CHAPTER 2 - Air Quality and Human Health

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KEY MESSAGES

- A substantial body of epidemiological evidence now exists that establishes a link between exposure to air pollution, especially airborne particulate matter, and increased mortality and morbidity, including a wide range of adverse cardiorespiratory health outcomes. Many time-series studies, conducted throughout the world, relate day to day variation in air pollution to health with remarkable consistency. A smaller number of longer-term cohort studies find that air pollution increases risk for mortality.
- Health effects are evident at current levels of exposure, and there is little evidence to indicate a threshold concentration below which air pollution has no effect on population health.
- It is estimated that the shortening of life expectancy of the average population associated with long-term exposure to particulate matter is 1-2 years.
- Recent epidemiological studies show more consistent evidence of lung cancer effects related to chronic exposures than found previously.
- In general, methodologic problems with exposure classification tend to diminish the risks observed in epidemiological studies so that the true risks may be greater than observed.
- Human clinical and animal experimental studies have identified a number of plausible mechanistic pathways of injury, including systemic inflammation, that could lead to the development of atherosclerosis and alter cardiac autonomic function so as to increase susceptibility to heart attack and stroke.
- The question of which physical and chemical characteristics of particulate matter are most important in determining health risks is still unresolved. There is some evidence to suggest that components related to traffic exhaust and transition metal content may be important.
- Despite continuing uncertainties, the evidence overall tends to substantiate that PM effects are at least partly due to ambient PM acting alone or in the presence of other covarying gaseous pollutants.
- Several studies of interventions that sharply reduced air pollution exposures found evidence of benefits to health. New findings from an extended follow up of the Six City study cohort show reduced mortality risk as $PM_{2.5}$ concentrations declined over the course of follow-up. These studies provide evidence of public health benefit from the regulations that have improved air quality.

2.1 Introduction

The primary objective of any air quality management strategy is to protect human health and the environment. From a policymaker's perspective, several key questions on the issue of health effects arise: i) what is currently known about the impacts of air pollution on public health, ii) which populations are most susceptible, iii) which sources are most damaging to health, iv) what levels of air pollution are safe and how much health improvement can be expected with air quality improvements. A background paper prepared for the NERAM III Colloquium *Strategies for Clean Air and Health* held in Rome in 2003 framed the discussion of scientific evidence on health effects around these key policy questions. A number of major critical reviews have since been published by the World Health Organization (2005, 2006), the US Environmental Protection Agency (2004; 2005; 2006) and Air & Waste Management Association (Pope and Dockery, 2006). This chapter will build on the Rome background paper by presenting new evidence and conclusions from these major reviews.

The focus of this capstone document, as for the NERAM Colloquium series, is on the scientific understanding of outdoor air pollution and its implications for evidence-based risk management. However, there needs to be recognition that air pollution is a broader public health problem with implications for children and adults worldwide. While much of the epidemiological evidence linking air pollution exposures to health impacts focuses on measures of air quality and health in North America and Europe, for millions of people living in developing countries, indoor pollution from the use of biomass fuel occurs at concentrations that are orders of magnitude higher than currently seen in the developed world. Deaths due to acute respiratory infection in children resulting from these exposures are estimated to be over 2 million per year (Brunekreef and Holgate, 2002). While indoor air pollution is responsible for up to 3.7% of the burden of disease in high mortality developing countries, it is no longer among the top 10 risk factors in industrialized countries in regard to burden of disease. More information about indoor air pollution and its consequences can be found in several recent reviews (WHO, 2002; CARB, 2005).

2.2 Effects of Air Pollution on Population Health

Air pollution is pervasive throughout the world, and represents one of the most widespread environmental threats to the population's health. The World Health Organization (2002) has identified ambient air pollution as a high priority in its Global Burden of Disease initiative, estimating that air pollution is responsible for 1.4% of all deaths and 0.8% of disability-adjusted life years globally. Although the magnitude of the estimated increased risk might appear to be small, the numbers of people affected are large when extrapolated to the entire population.

NERAM III convened 200 air quality scientists, policymakers, industry representatives and non-governmental organizations from 22 countries to exchange perspectives on the interface between policy and science on air pollution health effects, air quality modeling, clean air technology, and policy tools. The Conference Statement (http://www.irr-neram.ca/rome/rome.html), which was based on breakout group discussions, keynote presentations from North America and Europe and plenary discussions, highlighted the importance of air pollution as a local, national, and global public health concern.

Despite the seemingly consistent message from the public health community with regard to the need for reduction of risk to the extent possible, there are unresolved scientific issues with attendant uncertainties that are problematic for decision-makers. The recent decision by the United States Environmental Protection Agency (US EPA) to retain the annual average standard for $PM_{2.5}$ of 15 $\mu g/m^3$ averaged over 3 years, despite the recommendation of US EPA's Clean Air Scientific Advisory Committee (CASAC) for a lower value, is illustrative of how controversy can arise in the setting of uncertainty. In fact, as air pollution levels have declined in North America and Europe, epidemiological studies become less likely to detect the smaller absolute effects that would be

anticipated and methodologic concerns assume greater credibility as an alternative to causation in producing observed findings. Uncertainty continues to persist even though many methodological concerns around epidemiological studies have now been addressed and several key reanalyses have been carried out. For example, the extensive reanalysis of two prospective cohort studies, the Harvard Six Cities Study and the American Cancer Society's Cancer Prevention Study II (Krewski et al., 2000; 2004; 2005a; 2005b), confirmed the original findings. Large, pooled time series studies have also been carried out that produce more precise risk estimates than single city studies, as frequently reported in the past (Stieb et al., 2002).

