

**HUMAN HEALTH EFFECTS OF FINE PARTICULATE MATTER:
UPDATE IN SUPPORT OF THE CANADA-WIDE STANDARDS
FOR
PARTICULATE MATTER AND OZONE**

**PREPARED FOR THE
CANADIAN COUNCIL OF
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EXECUTIVE SUMMARY

Revised in July 2004

FINE FRACTION OF PM — HUMAN HEALTH EFFECTS

EXECUTIVE SUMMARY

As part of the development of a National Ambient Air Quality Objective (NAAQO) for particulate matter (PM), a Science Assessment Document (SAD) containing critical scientific groundwork and evaluation was prepared in 1997 and published in 1999. However, since the Canadian Council of Ministers of the Environment (CCME) identified PM as a priority substance in January 1998, it was agreed that NAAQOs for PM would no longer be developed. Rather, the Science Assessment Document produced for PM (1999 Ozone SAD) would form the Risk Assessment report for the development of a Canada-Wide Standard (CWS) under the Canada-wide Standards Sub-Agreement of the Harmonization Accord of the CCME.

The Canadian Environmental Protection Act/National Advisory Committee (CEPA/NAC) Working Group on Air Quality and Objectives Guidelines produced the SAD for PM and released it in July 1999. This PM SAD constitutes a literature review and critical analysis of all relevant information concerning the effects of PM on human health, animals, aesthetic effects and environment impacts. The information contained within this document is current to March 1997. Because PM toxicology and human health effect studies, including clinical and epidemiological research, and human exposure science are evolving rapidly, it was determined that an update to the CWS for PM should be brought forward to identify any issue from science which might materially alter or add to the existing Canada-wide Standards. The means to achieve this was, primarily, to assess individual research papers and determine if they contained any information relevant to the already in-place Standards for PM_{2.5}.

This PM CWS update brings together new information on the health effects of fine PM that has been published in peer-reviewed journals since completion of the 1999 PM SAD. It includes relevant information in the following areas: human exposure studies, animal and *in vitro* toxicology, clinical studies and epidemiology; the period covered in this update ranges from March 1997 to October 2002. New studies have been collected and critically reviewed in order to gauge the extent to which new information supports previous findings in the above-mentioned areas, and to determine if the conclusions reached in the 1999 PM SAD remain valid and whether new action is warranted.

In the Science Assessment Document (SAD) completed in 1997 (published in 1999), regarding the adverse health effects of ambient air particulate matter (PM), we identified several knowledge gaps that have hindered the inference of causality. These knowledge gaps include: 1) whether PM-mortality association is confounded by weather and co-pollutants; 2) which population is most susceptible to PM pollution; 3) what the impact is of exposure misclassification due to using data from fixed ambient monitors rather than from personal exposure monitoring; 4) whether PM only advances the death of very frail people by a brief interval, such as a single day, so that the net loss of life and public health implications would be limited—a concept known as “harvesting” or “mortality displacement”; and 5) whether freshly generated ambient PM-induced cardiorespiratory effects can be observed in human subjects in an experimental setting. Many problems have been identified with the widespread use of generalized additive models (GAMs) in time series studies of air pollution and health: one with the statistical software (S-Plus) commonly used to analyze these studies and another one with the statistical procedure itself. The question needs to be answered with regards to the impact of these problems on the risk estimates of PM.

Given the plethora of studies on ambient PM published since 1997, we decided to focus this update document on the new studies that had the objectives pertinent to the aforementioned knowledge gaps, instead of including all studies, a task with enormous workload. The topics that are not comprehensively reviewed in this document are regarding the risk estimates of fine PM on total and cardio-respiratory mortality, total and respiratory hospital admissions, field studies on acute respiratory health, and animal and human toxicological studies using artificial particles, as these subjects were extensively published before 1997, and thoroughly reviewed in the PM SAD (1999). For long-term exposure and the effects on cancer, we reviewed studies that examined the exposure to ambient PM rather than PM from diesel emissions.

Based on the present review, on balance, the evidence for adverse effects of PM on humans is qualitatively more certain than in 1997. Most of the new evidence gathered from epidemiological, laboratory (including human and animal) studies and exposure studies validates the conclusions reached in 1997. Most significantly, new epidemiology studies not only demonstrate a significant association between acute exposure to ambient fine PM and increased population mortality and morbidity, but also clearly delineate an association between long-term exposure to fine PM and increased mortality due to cardio-respiratory illness and lung cancer, and reduced lung function growth of children. New evidence is emerging on low birth weight, birth defects and infant mortality attributed to particulate air pollution. Significant questions remain regarding quantification and the exact relevance of the chronic exposure effects in Canadian populations.

Human Exposure Assessment of Particulate Matter

The 1999 SAD concluded that penetration of ambient air into indoor environments is more effective for fine particles than coarse particles. In Canada, where building construction emphasizes energy efficiency, and therefore low air exchange rates, the fractions of fine and coarse particles of ambient origin that will be found indoors under equilibrium will tend toward 50% or less, particularly in the winter. Once inside, the larger particles tend to settle out more quickly than smaller particles; however, the larger particles are more easily resuspended as a result of indoor activities. SAD (1999) reviewed studies that examined the correlations between ambient PM data obtained from fixed ambient monitors (FAMs) and personal exposure data obtained from personal exposure monitors (PEMs). When exposure studies were pooled together, most studies report poor cross-sectional personal-outdoor correlations. When individual (longitudinal) regressions of personal exposure with the nearest outdoor site are calculated, the correlations improve. One study group developed personal and population exposure models that combined ambient measurements of pollutants with information on age-specific time-activity and estimates of microenvironmental pollutant concentrations. Canadian estimates of exposure to PM_{2.5} were not yet been predicted through exposure modelling. Given the information, SAD (1999) concluded that ambient data alone may represent the lower range in the distribution of total particle exposures. Further studies were required to improve various components of the exposure model, including better characterization of indoor PM sources and penetration rates of ambient particles indoors, specifically in cold climates, since air exchange rates are a function of ambient temperature.

