine particle concentrations ($PM_{2.5}$ and SO_4^{2-}) were calculated to be about 7% over a period of seven years in a cohort study covering 151 metropolitan areas in the US (Pope et al., 1995a). Significant decreements in lung function (2.4 to 3.5%), lung capacity, growth and development, along with increased relative risks for bronchitis, were shown to result from chronic exposure of children to fine particles, as H^+, SO_4^{2-}, and $PM_{2.5}$, for all or most of their lives.

The development of new symptoms of chronic disease is considered to be an indication of a chronic effect on the system. Development of new cases of chronic bronchitis (18% per 10 $\mu g/m^3$ $PM_{2.5}$) was observed in a cohort of older adults, in association with fine particles measured for the 10 years before the developmental observation period began (Abbey et al., 1995a). Development of new cases of chronic bronchitis has also been observed in children (Dockery et al., 1989, 1996). This increased incidence of disease in childhood appears to convey additional chronic consequences due to carryover of increased susceptibility into adulthood (Abbey et al., 1995a). Increases in the severity of respiratory symptoms over a period of 10 years have been associated with exposure to fine particles from the concurrent 10 years' exposure, and increases in the severity of asthma with exposures from the 10 years preceding the study (Abbey et al., 1995a).

Chronic (or subchronic) exposure to fine particulate air pollution was also shown to be associated with the development of lung cancer, but this association was very small in magnitude by comparison to other lifestyle factors, particularly smoking.

12.8.5 Fine Particles versus Coarse Particles

A few studies have directly compared the coarse fraction of inhalable particles (PM_{10}) with the finer fraction $\leq$ 2.5 µm and/or with more chemically defined fractions, generally sulphate, but sometimes particle strong acidity (PSA or H^+). The role of the coarse fraction was examined carefully in the recent re-analysis of daily mortality in the six-city study (Schwartz et al., 1996; US EPA 1996). In the overall results for all six cities, coarse particles were not associated with mortality, nor was there any association in any of the individual cities except the only city in which the correlation coefficient between $PM_{2.5}$ and CP was high, strongly suggesting attribution of the $PM_{2.5}$ effect to CP in this case. These results were supported by the chronic results for the same six cities, and by two smaller mortality studies, as well as by one of the two respiratory hospitalization results for Toronto (Thurston et al., 1994).

Crustal or soil-derived coarse particles were not associated with any great increases in respiratory disease in two studies carried out in western North America, despite extremely high concentrations on some occasions (Gordian et al., 1996; Hefflin et al., 1994). This indicates that control of dust, for example from roadways or construction sites, will be less effective in reducing adverse health outcomes than controlling sources of finer sized particles.

In almost all cases in both the acute and longer term studies, fine particles, as $PM_{2.5}$, had a stronger and more significant association with mortality, hospitalizations, and symptoms than measures of coarser particles including $PM_{10-2.5}$ themselves,

PM_{10}, or TSP. Sulphate appeared to have as strong or stronger an association as $PM_{2.5}$ with increased mortality and hospitalizations. In one study in which SO_4^{2-} and the non-SO_4^{2-} fraction of $PM_{2.5}$ were directly compared, the non-SO_4^{2-} portion was equally as, or more toxic than SO_4^{2-} itself, suggesting that SO_4^{2-} would be an inadequate surrogate for all fine particle effects.

BS, despite its smaller size by comparison to PM_{10}, was not always found to be a predictor of either increased mortality or hospitalizations. This has been suggested to be due to its inadequacy as a surrogate for combustion-related and secondarily produced particles from gasoline engines, although it represents the carbon-based soot particles from diesel engines and stationary sources very well. The type of particle pollution that is prevalent in European cities today has changed from soot-based particles to secondarily formed particles from gasoline combustion (Anderson et al., 1996).

The results for acidity have been mixed; some authors have consistently found H^+ to rank highly in associations with respiratory disease endpoints (Thurston et al., 1994; Gwynn et al., 1996) while others have found acidity to rank at or near the bottom (Schwartz et al., 1996; Burnett et al., 1997).

The correlation coefficients between various particle metrics in any one location have generally been sufficiently high to preclude co-regressions, thus making any separation of effects of the various types of particles difficult or impossible.

Overall, the majority of the studies support the hypothesis that it is largely the fine fraction which is involved in exacerabtions of cardiorespiratory disease. There is some suggestion, however, that coarser particles may play some role in cardiovascular disease and in COPD.