Scope of Health Concerns

The range of adverse health effects associated with exposure to air pollution has often been depicted as a pyramid (Figure 2.1). In this formulation, a smaller proportion of the population is affected by the most severe health outcomes such as premature death, hospital admissions and emergency room visits and a greater proportion is impacted by conditions that affect quality of life such as asthma exacerbations that result in work or school absences and by subclinical effects, such as slowed lung function growth in childhood and accelerated development of atherosclerosis. The range of effects is broad, affecting the respiratory and cardiovascular systems and impacting children, the elderly, and those with pre-existing diseases such as chronic obstructive pulmonary disease (COPD) and asthma. The risk for various adverse health outcomes has been shown to increase with exposure and there is little evidence to suggest a threshold below which no adverse health effects would be anticipated (WHO, 2005).

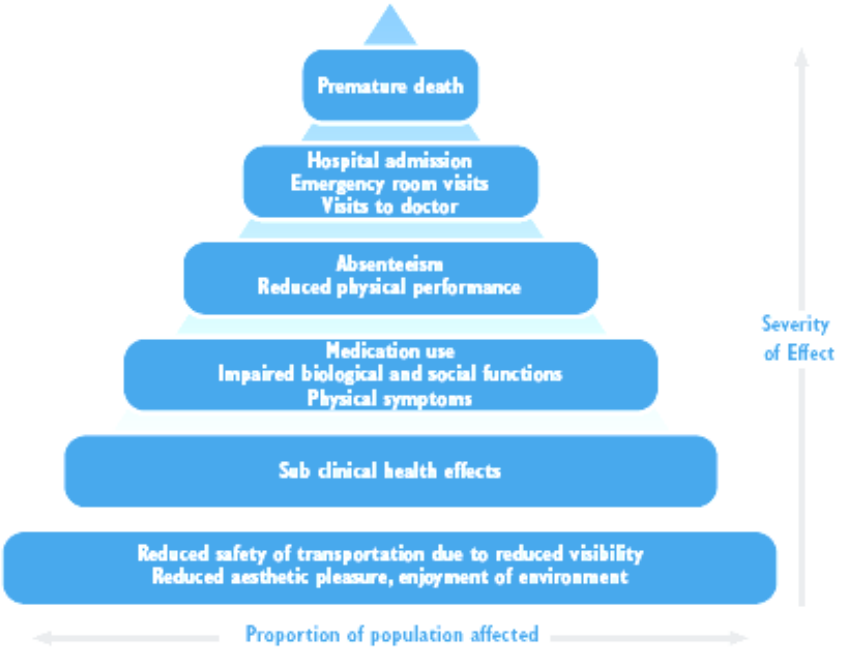

Figure 2.1. Pyramid of air pollution health effects.

Source. British Columbia. Provincial Health Officer (2004). Every Breath you Take. Provincial Health Officer's Annual Report 2003. Air Quality in British Columbia, a Public Health Perspective. Victoria, BC. Ministry of Health Services. Adapted from Health Effects Air pollution (Pyramid of Health Effects), by Health Canada.

Figure 2.2 describes the range of health outcomes measured in epidemiological and human clinical studies. The impacts of short term and long term air pollution exposures have been studied extensively in North America and Europe for health endpoints towards the peak of the pyramid (i.e. premature death, hospital admissions and emergency room visits). More recent studies have examined the health effects of air pollution in low and middle income countries where air pollution levels are the highest. The scope of health concerns has broadened from an emphasis on total morbidity and mortality from respiratory causes, such as exacerbations of chronic respiratory diseases, including COPD and asthma, and the respiratory health of children to several adverse cardiac and reproductive outcomes and impacts on susceptible subpopulations, including those with preexisting cardiopulmonary illnesses, children and older adults. Numerous recent single-city studies have expanded the health endpoints reported to be associated with PM exposures including 1) indicators of the development of atherosclerosis with long-term PM exposure; 2) indicators of changes in cardiac rhythm, including arrhythmia or ST-segment changes; 3) effects on developing children and infants; 4) markers of inflammation such as exhaled NO; and 5) effects on organ systems outside the cardiopulmonary systems (USEPA, 2006). The long-range implications for individuals of some of the intermediate markers of outcome remain to be established, but nonetheless they offer usual indicators of population health.

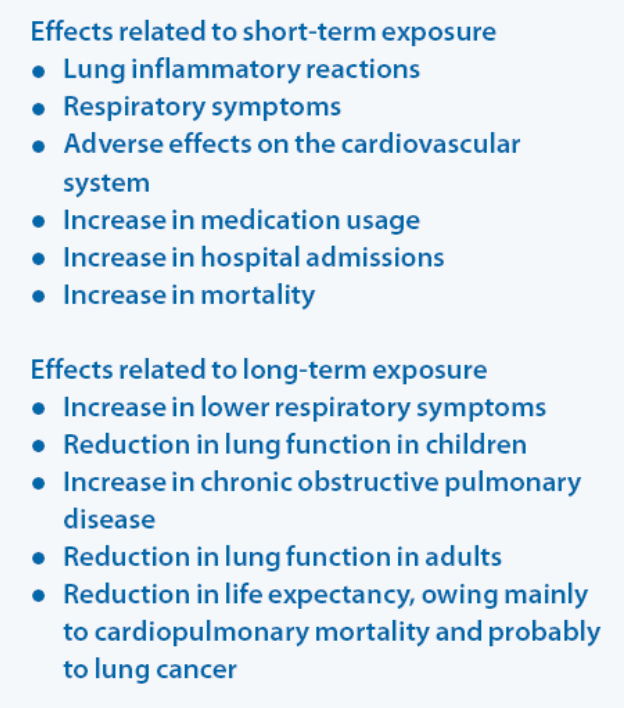

Figure 2.2. Health outcomes measured in studies of epidemiological and human clinical studies
Source: WHO (2006).

2.3 Lines of Evidence

Sources of evidence from which to assess the health effects associated with air pollution exposures include observational epidemiology, toxicological and clinical studies. The findings of these different lines of investigation are complimentary and each has well-defined strengths and weaknesses. The findings of epidemiological studies have been assigned the greatest weight in standard-setting for airborne particles because they characterize the consequences of the exposures that are actually experienced in the community setting.