Since 1998, there has been a large number of publications relevant to the assessment of human exposure to PM. A number of key issues have been discussed and are summarized below.

1. There has been much discussion about the use of ambient monitoring data in epidemiological time-series studies when total personal exposure is generally uncorrelated with ambient levels and people are known to spend most of their time indoors. It has been argued, however, that ambient PM concentrations are well correlated with personal exposure to ambient-generated PM (but not to non-ambient or total PM). This has been the subject of several novel experimental protocols and modeling. Moreover, it has been shown that a considerable amount of fine particles penetrate into the indoor environment. Hence, because indoor-generated PM is likely independent from ambient-generated PM, it is unlikely to confound any relationship between ambient PM and health outcomes.
2. Much work has been done and is ongoing regarding further physical and chemical characterization of PM. This includes identification and measurement of PM attributes other than mass, including particle number, particle size, total surface area and specific chemical and biological components in ambient, micro-environment and personal exposure samples. This work shows potential in identifying sources of PM. It will also assist in identifying the key attributes of PM that cause health effects. Such work is expected to provide input to future toxicological, clinical and epidemiological health effects work.
3. A number of studies have looked at factors affecting the amount of ambient PM found indoors and the contribution of ambient to total personal exposure, such as building characteristics, weather and particle size. Considerable variability in indoor/outdoor (I/O) ratios of PM in different houses and office buildings has been reported. In most residential dwellings I/O ratios of PM are greater than 1.
4. Levels of indoor-generated PM can be significant and make a considerable contribution to total personal exposure; there is evidence that the composition of indoor-generated PM is different from ambient-generated PM. As stated in Section 1, exposure to indoor-generated PM is unlikely to confound the relationship between ambient PM and health outcomes. It should be noted however that the studies to date have largely involved healthy persons and not those likely to be in a susceptible population.
5. Exposure to PM arising from transportation is ubiquitous in urban environments. Considerable work has been undertaken over the last few years to characterize traffic-related PM, with a variety of experimental designs utilized. To date, it has been found that microenvironments have the potential to create very high levels of personal exposure—this area needs more investigation. This is possibly true for other sources (e.g. industrial, wood smoke) but these have not been as well studied.

Epidemiological Studies

Epidemiological studies of the effects of ambient PM on human health explore associations between changes in ambient levels of PM and changes in the occurrence of cardiovascular and respiratory health problems in the population. These are categorized into: acute exposure and mortality, acute exposure and hospital admissions, acute exposure and emergency room visits (ERVs), health effects

of long-term exposure, and field studies. The field studies examine cardiovascular responses such as changes in electrocardiographs, respiratory symptoms, medication use, pulmonary function changes and other biological markers of each study participants.

Epidemiological studies on acute effects included in this update document are reviewed on the aspects of (1) population size; (2) years covered; the first two aspects determine the sample size of the study; (3) concentrations of pollutants to determine the relevance to Canadian environment; (4) correlations among variables; this helps to determine whether or not single- or multi-pollutant models of choice are sound; (5) whether or not confounding variables such as weather, seasons, and day-of-week were examined in the study; (6) whether smoothing techniques were used to adjust for trends, and whether they were parametric or non-parametric. For studies on long-term effects we also examined whether the study type was a cross-sectional or a longitudinal cohort study, the latter bearing more weight for inference of causality.

Acute Exposure and Mortality

The 1997 PM SAD (1999) concluded that increases in all-cause mortality in studies carried out in 20 cities across North and South America and Europe were significantly associated with daily or short-term (several days) variations in PM, as PM₁₀, BS, PM_{2.5} or SO₄. The magnitude of the risk for PM₁₀ was small, varying between 0.4 and 1.7% per 10 µg/m³ increase, with a mean of 0.8% and a median also of 0.8% (n = 23), for a wide range of mean concentrations from 28 to 115 µg/m³. For the fine fractions PM_{2.5} and BS, the mean relative risks (RRs) of death for an increase of 10 µg/m³ were also elevated, at 1.5% for PM_{2.5} (n = 9) and 1.0% for BS (n = 6). For the sulphate fine fraction, one study provided an estimate of a 2.2% increase in mortality per 10 µg/m³ increase in sulphate. The independence, consistency, robustness and magnitude of the PM association across so many locations with differing air pollutant mixtures supports the position that PM of some kind is the best indicator of the air pollution effect on mortality, although effects due to (an)other independently acting air pollutant(s), notably ozone, are also likely in some locations.

The SAD did, however, acknowledge the uncertainties or limitations derived from these time-series studies, such as: 1) what are the components and sources of the particle mixture that have the greatest effect on health? 2) what are the health effects of ultrafine particles? and 3) what is the impact of exposure misclassification due to using data from fixed ambient monitors rather than personal exposure data? Moreover, on the issue of mortality displacement or harvesting, arguments have been made that the results of time-series studies might reflect the effect of air pollution on very frail people whose timing of death has been advanced by only a brief interval, such as a single day, so that the net loss of life and public health implications would be limited.

In this PM Update document, we have reviewed more than 40 acute mortality studies published since 1997. These studies were conducted not only in North America and Europe, but also in Australia and Asia, and included diverse climates, socio-economic factors and lifestyles. Using single- and multi-pollutant models, the majority of these studies demonstrate significant association between PM and mortality. Most studies using multi-pollutant models show that gaseous pollutants did not substantially attenuate PM associations, while a few others indicate a diminished PM association, suggesting that the PM effect may be less than that attributable to the mixture as a whole.