Epidemiologic Evidence

The evidence on airborne PM and public health is consistent in showing adverse health effects at exposures experienced in cities throughout the world in both developed and developing countries. The epidemiological evidence shows adverse effects of particles associated with both short term and long term exposures. Adverse health effects have been demonstrated at levels just above background concentrations which have been estimated at 3-5 ug/m^3 in the United States and western Europe for $PM_{2.5.}$ (WHO, 2005).

Mortality and Long term PM exposure

Associations between air pollution exposure and mortality have been assessed mainly through two types of epidemiological studies. Cohort studies follow large populations for years and typically relate mortality to an indicator of average exposure to PM over the follow-up interval. Time series studies investigate the association between daily mortality and variation in recent PM concentrations. To establish standards for short term exposures, regulatory agencies rely on the findings of time series studies while findings of cohort studies are used to establish annual standards.

Long term cohort studies of PM and mortality are fewer in number than those of day to day variations. They are typically expensive to carry out and require a substantial number of participants, lengthy follow-up and information on PM exposure as well as potential confounding and modifying factors. Most of the studies have been carried out in the US but findings have also been reported for two European studies. Two studies of the health effects of long term exposure to air pollution in large populations have been used extensively in the development of ambient air quality standards for PM_{10} and $PM_{2.5}$.

The Harvard Six Cities Study (Dockery et al., 1993) was the first large, prospective cohort study to demonstrate the adverse health impacts associated with long term air pollution exposures. This study demonstrated that chronic exposure to air pollutants is independently related to cardiovascular mortality. In the group of 8,111 adults with 14 to 16 years of follow up, the increase in overall mortality for the most-polluted city versus the least polluted city was 26%. The range of exposure to PM across the six cities was 11 to 29.6 μg/m^3 for fine particles

The American Cancer Society established its Cancer Prevention Study (CPS) II in the early 1980s. A subcohort with air pollution data available for counties of residence has been used to assess mortality in relation to air pollution (Pope et al., 1995). The cohort includes approximately 552,138 adults who resided in all 50 states. This study linked chronic exposure to multiple air pollutants to mortality over a 16 year period. In these two studies robust associations were reported between long term exposure to $PM_{2.5}$ and mortality (Dockery et al., 1993; Pope et al., 1995).

An independent reanalysis of these two studies was undertaken by the Health Effects Institute in response to industry demands and a Congressional request (Krewski et al., 2000, Pope 2002). The HEI re-analysis largely corroborated the findings of the two studies. In the Six Cities Reanalysis the increase in all-causes of death linked to fine particles was 28 percent across the pollution gradient from the most to the least polluted city, compared to the original estimate of 26%. For the ACS study, the increased risk of all cause death associated with fine particles was 18% in the reanalysis, compared to 17% reported by the original investigators. An extended follow up of the ACS study indicated that the long term exposures were most strongly associated with mortality from ischemic heart disease, dysrhythmias, heart failure and cardiac arrest (Pope et al., 2004). For

these cardiovascular causes of death, a 10 μg/m^3 elevation of $PM_{2.5}$ was associated with an 8-18% increase in risk of death. Mortality attributable to respiratory disease had relatively weak associations. Recent analysis of the Los Angeles component of the ACS cohort suggests that the chronic health effects associated with within-city gradients in exposure to $PM_{2.5}$ may be even larger than those reported across metropolitan areas (Jerrett et al., 2005).

An extended analysis to include deaths to the year 2000 confirmed previous findings. The increased risk of all cause and cardiopulmonary and lung cancer death rose 18 to 30 percent respectively, though that of lung cancer was 2 % (Pope et al., 2002).

Laden's (2006) report on the extended follow up of the Harvard Six Cities Study found effects of long term exposure to particulate air pollution that are consistent with previous studies. Total, cardiovascular, and lung cancer mortality were positively associated with ambient $PM_{2.5}$ concentrations. Reduced $PM_{2.5}$ concentrations (mean $PM_{2.5}$ concentrations across the six cities were 18 μg/m^3 in the first period and 14.8μg/m^3 in the follow up period) were associated with a statistically significant reduction in mortality risk for deaths due to cardiovascular and respiratory causes, but not for lung cancer. This is equivalent to a relative risk of 1.27 for reduced mortality risk, suggesting a larger effect than in the cross sectional analysis. The study strongly suggests that reduction in fine PM pollution yields positive health benefits; however, $PM_{2.5}$ concentrations for the more recent years were estimated from visibility data, which introduces uncertainty in the interpretation of the results of the study.

The Adventist Health and Smog (AHSMOG) study followed cancer incidence and mortality for six years in a group of 6,338 nonsmoking California Seventh-day Adventists, from 1977 to 1987. In 1999, researchers updated the study to follow the group through 1992. In the original analysis, levels of inhalable particles (PM_{10}) were estimated. In the update, data from pollution monitors were available. Among men, increased particle exposure was associated with a rise in lung cancer deaths of 138 percent and in men and among women exposure was associated with increased mortality from non-malignant respiratory disease of 12 percent (Abbey et al., 1999). In 2005, 3239 nonsmoking non-Hispanic white adults who had been followed for 22 years were examined. Monitoring data was available for both PM_{10} and $PM_{2.5}$. As levels of $PM_{2.5}$ rose, the risk of death from cardiopulmonary disease increased by 42 percent (Chen et al., 2005).

The relative risk estimates from the major North American cohort mortality studies are summarized in Figure 2.3.

A new study involving selected California participants in the first CPS study indicated an association between $PM_{2.5}$ and all-cause death in the first time period of the study (1973-1982) but no significant association in the later time period (1983-2002) when $PM_{2.5}$ levels had declined in the most polluted counties. It is noted that the study's use of average $PM_{2.5}$ values for California counties as the exposure indicator likely leads to exposure error as California counties are large and quite topographically variable (Enstrom et al., 2005).