It is well recognized that for time-series studies, both the series of daily mortality rate and the series of daily air pollution concentrations are subject to strong seasonal, subseasonal, day-of-the-week variations and long-term trends. Several approaches have been considered to adjust time series of mortality for temporal fluctuations. In recent years, the method that has become a standard in time-series studies on the associations between air pollution and health effects is the GAM because it allows for non-parametric adjustments (LOESS smoothers) for non-linear confounding effects of seasonality, trends and weather variables. It is a more flexible approach than fully parametric alternatives such as Fourier series (using a combination of polynomials in time and trigonometric functions) and Shumway (the moving average linear filter with more weights given to observations close to the day of observation). Very recently, however, it has been discovered that there is a software error in the S-Plus package for the widely used GAM method, which may have significant impact on the outcomes of time-series air pollution and health studies. The GAM method can provide biased estimates of regression coefficients and standard errors, and substantially overestimate the risk estimates. Most studies reviewed in this document used GAM with non-parametric smooth functions to adjust for confounding of time trends and weather variables on mortality time series. Three studies compared the results using GAM versus other statistical tools. Clearly non-GAM models resulted in much smaller risk estimates of daily mortality for PM than did GAM models. Nevertheless, in most cases, the PM₁₀ risk estimates were still statistically significant.

In addition to time-series analyses, several researchers also investigated the use of case-crossover design. Their findings demonstrate similar risk estimates for airborne particles, albeit the effect size was smaller than those obtained by time-series design. Nevertheless, the case-crossover design is believed to be a valid method in that it adjusts the confounding of the day-of-week and seasonality factors, and avoids using GAMs with non-parametric smooth functions.

There has been a controversy about whether the increase in mortality is only among extremely frail individuals whose remaining life expectancy would be short even in the absence of pollution. The possibility that only extremely frail individuals die from exposure to air pollution has been termed the “harvesting” hypothesis, as well as “mortality displacement.” If the association between PM pollution and acute mortality were due solely to the deaths of frail individuals, which are brought forward by only a few days, then the public health significance of exposure would be small. Three groups of statisticians used different methods to examine the mortality displacement using data from the United States and Europe. Using data from a single city or multiple cities, they looked at the PM association with mortality at longer time scales. Consistently, all results indicate that as the focus moved from daily patterns to monthly patterns, not only did the risk estimates of PM fail to diminish, but they also increased. Thus the PM effects observed in daily time-series studies are not likely due primarily to short-term mortality displacement.

Misclassification of exposure (also called measurement error) is a well-recognized inherent limitation of epidemiological studies of disease and the environment. For many agents of interest, exposures take place over time and in multiple locations. Accurately estimating the relevant exposures for an individual participant in epidemiological studies is very challenging and in particular is limited by feasibility, participant burden and cost. There are strong concerns about accurately interpreting the associations between ambient air pollution and mortality and morbidity, given the potential errors in the exposure measurements.

Two groups of researchers have investigated the issue of exposure misclassification for PM by modeling the unavailable personal exposure data from the available ambient and personal exposure data. They found that measurement error occurred when exposure data from fixed ambient monitors were used, and caused an underestimate, rather than overestimate, of mortality risk of PM_{10} . These analyses were all conducted using single pollutant models. It remains unclear to which direction and to what extent multiple pollutants with several layers of measurement errors may bias a PM risk estimate. Moreover, given that recent personal exposure studies have shown that ambient PM concentrations are well correlated with personal exposure to ambient-generated PM (but not to non-ambient or total PM), and that a considerable amount of fine particles has been shown to penetrate into the indoor environment, indoor-generated PM is unlikely to confound the relationship between ambient PM and health outcomes.

The chemical constituents on fine particles are known to be associated with certain sources, and some elements are more source-specific than others. For example, iron and zinc are linked to steel production and nickel is linked to oil combustion, while sulphur in Canada comes mainly from coal and oil combustion at power plants, smelters and oil and gas extraction and refining industry. Some of the constituents of fine particles, such as nickel, iron and zinc, are known toxicants. Others, such as sulphate, play a role in the conversion of transient metals into a bioavailable and toxic form. Therefore, the study of the effects of particle components may shed light on both source emissions and on potential toxic mechanisms of ambient particles. Several studies using factor analyses indicate that combustion particles in the fine fraction from mobile and coal combustion sources but not fine crustal particles are associated with increased mortality. Sulphate aerosol, carbon and zinc (as a tracer for industrial source), and nickel and iron to a lesser extent, stood out as having comparatively high associations with mortality among elements. Fine particles (represented by particle mass) and ultrafine particles (represented by particle number) seem to have independent effects on mortality at ambient concentrations. Only one study was conducted on ultrafine particles, which precludes us from concluding which size of PM has a greater association with mortality.

We have reviewed four new Canadian studies that have used various PM metrics, using single- and multi-pollutant models. Consistent with international studies and with previous Canadian studies reviewed in the 1997 PM SAD, the Canadian results all demonstrate significant associations between PM and cardiovascular and respiratory mortality.

With respect to susceptible populations, two studies demonstrate that persons who had had cancer, acute lower respiratory diseases, any form of cardiovascular disease, chronic coronary artery diseases, and congestive heart failure before death had a higher risk estimate of PM metrics than people without these conditions..

The issue of threshold has also been investigated by some researchers. Among eight studies reviewed, seven suggested that linear relationships between PM and mortality without a threshold are appropriate for assessing the effect of particulate air pollution on daily mortality even at current levels. One study found that there appears to be a threshold at $25 \mu\text{g}/\text{m}^3$, above which both coarse and fine particles had a significant association with total mortality.