The EPRI-Washington University Veterans' Cohort Mortality Study used a prospective cohort of up to 70 000 middle-aged men (51 ±12 years) assembled by the Veterans Administration several decades ago. No consistent effects of PM on mortality were found. However, statistical models included up to 230 terms and the effects of active smoking on mortality in this cohort were clearly smaller than in other studies, calling into question the modelling approach. Also, only data on total mortality were reported, precluding conclusions with respect to cause-specific deaths. A recent analysis of the Veteran's cohort data reported a larger risk estimate for total mortality related to $PM_{2.5}$ in single pollutant models than reported in the previous analysis. There was a strong relationship between mortality and long term exposure to traffic (traffic density based on traffic flow rate data and road segment length) than with $PM_{2.5}$ mass. In multi-pollutant models including traffic density, the association with $PM_{2.5}$ was not statistically significant (Lipfert et al., 2006).

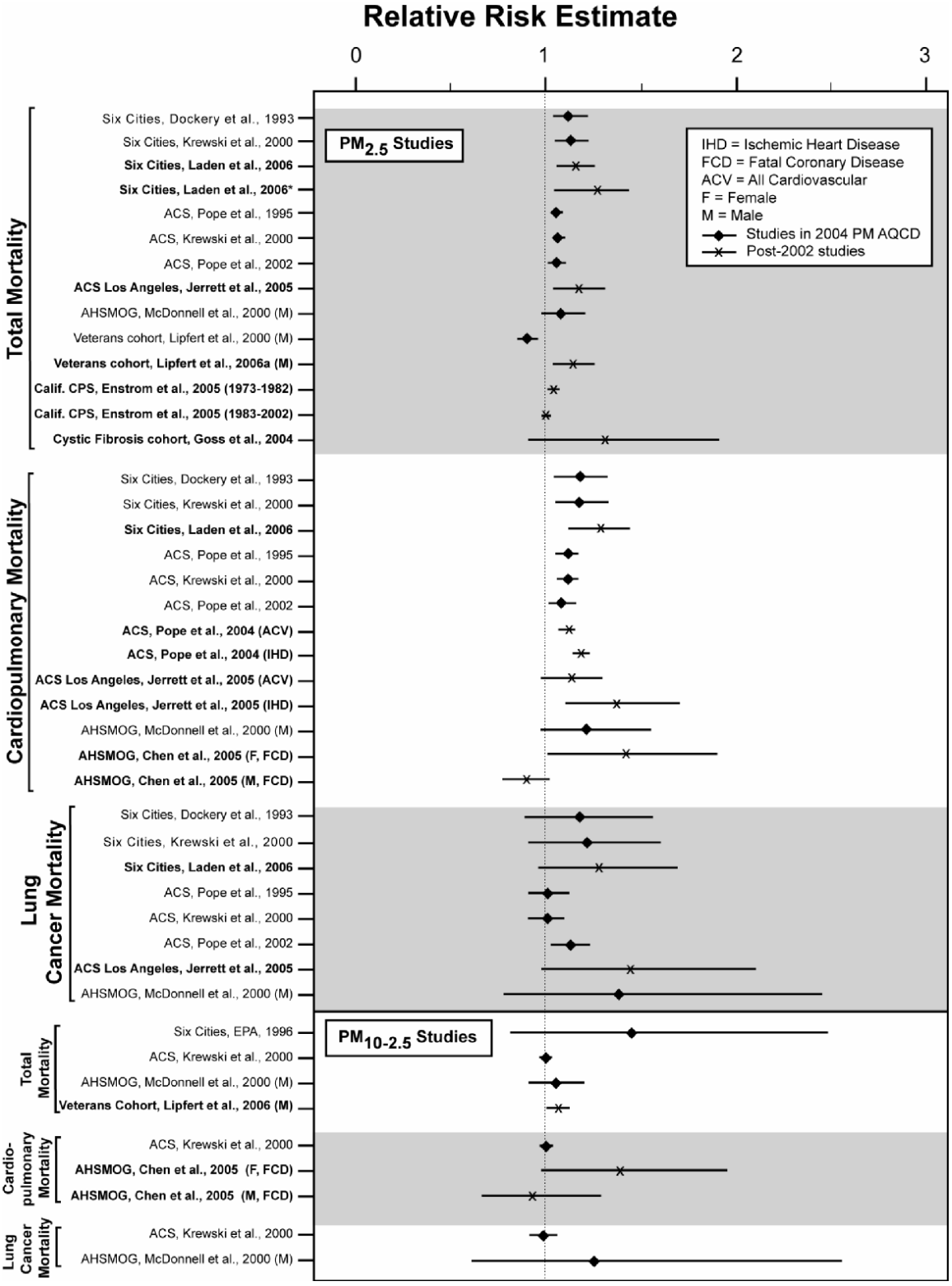

Figure 2.3. Relative risk estimates (and 95% confidence intervals) for associations between long-term exposure to PM (per 10 $PM_{10-2.5}$) and mortality. *Note the second result presented for Laden et al. (2006) is for the intervention study results. Source: US EPA (2006).

A positive but not statistically significant association was reported in a cohort of persons in the US. with cystic fibrosis cohort that focused primarily on evidence of exacerbation of respiratory symptoms. The power of the study to detect association was limited as only 200 deaths had occurred in the cohort of over 11,000 people. The mean $PM_{2.5}$ concentration was 13.7 $\mu g/m^3$ (Goss et al., 2004).

Further evidence to support an association between long-term air pollution exposure and fatal cardiovascular disease comes from recent cohort studies conducted in Sweden (Rosenlund et al., 2006) and Germany (Gehring et al., 2006). These European studies support US studies and increase confidence in the global applicability of the observations.

Mortality and short term exposure studies

Daily time series studies examine variations in day-to-day mortality counts in relation to ambient PM concentration measured by air quality monitoring networks. In general, the evidence from daily time series studies shows that elevated PM exposure of a few days is associated with a small increased risk of mortality. Large multi-city studies in Europe (APHEA2 (Air Pollution and Health: A European Approach 2), and the US (NMMAPS based on the largest 90 US cities) indicate that the increase in daily all-cause mortality risk is small but consistent. Concern over the statistical software used in the original analyses prompted a re-analysis of the NMMAPS and APHEA data, along with some other key studies, that was organized by the Health Effects Institute (HEI).