Acute Exposure and Hospital Admissions

In the 1997 PM SAD (1999), we reviewed 22 studies on associations between PM and hospital admissions, all conducted in North America and Europe. Only 4 of these examined cardiovascular admissions, while the rest studied respiratory admissions. None studied the effects on children. The strongest and most consistent association of particulate matter with respiratory hospitalizations is considered to be with sulphate. A 2.0% - 2.7% increase per $10 \mu\text{g}/\text{m}^3$ increase in sulphate (co-regressed with ozone) was reported in southern Ontario in the best conducted study of the series of eight examined. This was calculated to be equivalent to a 1.1% increase per $10 \mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$, based on site-specific monitoring and conversion factors. The correlations between ozone and sulphate were high (0.5 - 0.8) in all eight studies, which causes difficulties in separating out the effects of one from the other. Overall, there is good evidence for an association between sulphate and respiratory hospitalizations and sulphate is considered to be a good surrogate for fine particles from combustion sources. This does not mean that the sulphate is itself directly toxic however. An association between BSS (a somewhat smaller particle than PM_{10}) and respiratory hospitalizations exists, but is considered to be weak, presumably because this PM metric does not adequately represent secondary PM (much of which is colourless), being an optical measurement of dark coloured particles. Results for acidity (H^+) were inconsistent, with strong associations and high significance in some studies, and none in others. No evidence for a threshold of effects for respiratory hospitalizations associated with particulate matter or other air pollutants was found at the low (10 to $100 \mu\text{g}/\text{m}^3$ PM_{10}) concentration ranges examined. Curves appear to increase monotonically, with steep slopes at low concentrations and some suggestion of curvilinear responses (lower slope) at higher concentrations. Like acute mortality, there also exists controversy on the issue of harvesting in hospital admission studies.

In the PM Update document, we have reviewed more than 25 studies that investigated the associations between various PM metrics and cardiovascular and respiratory admissions. These studies were conducted not only in North America and Europe, but also in Australia and Asia, and included diverse climates, socio-economic factors and lifestyles. Using single-pollutant models, the majority of these studies demonstrate a significant association between PM and hospital admissions. Seventeen studies used multi-pollutant models: eight of them show that gaseous pollutants did not substantially attenuate PM associations, while others indicate a diminished PM association. These latter studies suggest that the effect of the pollutant mixture on hospital admissions may be greater than that of PM alone; some health outcomes may be attributed to gaseous pollutants.

Most studies reviewed used GAMs with non-parametric smooth functions to adjust for confounding of time trends and weather variables on hospital admission time series.

Six studies did not use GAM, and the results are similar to those from the GAM analyses. The consistency of the risk estimates regardless of the statistical methods, age, location, health status and socio-economic status further support an underlying relationship between ambient PM pollution and cardiovascular and respiratory hospital admissions.

In the 1997 PM SAD, very few studies investigated the effects of PM on cardiac hospital admissions. Since 1997, however, quite a few reports have come to light on cardiovascular ERVs. In this update document, we have reviewed 18 studies on cardiovascular admissions. Using single-pollutant models, 16 of these studies demonstrate a significant association between PM and hospital admissions. Twelve studies used multi-pollutant models, and 6 of them show that gaseous pollutants did not substantially attenuate PM associations, while the other 6 indicate a reduced PM association.

We have reviewed the studies that compared the strength of the association between PM pollution and hospital admissions among groups with various health statuses, age groups, races and socio-economic status. Results from studies on health status support the assumption that people with pre-existing health conditions have a higher risk to the adverse effects of ambient PM pollution. These health conditions include cardiovascular and respiratory illness and diabetes. We have reviewed four studies on children respiratory admissions with various PM metrics, in North and South American cities. These studies consistently demonstrate a significant association between PM pollution and respiratory admissions. Very young children (<2 years) appear to be more vulnerable to the effects of PM pollution, with a higher risk estimate of respiratory hospital admissions than adolescents. We reviewed 10 studies on cardiac and respiratory hospital admissions of the elderly, with various PM metrics, at cities in Australia and Asia, as well as in North America and Europe. All these studies demonstrate a significant association between PM pollution and hospital admissions due to either cardiovascular or respiratory disease in single-pollutant models. Between cardiovascular and respiratory admissions, the elderly tend to have stronger association between PM pollution and cardiac admission than respiratory admissions. In some studies in which various age groups were compared, PM shows stronger association with hospital admissions in the elderly than in the younger group. PM effects were often attenuated by gaseous pollutants when regressed in the multi-pollutant models, suggesting that some effects may be attributed to gaseous pollutants.

In terms of race, the two studies we have reviewed do not consistently demonstrate that a certain race was more susceptible than other races to the effect of PM pollution on hospitalization. Results seem to be more convincing when data were broken down by income: regardless of race, low income populations were more vulnerable to PM-related health effects.

Comparing the components of PM, these studies demonstrate that ambient fine particles have a stronger association with hospitalizations than larger particles; however, the effect of coarse particles (PM_{10-2.5}) cannot be completely dismissed. Aerosol acidity and sulphate do not seem to have a stronger association with hospitalization than other PM components. Emissions from transportation sources contribute substantially to PM effects. The air conditioner study serves as an example of intervention to demonstrate that reduction of exposure to airborne particles may reduce adverse health effects.

Some have questioned whether hospital admissions associated with airborne particles occur only among persons who would enter the hospital within a few days anyway regardless of air pollution. This concept is referred to as the “harvesting effect,” and it has socio-economic implications for policy-makers. It challenges the necessity of establishing more stringent regulations for air pollutants because this would involve substantial costs. Only one study attempted to address this issue. The author used STL (seasonal and trend decomposition using a locally weighted smoother) algorithm to decompose hospital admission data into different time scales. By varying the time scale, the author could look at effects on successively larger time scales, ranging from 15 to 60 days. Results show

that PM10 risk estimates remained significant up to 60 days without diminishing, suggesting that PM10 exposure does not just push people to a hospital a few days earlier but that most of the adverse health events are advanced by at least a few months.

We have reviewed four new Canadian studies that have used various PM metrics and observed various age groups. Consistent with international studies and with previous Canadian studies reviewed in the 1997 PM SAD, the Canadian results all demonstrate significant associations between PM and cardiovascular and respiratory admissions.

Three studies examined the issue of a threshold for PM effects. At PM10 concentrations below 50 $\mu\text{g}/\text{m}^3$, only one third of the National Ambient Air Quality Standard (NAAQS) for PM10, the association of PM10 with cardiac and respiratory admissions was still evident. One study even demonstrates that the effect size is larger by 20% at PM10 concentrations below 50 $\mu\text{g}/\text{m}^3$ when compared with the effect size at PM concentrations above 50 $\mu\text{g}/\text{m}^3$. Based on all three studies, there is not likely a threshold for PM10.

It should be noted that given the dearth of studies on issues of harvesting, susceptibility of people with pre-existing health conditions and various socio-economic status, more studies are warranted to corroborate these findings.

Acute Exposure and Emergency Room Visits

In the PM SAD (1999), only five studies were available for review on emergency room visits (ERVs) and doctors' office visits. Only respiratory ERVs were investigated in these studies. Two studies used multi-pollutant regression models to adjust for the confounding effect of co-pollutants. These studies contained limited data on ERVs and PM exposure (1 year or 2 summers, usually in one location), which provided only limited statistical power for detecting a significant relation. Overall, the results from these studies show a positive association, although in some cases not statistically significant, between ERVs and various PM metrics. High correlation coefficients between PM and gaseous pollutants were reported, which suggests possible confounding effects of these co-pollutants. Because of the diverse PM metrics, including PM10, PM2.5 and BS, used in the small number of studies, no corporate risk estimate can be drawn from them.

Compared with the 1997 SAD, there has been a significant increase in research on ERVs. We have reviewed 14 studies in this update document. The ERV studies were conducted in North and South America, Europe and Asia, and included diverse climates, socioeconomic factors and lifestyles. Using single- and multi-pollutant models, the majority of these studies demonstrate a significant association between PM and respiratory ERVs of children and the elderly. Most studies using multi-pollutant models show that gaseous pollutants did not substantially attenuate PM associations with respiratory ERVs. Most studies did not use GAM. These studies demonstrate results that are consistent with those from GAM analyses. Only one study investigated cardiac ERVs for the elderly, and it shows a significantly positive association for PM10 and PM2.5 but not for sulphate and coefficient of haze (CoH) using single-pollutant models. With multi-pollutant models, the association between PM and cardiac ERVs disappeared, suggesting that a large part of cardiac effects may be attributed to gaseous pollutants. Since only one study looked at cardiac ERVs, more research should be done on this subject.

Long-Term Exposure and Health Effects

A major concern arising from the SAD (1999) review was that most of the long-term effect studies used a cross-sectional design, the results of which cannot infer a causal relationship due to the absence of information on time sequence. In SAD (1999) we reviewed two cohort studies that have substantially improved the knowledge of long-term mortality effects of PM (Dockery et al. 1993; Pope et al. 1995). As part of the Harvard Six Cities Study, Dockery et al. (1993) had prospectively followed a cohort of 8,111 adult subjects in the northeast and midwest United States for 14–16 years beginning in the mid-1970s. The authors found that higher ambient levels of fine particles (PM_{2.5}) and sulphate were associated with a 26% increase in mortality from all causes when comparing the most polluted to the least polluted city, and that an increase in fine particles was also associated with increased mortality from cardiopulmonary disease. The RRs in all-cause mortality were associated with a difference (or range) in ambient fine particle concentrations of 18.6 µg/m³ and a difference of ambient sulphate concentrations of 8.0 µg/m³, comparing the least polluted to the most polluted city. This study did not control for co-pollutants.

In the much larger American Cancer Society (ACS) Study, Pope et al. (1995) followed 552,138 adult subjects in 154 U.S. cities beginning in 1982 and ending in 1989. Again, higher ambient levels of fine particles were associated with increased mortality from all causes and from cardiopulmonary disease in the 50 cities for which fine particle data were available (sampled 1979–1983). Higher ambient sulphate levels were associated with increased mortality from all causes, cardiopulmonary disease, and lung cancer in the 151 cities for which sulphate data were available (sampled 1980–1982). The differences between all-cause mortality in the most polluted city and the least polluted city were 17 and 15% for fine particles and sulphate, respectively (with a range of 24.5 µg/m³ for fine particles and of 19.9 µg/m³ for sulphate). This study also did not control for co-pollutants.

SAD (1999) also reviewed studies on chronic respiratory illness. The increases in prevalence and incidence of chronic bronchitis and decreases in lung function, capacity, growth and development that were shown in children across North America after chronic or lifetime exposure to acidity, sulphate and fine particulate pollution, should be considered to be true chronic effects. There were indications also from a long term (20–25 years) cohort study in older adults that this increased incidence of disease, and probably also the reduced lung capacity that accompanies it, are carried over into adulthood as increased susceptibility to adverse effects of air pollutants. Although the development of lung cancer was also associated with fine particulate air pollution, the associations were weak by comparison with other lifestyle factors such as smoking.

Mortality of general population

In this Update document, we have reviewed nine new reports on long-term exposure to various airborne particle metrics and mortality, including the reanalysis of the Harvard Six Cities Study and the American Cancer Society (ACS) study. All of them used prospective study designs by which the researchers followed the participants over years until death occurred, thus illustrating an exposure-to-outcome time sequence. The outcomes include total mortality, cardiovascular and respiratory mortality, and mortality due to lung cancer. Five studies used multi-pollutant models to adjust for co-pollutants. The majority of the studies demonstrate significant associations between PM and various mortality outcomes. Studies that used multi-pollutant models show that gaseous pollutants,

especially SO₂, reduced risk estimates for PM to some degree, yet the statistical significance of PM associations remained.

Studies that examined the effects of both fine and coarse particles show that fine particles had a stronger association with respiratory effects than coarse particles, and the size of risk estimates follows the sequence of PM_{2.5} > PM₁₀ > PM_{10-2.5}.

Two studies attempted to tease out the effect of indoor exposure to particles by applying an indoor/outdoor exposure factor (derived from time activity pattern of participants) to ambient particle concentrations. The risk estimates for outdoor PM_{2.5} and PM₁₀ were not affected by this treatment.