The NMMAPS estimate, based on the largest 90 cities was revised downward from 0.51% to 0.21% per 10 $\mu g/m^3$ PM_{10} (95% CI, 0.09 – 0.33) and from 0.51% to 0.31% for cardiorespiratory mortality. The APHEA mortality data reanalysis revealed that European results were more robust to the method of analysis. The WHO meta-analysis estimate (21 of 33 estimates from APHEA2) was 0.6% per 10 $\mu g/m^3$ (95% CI, 0.4-0.8) for daily all cause mortality and 0.9% for cardiovascular mortality. For PM_{10} and $PM_{2.5}$ the effect estimates are larger for cardiovascular and respiratory causes than for all-cause mortality. The higher European estimates may be due to differences in analytic approaches and other aspects of the methodology as well as the possibility of a difference in the true effect of PM arising from differing pollution or population characteristics or exposure patterns in the two continents. Figure 2.4 shows pooled estimates of the relative risks of mortality for a 10 $\mu g/m^3$ increase in various pollutants for all cause and cause-specific mortality from the meta-analysis of European studies (WHO, 2004).

A review of time series studies conducted in Asia also indicates that short-term exposure to air pollution is associated with increases in daily mortality and morbidity (HEI, 2004).

Morbidity

Evidence of associations between exposures and morbidity is complimentary to the information on mortality as it covers a broad range of adverse health effects from changes in biomarkers to clinical disease. Numerous studies have measured the short-term effects of air pollution on morbidity, using clinical indicators such as hospital admissions, counts of emergency room or clinic visits, symptom status, pulmonary function and various biomarkers. These studies have include multi-city time series studies (APHEA-2 hospital admission study; NMMAPS), panel studies of volunteers (PEACE- Pollution Effects on Asthmatic Children in Europe) which have provided data on acute effects on respiratory and cardiovascular systems, and objective measures of lung or cardiac function on a daily or weekly basis, and cross-sectional studies. The case-crossover design has been used to measure risk for acute events, such as myocardial infarction and stroke. In this design, the individual is the unit of analysis and exposures are compared in the "case" period during which the event of interest took place and in one or more "control" periods.

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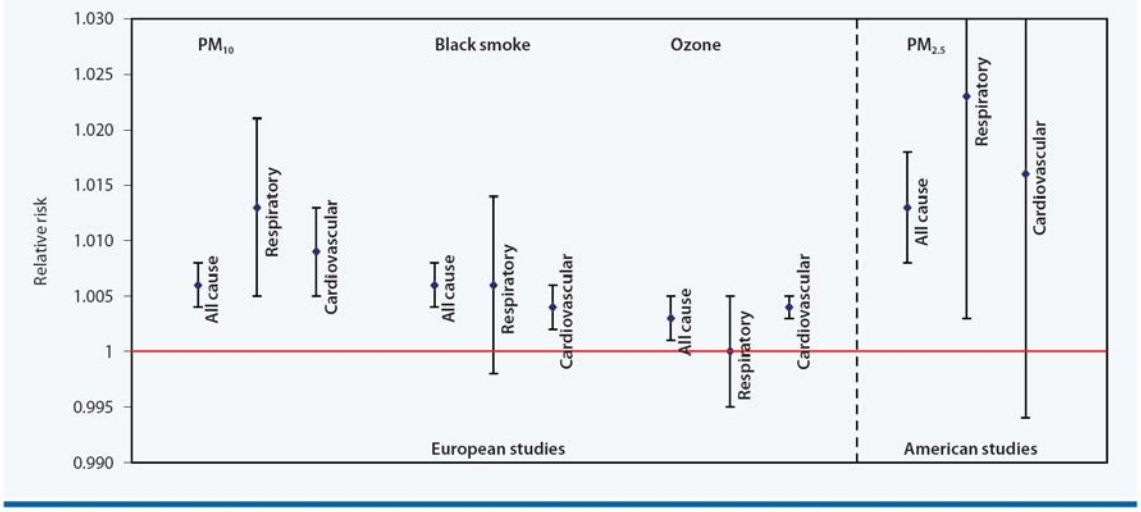

Figure 2.4. Pooled estimates of relative risks of mortality for a 10ug/m^3 increase in pollutant from Meta-analysis of European time series studies. Source: WHO (2006).

Figure 2.5 provides a summary of risk estimates for hospital admission and emergency department visits for cardiovascular and respiratory diseases from US and Canadian studies including aggregate results from one multi-city study. There is consistent evidence of increased risk for hospitalization and emergency room admissions for cardiovascular and respiratory diseases. Recent studies, including a new multi-city study of 11.5 million people in 204 US counties provide further evidence of increased risk for cardiovascular and respiratory disease hospitalization related to short term $PM_{2.5}$ exposure in individuals over 65 years (Dominici et al., 2006). A number of recent Canadian studies show significant associations between respiratory hospitalization and acute exposure to $PM_{10-2.5}$. For example, studies in Vancouver show increased risk of hospitalization for respiratory illness among children under 3, and for COPD and respiratory in the elderly. Studies in Toronto found an increased risk of hospitalization for asthma in children and associations with respiratory illness in the elderly.

Public Health Burden of Mortality

Time series and cohort studies indicate that both short-term and long-term exposures to particulate matter can lead to increased mortality. It is important for public health planning to understand the amount of life-shortening that is attributable to those premature deaths. Researchers have investigated the possibility that short-term exposures may primarily affect frail individuals with pre-existing heart and lung diseases. Studies by Schwartz (2000), Zanobetti et al. (2000a), Zanobetti et al. (2000b); Fung et al. (2003); reanalysis by Zanobetti and Schwartz (2003); Zeger et al.'s analysis (1999); reanalysis by Dominici et al. (2003a, 2003b) all indicate that that the so-called "harvesting" hypothesis cannot fully explain the excess mortality associated with short term exposures to particulate air pollution. These studies suggest that any advance of the timing of death by PM is more than just a few days. Brunekreef (1997) estimated a difference in overall life expectancy of 1.11 years between exposed and clean air cohorts of Dutch men at age 25 using risk estimates from the Dockery et al. (1993) and Pope et al. (1995) cohort studies and life table methods. Similar calculation for US white males yielded a larger estimated reduction of 1.31 years at age 25 (US EPA, 2004). These calculations are informal estimates that provide some insight into the potential life-shortening associated with ambient PM exposures.