Two studies used both annual mean PM₁₀ concentrations and PM₁₀ (100) (denoting days per year when PM₁₀ was above 100 µg/m³). The results indicate that PM₁₀ (100) had a stronger association with respiratory mortality and lung cancer mortality than annual PM₁₀ concentration did. This suggests that daily PM₁₀ concentrations may be a better indicator of health effects. Since the two studies were conducted by the same group of researchers on the same population (California non-smoking, non-Hispanic white Seventh-day Adventists), the results need to be confirmed independently using other datasets.

With respect to people who may be more susceptible to long-term effect of PM, male subjects and subjects with lower education levels seem to be more at risk of ambient particle pollution.

Most studies used the Cox proportional hazards survival model to analyze data. Two studies used a non-parametric spatial smooth component (LOESS) with GAM framework to account for potential spatial autocorrelation. These two studies show that spatial autocorrelation did exist in the ACS dataset, and yet correction of this did not fundamentally change the risk estimates of PM.

Effects on cancer incidence

Among four studies that investigated the associations between long-term exposure to ambient PM and lung cancer, three of them demonstrate a significant association between chronic exposures to PM₁₀ or PM_{2.5} and lung cancer incidence or mortality. These studies are longitudinal cohort studies by design, and used Cox proportional hazards models to analyze the associations, with adjustment of potential confounding factors including (but not limited to) cigarette smoking, occupational exposure, age, gender, and body mass index.

We reviewed 5 case-control studies that examined the relationship between long-term exposure to traffic-related air pollution and adult lung cancer or childhood cancers. The researchers used Geographic Information System to map the distribution of traffic in the communities and to estimate the exposure levels to each residence. They used either nitrogen dioxide or traffic density as an indicator of traffic-related air pollution, and none of the studies provided PM monitoring information. Cases were matched by age, gender, calendar year and in most studies by neighbourhoods. Four of these studies demonstrate a significant association between traffic and lung cancer incidence or childhood leukemia or lymphoma. These results suggest that automobile vehicle emissions may be a particularly important source for air pollution-related cancer mortality or incidence. Although these traffic studies do not deliver direct evidence to show the linkages

between PM pollution and cancer incidence, given that fine PM and its precursors such as NO_x and SO₂ constitute a major component of motor vehicle emissions, results from these studies still provide useful evidence for the association between PM emissions and cancer development.

Respiratory effects on children

We have reviewed six studies that investigated the relationship between long-term exposure to air pollution and respiratory symptoms, lung function changes and new cases of asthma (incidence) of children from Southern California communities. Three studies used a cross-sectional method to examine the prevalence of symptoms and lung function, while three studies used prospective method to follow up the subjects and observe the effects of air pollution on lung function growth and the health impacts of air pollution intervention. All six studies demonstrate significant association between PM (PM₁₀, PM_{2.5} and aerosol acidity) and adverse respiratory endpoints. Prospective studies demonstrate that high PM₁₀ was associated with a significant reduction in lung function growth and an increase in new cases of asthma over time. The study that examined the changes of lung function growth rate due to migration of children provides an objective support to a causal relationship of PM pollution with adverse effect on children, and it gives an interesting insight into positive intervention.

When gaseous pollutants were adjusted in the analytical models, the results show similar trend for airborne particles. Studies that examined the effects of both fine and coarse particles show that fine particles and aerosol acidity appear to have stronger association with respiratory effects than coarse particles.

Susceptibility studies show that children who had asthma and those who spent more time outdoors seem to be more at risk than those without asthma or those who spent less time outdoors.

All studies used logistic regression and linear regression rather than GAM for data analyses.

Effects on low birth weight, birth defects, and infant mortality

We have reviewed three studies on low birth weight, one study on birth defects and two studies on mortality. The results demonstrate that long-term exposure to airborne particles was associated with low birth weight (LBW). The effect of PM on birth defects is ambiguous and needs to be investigated further. The study on intrauterine mortality using a time-series method shows no significant association between acute exposure to PM₁₀ and foetal mortality. The study examining long-term exposure reports significant associations between annual averages of PM (PM₁₀, sulphate and non-sulphate PM₁₀) and infant mortality. The association of infant mortality with fine PM was stronger for LBW infants than for normal-birth-weight infants. Given the relatively small number of studies and the relative importance of the endpoints, additional work needs to be carried out to verify the epidemiological findings and to examine the biological mechanisms.

Field Studies

Field studies are epidemiological studies designed to examine groups of people engaged in normal activities in the natural environment in which pollutant levels may be closely monitored, and exposures are usually to the ambient mix of pollutants. These studies have the advantage that the subjects may be either healthy people or patients with pre-existing disease(s), of all ages, and their

medical histories, lifestyles and activity patterns and episodes of illness are closely followed. Endpoints studied may be clinical, biochemical or physiological changes. Personal exposure may be conducted to reduce exposure misclassification.

All the field studies reviewed in the 1997 PM SAD focused on the respiratory effects of air pollution, including lung function changes and respiratory symptom reports, mostly on children. No study examined effects on cardiovascular system. A very limited amount of information on health effects on the elderly was reported and reviewed. The review documented an association between PM pollution and small reversible decrements in lung function in healthy children, and in both adults and children who have some form of pre-existing respiratory conditions, particularly asthma. These changes were often accompanied by increases in respiratory symptoms. Respiratory illness-related restrictions in activity severe enough to result in an increased number of lost work days in adult workers and in school absences in children were also demonstrated to be associated with increased concentrations of ambient PM. Because of the findings in time-series studies that show significant associations of PM with cardiovascular mortality and hospital admissions, some researchers have turned their attention to PM effects on the cardiovascular system and hematology in the elderly, and on the immune system. Of course, there also have been more data published on respiratory effects.

In recent years, researchers have significantly advanced knowledge on particle-related adverse health effects in field (panel) studies. The new research includes the following:

1. In addition to respiratory effects, effects on cardiovascular system and hematology have also been investigated. This constitutes an attempt to find evidence from another angle to corroborate the findings from time-series studies. Overall studies have demonstrated that PM pollution is associated with increased heart rate and decreased heart rate variability (HRV) in adults. PM pollution has also been found to be associated with increased blood plasma viscosity, accompanied by an increase in plasma fibrinogen in adults. One study found that in the elderly PM pollution was associated with a decrease in blood fibrinogen, platelets and hemoglobin, which might be attributed to an early consumption of coagulate factors. It has been proposed that PM pollution may initiate autonomic nervous system-activated changes in heart rate and HRV, blood pressure and blood viscosity, which consequently may increase the likelihood of sudden cardiac death.
2. Studies using traffic density or the distance between motorways and homes or schools as indicators of air pollution demonstrate significantly positive association between traffic-related pollution and children's respiratory symptoms, lung function decrements, and allergy. One study reported that lung function decrements had a stronger association with truck traffic density than with automobile, suggesting that diesel exhaust might contribute more to the adverse respiratory effects than gasoline exhaust. However, most of the studies did not characterize which of the air pollutants from vehicle emissions contributed to children's respiratory health problems, though 2 studies used black smoke (BS) as an approximation to diesel exhaust particles, and reported a significant association between black smoke concentrations in schools and lung function decrements and symptoms. Overall, these studies are cross-sectional or case-control in design, and thus the results should be interpreted with caution when inferring a causal relationship between vehicle emission-related particulate matter and adverse health effects. Nevertheless, these studies present a fresh and novel direction on conducting a sector-related health effect study.

3. Many more field studies on children's health have been conducted world-wide in various meteorological and socio-economic conditions and air pollution combinations. The majority of recently published studies demonstrate a significant association between particulate air pollution and children's respiratory health effects. Studies using prospective design to follow children for several years demonstrate that lung function growth in children is slowed by particulate pollution. Two studies also show that following a cleaning-up of particulate air pollution there was a substantial reduction in the prevalence of children's respiratory illness. These intervention studies from another angle further corroborate the claim that particulate pollution causes adverse health effects in children. These studies also demonstrate that air quality improvement contributes significantly to socio-economic benefits.

A 14-European city meta-analysis (PEACE), an important study, did not show a consistent association between PM_{10} or black smoke and lung function changes. The authors thought that the coincided influenza epidemic might have confounded the outcomes.

4. Two studies reported a seemingly protective effect of antioxidant vitamin supplements against PM_{10} -associated lung function decrements, suggesting a mechanism of pollutant-induced oxidative stress in the body. These studies also support a causal relationship between air pollution and adverse respiratory health effects.
5. In terms of susceptible groups, studies examining changes in electrocardiography have shown that persons with cardiovascular conditions or with high blood viscosity had significantly more changes in heart rate and heart rate variability in response to variation of daily $PM_{2.5}$ or total suspended particulate (TSP) concentrations compared with normal subjects. Most studies that compared the responses of healthy persons with persons with respiratory conditions show that children or adults who had increased IgE, bronchial hyperresponsiveness, or asthma, had more respiratory symptoms and more decrements in lung function in association with ambient PM_{10} or $PM_{2.5}$, than their healthy counterparts.
6. In addition to findings on conventional health effect markers such as symptoms and lung function, some researchers also looked into other biological markers. The immunological biomarkers detect subtle sub-clinical modifications of immune system in relation to air pollution, and thus may provide mechanistic evidence for the adverse effects of particulate pollution. The results from a cross-sectional study, although cannot conclude an etiological linkage between $PM_{2.5}$ pollution and immunological effects, warrant further exploration in this field.
7. Other biological markers that have been developed based on particle toxicological mechanisms include the oxidation of low density lipoprotein, nasal lesions, DNA aberration and mutation of p53 tumor suppression gene in nasal biopsy, X-ray films for lung hyperinflation, serum Clara cell protein, and nitric oxide. Some of these biomarkers, such as DNA aberration and lung hyperinflation, represent chronic effects of exposure. These markers to certain degree have all shown some significance in association with air pollution. Yet none of these biomarkers are specific for airborne particles. Well-designed experimental studies or field studies with good statistical tools may overcome this shortcoming.

Controlled Human Exposure Studies (Clinical Studies)

SAD (1999) concluded that overall the clinical data did not lend much support to the observations in the epidemiological studies. Controlled exposure to ambient concentrations of acid aerosol or acid sulphate or nitrate aerosols had not produced much adverse changes in lung function, mucociliary clearance and airway reactivity in normal subjects, although asthmatic children and adolescents appeared responsive to lower concentrations of acidic aerosols. We recognized that data from these types of studies were very limited, and most of these studies had been conducted using artificial particles that do not reflect the complexity of ambient particles. These clinical studies did not report whether exposure to particles caused any cardiovascular effects as observed in epidemiological studies.

Newly published human clinical studies have had significant improvements with respect to using freshly produced “real world” particles such as concentrated ambient particles or diesel exhaust particles (DEP), at levels often encountered by general population or by occupational groups. The observation endpoints consist of not only respiratory effects but also cardiovascular effects. Particle deposition studies compared depositions in healthy subjects against those in various subgroups such as smokers and individuals with cardiorespiratory diseases.

Controlled human exposure studies using real-time ambient particles show that outdoor fine particles at concentrations sometimes encountered by the general population appear to be capable of inducing a mild inflammation in the lower respiratory tract in healthy subjects. Ambient particles also induced an increase in blood fibrinogen concentration, a blood coagulation factor whose increase has been linked to increased blood viscosity and coagulation. A very recent study demonstrates that concentrated $PM_{2.5}$ with ozone caused significant reduction in arterial vasodilation in healthy adults, suggesting a response of vasoconstriction. Data from these studies warrant further research to investigate ambient particle effects on various age groups and on subjects with various health conditions.