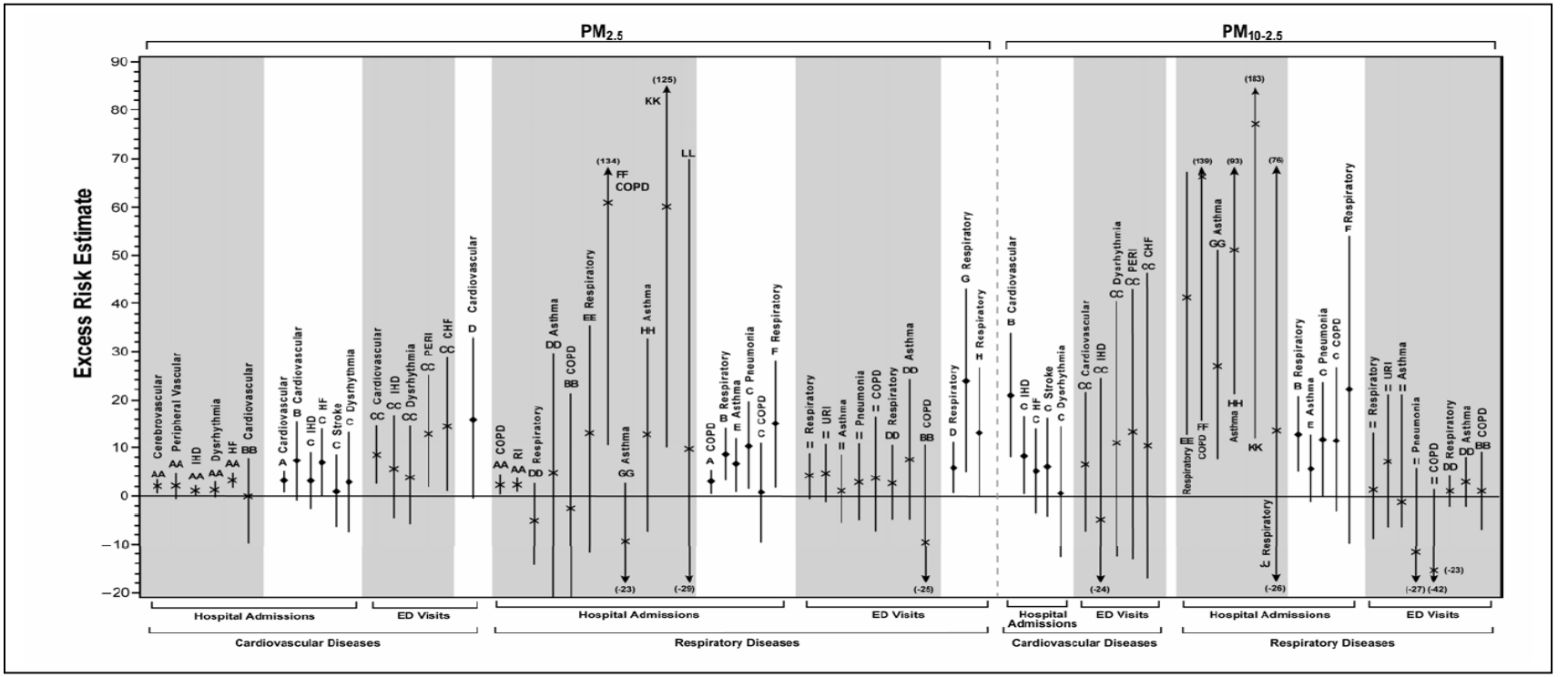

Figure 2.5. Excess risk estimates for hospital admissions and emergency department visits for cardiovascular and respiratory diseases in single-pollutant models for U.S. and Canadian studies, including aggregate results from a multicity study (denoted in bold print below). PM increment used for standardization was 25 μg/m^3 for both $PM_{2.5}$ and $PM10_{-2.5}$. Results presented in the 2004 PM AQCD are marked as ♦, in the figure (studies A through H). Results from recent studies are shaded in grey and marked as × in the figure (studies AA through JJ). (CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; HF = heart failure; IHD = ischemic heart disease; PERI = peripheral vascular and cerebrovascular disease; RI = respiratory infection; URI = upper respiratory infection). Source: USEPA (2006)

A. Moolgavkar (2003), Los Angeles	**AA. Dominici et al. (2006), 204 U.S. counties (age >65 yr)**	GG. Lin et al. (2002), Toronto, Canada (age 6-12 yr, boys)
B. Burnett et al. (1997), Toronto	BB. Slaughter et al. (2005), Spokane (age 15+ yr)	HH. Lin et al. (2002), Toronto, Canada (age 6-12 yr, girls)
C. Ito (2003), Detroit	CC. Metzger et al. (2004), Atlanta	II. Peel et al. (2005), Atlanta
D. Stieb et al. (2000), St. John	DD. Slaughter et al. (2005), Atlanta	JJ. Yang et al. (2004), Vancouver, Canada (age >3 yr)
E. Sheppard (2003), Seattle	EE. Chen et al. (2005), Vancouver, Canada (age 65+ yr)	KK. Lin et al. (2005), Toronto, Canada (age <16 yr, boys)
F. Thurston et al. (1994), Toronto	FF. Chen et al. (2004), Vancouver, Canada (age 65+ yr)	LL. Lin et al. (2005), Toronto, Canada (age <16 yr, boys)
G. Delfino et al. (1997), Montreal		
H. Delfino et al. (1998), Montreal		

Susceptible Populations

The question of who is most at risk for PM health effects depends on the level and length of exposure, as well as individual susceptibility. For acute or short-term exposures to moderately elevated PM concentrations persons with COPD, influenza, and asthma, especially among the elderly or very young are most likely to be susceptible. Although there may be broad susceptibility to long-term repeated exposure, the cumulative effects are most likely to be observed in older age groups with longer exposures and higher baseline risks of mortality (Pope and Dockery, 2006). Recent work suggests that effects on life expectancy are not uniformly distributed but depend on factors such as educational attainment and socio-economic status (Krewski et al., 2000) suggesting that life expectancy could be reduced among disadvantaged population groups (Brunekreef, 2002).

Toxicity of PM Components

The question of which air pollutants, sources, or combinations of pollutants are most responsible for health effects is still unresolved. The literature provides little evidence of a single source or well-defined combination of sources most responsible for health effects. With respect to particle size, the epidemiological, physiological and toxicological evidence suggests that fine particles ($PM_{2.5}$) play the largest role in affecting human health. These particles are generated by combustion processes and can be breathed deeply into the lungs. They are relatively complex mixtures including sulfates, nitrates, acids, metals and carbon particles with various chemical adsorbed onto their surfaces. The roles of coarse particles and ultrafine particles are yet to be fully resolved as are the roles of atmospheric secondary inorganic PM. Other characteristics of PM pollution that are likely related to relative toxicity include solubility, metal content and surface area and reactivity.

Role of Gaseous Co-pollutants

A major methodological issue affecting epidemiology studies of both short-term and long-term exposure effects relates to the use of appropriate methods for evaluating the extent to which gaseous co-pollutants (e.g. O_3, NO_2, SO_2, CO), air toxics, and/or bioaerosols may confound or modify PM-related effects estimates (US EPA, 2004). Gaseous co-pollutants are candidates for confounders because all are known to cause at least some adverse health effects that are also associated with particles. In addition, gaseous pollutants may be emitted from common sources and dispersed by common meteorological factors. For example, both CO and particles are emitted from motor vehicles, SO_2 and $PM_{2.5}$ are both emitted from coal-fired power plants. Krewski et al. (2000) found significant associations for both PM and SO_2 in their reanalysis for the Health Effects Institute of the Pope et al. (1995) study. Numerous new short-term PM exposure studies not only continue to report significant associations between various PM indices and mortality, but also between gaseous pollutants and mortality. In some cities the estimated PM effect is relatively stable when the co-pollutant is included in the model, whereas the estimated PM effect in other cities changes substantially when certain co-pollutants are included. Despite continuing uncertainties, the evidence overall tends to substantiate that PM effects are at least partly due to ambient PM acting alone or in the presence of other covarying gaseous pollutants (US EPA, 2004).

2.4 New Insights

The body of epidemiological, toxicological and clinical evidence on health effects has strengthened considerably over the past few years. A number of areas of advancement in the understanding of PM health effects have emerged (Chow, 2006). While new studies provide important insights, in general they support previous evidence regarding health effects of air pollution exposures (USEPA, 2006).

Cardiovascular Effects: While earlier research focused on the respiratory effects of PM exposure, evidence on cardiovascular outcomes has grown rapidly since 2000. A scientific statement published by the American Heart Association in 2004 indicated concern that the association of airborne particles with adverse

cardiovascular outcomes is causal (Brook et al., 2004). Recent epidemiological, clinical and toxicologic studies report new evidence linking long-term exposure to fine particles with the development of atherosclerosis. A meta-analysis of cardiovascular hospitalization studies in Europe and the US consistently shows an increase in relative risk of cardiovascular hospitalizations associated with increments of 10ug/m^3 and 20 ug/m^3 $PM_{2.5}$. (Pope and Dockery, 2006). Numerous new studies have reported associations between ambient $PM_{2.5}$ and subtle cardiovascular effects such as changes in cardiac rhythm or heart rate variability (EPA, 2006). An extended follow up of the Harvard Six Cities adult cohort study found that cardiovascular (and lung cancer) mortality was associated with $PM_{2.5}$ exposure (Laden et al., 2006).

Mechanisms of Effect: Substantial progress has been made in understanding the biological and chemical mechanisms and pathways by which PM causes adverse effects on human health. Recent research has increased confidence that PM-cardiopulmonary health effects observed in epidemiologic studies are "biologically plausible." Figure 2.6 indicates the various hypothetical pathways of effect that have been explored. Much remains to be learned; however, it appears from human and animal experimental studies that multiple pathways linking exposure to cardiopulmonary health effects are involved with complex interactions and interdependencies. While the evidence is still evolving and is not yet definitive, there is some evidence to suggest that PM exposure is associated with increased heart rate and reductions in heart rate variability suggesting adverse effects on cardiac autonomic function. Other studies have observed, but not consistently, pulmonary or systemic inflammation and related markers of cardiovascular risk such as cardiac arrhythmia, blood pressure changes, arterial vasoconstriction, ST-segment depression, and changes in cardio repolarization (Pope and Dockery, 2006). It is hypothesized that low to moderate grade inflammation induced by long-term chronic PM exposure may initiate and accelerate atherosclerosis. Short-term elevated exposures and related inflammation may increase the risk of making atherosclerotic plaques more vulnerable to rupture, clotting and eventually causing heart attack or stroke.

Exacerbation of existing pulmonary disease, oxidative stress and inflammation, changes in cardiac autonomic functions, vasculature alterations, translocation of PM across internal biological barriers, reduced defense mechanisms and lung damage have all been related to different levels of PM exposure, as well as to different particle sizes and compositions.

Local Level Mortality Risk: A new analysis of ACS data focused on neighbourhood to neighbourhood differences in urban air pollution in Los Angeles using more precise exposure assessment methods found death rates from all causes and cardiopulmonary diseases at least two times higher than previously reported in analyses of the ACS cohort (Jerrett et al., 2005). The highest estimated from original ACS study (Pope et al., 2002) for all cause mortality was 6 percent. Taking into account neighbourhood confounders, the risk was about 11 percent. The annual average level of $PM_{2.5}$ in the most contaminated area was about 24 ug/m^3.