Data from studies using controlled exposure to diesel exhaust show a marked inflammatory cell infiltration in the airways of healthy subjects. The levels of DEP used in these studies often occur in work settings. Although the respiratory effects seem to be attributable to particles, other studies using similar exposure facility but with a particle trap have shown that a reduction of particles in diesel exhaust by 50% was not sufficient to completely abolish adverse respiratory effects. These data suggest that finer particles and gaseous compounds together in diesel exhaust induce lung inflammation.

The Utah Valley particle study, although using an unnatural exposure means (i.e. intratracheal instillation), provides some mechanistic interpretation to the epidemiological findings of particle-associated adverse health effects in Utah Valley. This study suggests that metals in PM_{10} may play a role in adversely affecting lung macrophage function and causing cell death.

Results from deposition studies demonstrate that smokers and individuals with respiratory diseases tend to have more particles deposited into their lungs compared with healthy subjects, which may lead to more severe lung injury. The data may contribute to providing a biologically plausible explanation for the epidemiological findings that people with pre-existing cardiorespiratory

illnesses are more at risk for particle pollution-related mortality and morbidity.

Toxicological Studies

The 1999 PM SAD concluded that particles may cause toxicological effects in experimental animals and in cultured cells. These effects include decreased lung function, decreased (or in some cases increased) particle clearance from airways, altered alveolar macrophage numbers and functions, modified immunological function, cytotoxicity and histological changes, and cardiographic abnormalities. There is also evidence that long-term exposure to high levels of particles can lead to lung cancer in rats. Bronchial hypersensitivity to non-specific stimuli and increased morbidity from cardiorespiratory symptoms would most likely occur in animals pre-disposed to cardiorespiratory diseases. Particles in the ambient atmosphere that are most likely to induce acute adverse effects include the fine particle mode, such as acidic sulphates, possibly occurring as a coating on fine or even ultrafine carrier particles. The ultrafine particle mode appears to be of significant toxicological importance, although most ultrafine particles used in these laboratories were of higher toxicity in nature than ambient particles. On the other hand, the coarse particle mode is less likely to induce acute adverse responses. The particle deposition data clearly indicate that total suspended particulate (TSP) is not an appropriate measure of PM for human health effects, as only particles <10 µm in diameter (and possibly up to 15 µm in diameter during mouth breathing) penetrate to the lungs. The interaction between ozone and sulphuric acid evidently is one in which sulphuric acid aerosols enhance the damaging effects of the ozone in the centriacinar region of the lung.

However, in the 1997 PM SAD, the majority of animal studies have used very high concentrations of artificial particles or ambient dusts that had been stored for a long time, which may not reflect the complexity of freshly generated ambient particles encountered by humans. These particles rarely cause animal mortality. Little information was reported on whether age and health conditions affected the susceptibility of animals to particle pollution. Most studies focussed on respiratory effects and reported very little information on particle-induced cardiovascular changes. Because of the uncertainties in extrapolating data from animal and *in vitro* studies to humans due to species differences in anatomy, physiology and biochemistry, the interpretation of results from experimental animal and *in vitro* studies has posed a great challenge. Therefore, the animal studies contribute primarily to an understanding of the mechanisms that may lead to particle effects in humans. These uncertainties limit the application of animal and *in vitro* toxicological data for developing particulate matter control policy.

Significant advancement has been achieved on toxicology research of PM since the 1997 PM SAD was completed. The largest achievements include the following.

1. Concentrated ambient air fine particles have been used to expose to animals by inhalation at doses close to ambient concentrations to allow for examination of adverse health effects of real world particles rather than artificial particles. Many of these studies demonstrate that outdoor fine particles can induce a moderate inflammation in the respiratory system and lung function changes, and anomalies in electrocardiograph.
2. In addition to the investigation of conventional endpoints such as respiratory effects, researchers have started to look into the adverse effects on the cardiovascular system, immune system and neural pathways, trying to figure out why exposure to particles via the respiratory tract may

result in the cardiovascular outcomes seen in epidemiological studies. Cardiovascular effects include abnormal ECG, decreased core body temperature and changes in blood coagulation factors. The immunological effects include severely damaged macrophage function, resulting in reduced responsiveness of macrophages to bacteria endotoxin and reduced production of cytokines, reduced ability to combat bacteria, and reduced production of antiviral agents. Particulate matter may increase the allergic responses initiated by an allergen such as house dust mites and may potentiate allergen-induced lung inflammation. The investigation on neural pathways is still at its beginning stage. Based on the studies using allergens, viruses and tobacco smoke, it has been proposed that PM may activate neural pathways and enhance the sensitivity and reactivity of neural reflex arcs, thus providing a mechanism for the amplification of respiratory cardiovascular effects.

3. New animal models have been designed to mimic the health situation of persons with pre-existing disease. These models allow us to examine whether animals with compromised cardiovascular and respiratory systems are more at risk to particle pollution. These studies demonstrate that animals with pre-existing pulmonary or cardiovascular conditions are more responsive to urban particles, ultrafine metals and ROFA than their healthy counterparts. The particle-induced adverse effects are more severe in those animals with cardiorespiratory illness, and mortality occurred only in these animals when exposed to particles.
4. New studies further demonstrate that oxidative stress induced by PM, especially metal-rich particles, is a very important mechanism in causing cell death, lung inflammation and cardio-physiological responses. There is a wealth of evidence to indicate that reactive oxygen species induced by PM, especially metal-rich particles, may cause oxidative stress and destabilize essential proteins and lipids. This is demonstrated by the capability of airborne particles to deplete endogenous antioxidants, by inhibition of cytotoxicity of particles by radical scavengers, but enhancement of toxicity by a metal chelator. Consequently, we see cell death, lung tissue injury and cardiovascular system disorder.
5. There is very limited analysis on comparative dosimetry of PM, although this is a very important issue, as many of the particle toxicology studies were carried out on animals at particle exposure concentrations far above ambient concentrations. Based on the differences in airway anatomy and physiology between species, a reasonable argument can be made that humans are more susceptible with respect to receiving particles in the alveolar region than are rodents when given the same dose. Doses used in some animal studies are thought to be relevant to human exposure.