Risks to Diabetics: There is growing evidence to suggest that people with diabetes are more sensitive to cardiovascular effects from air pollution (Jerrett et al., 2005, O'Neill et al., 2005, Zanobetti et al., 2001; Goldberg et al., 2001). Goldberg et al. (2006) reported significant associations between $PM_{2.5}$ and diabetes deaths, as well as total mortality in people with previous diagnoses of diabetes. The acute risk for cardiovascular events in patients with diabetes mellitus may be two-fold higher than for non-diabetics. A study of Boston-area residents found that blood vessel reactivity was impaired in people with diabetes on days when concentrations of particles from traffic and coal-burning power plants were elevated (O'Neill, 2005). These findings are of particular concern given the increasing incidence of diabetes in North America. A recent study has indicated mechanistic evidence for diabetes-related susceptibility (Proctor et al., 2006).

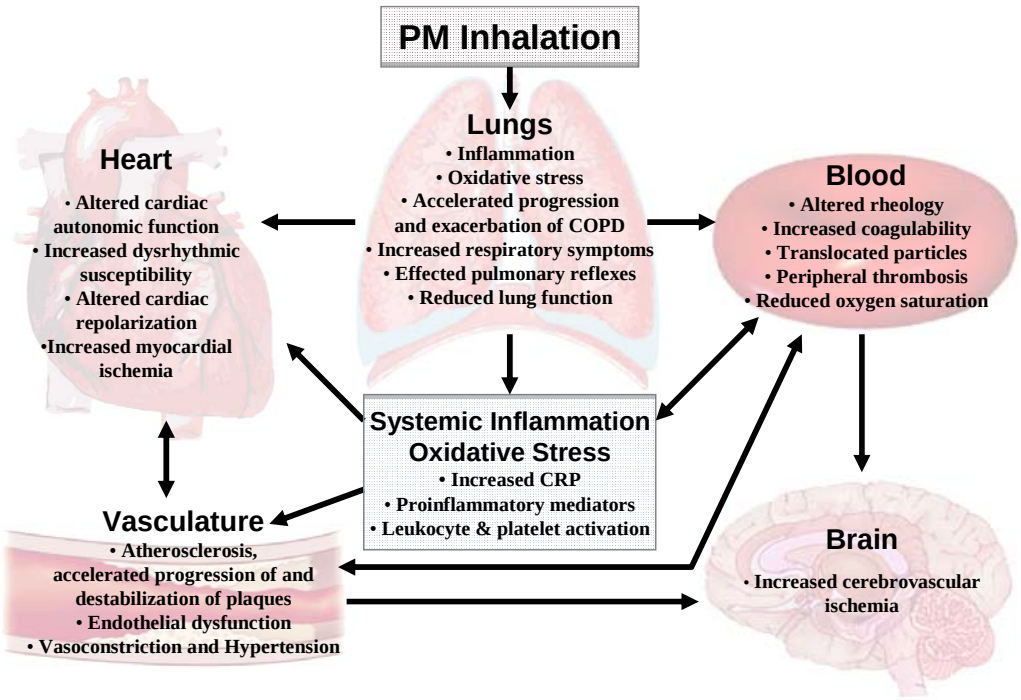

Figure 2.6: Hypothesized pathophysiological pathways linking PM exposure with cardiopulmonary morbidity and mortality. Source: Pope and Dockery (2006).

Risks to Diabetics: There is growing evidence to suggest that people with diabetes are more sensitive to cardiovascular effects from air pollution (Jerrett et al., 2005, O'Neill et al., 2005, Zanobetti et al., 2001; Goldberg et al., 2001). Goldberg et al. (2006) reported significant associations between $PM_{2.5}$ and diabetes deaths, as well as total mortality in people with previous diagnoses of diabetes. The acute risk for cardiovascular events in patients with diabetes mellitus may be two-fold higher than for non-diabetics. A study of Boston-area residents found that blood vessel reactivity was impaired in people with diabetes on days when concentrations of particles from traffic and coal-burning power plants were elevated (O'Neill, 2005). These findings are of particular concern given the increasing incidence of diabetes in North America. A recent study has indicated mechanistic evidence for diabetes-related susceptibility (Proctor et al., 2006).

Risks to Children: There is substantial evidence to indicate that PM exposure in children is associated with adverse effects on lung function, aggravation of asthma, increased incidence of cough and bronchitis. In addition, there is evidence to suggest an increase risk of postneonatal respiratory mortality as concentrations of $PM_{2.5}$ risk by $\mu g/m^3$. Studies on birth weight, preterm births and intrauterine growth retardation also suggest a link with air pollution, but these studies are not sufficient to draw conclusions about causality (WHO, 2005).

Traffic Exposures: Recent evidence has shown that exposures of people living near busy roads are insufficiently characterized by air pollution measurements obtained from urban background locations (Finkelstein et al., 2004; Jerrett, 2005; Brunekreef et al., 2003). In some cities, a significant part of the urban population may be affected by roadway sources. In some

urban areas, elevated exposures may particularly affect socially disadvantaged groups (Finkelstein et al., 2003; Finkelstein et al., 2005; Gunier et al., 2003). A new analysis of the Veterans cohort data reported a stronger relationship between mortality with long-term exposure to traffic than with $PM_{2.5}$ mass (Lipfert et al., 2006).

Thoracic coarse particles: While the 2004 US EPA Air quality criteria document concluded that there was insufficient evidence of an association between long-term exposure to thoracic particles ($PM_{10-2.5}$) and mortality the ASHMOG (Chen et al., 2005) and Veterans cohort study (Lipfert, 2006) provide limited suggestive evidence for associations between long-term exposure to $PM_{10-2.5}$ and mortality in areas with mean concentrations from 16 to 25 ug/m^3. The extended analyses of the Six Cities and ACS cohort studies did not evaluate linkages between health effects and exposure to $PM_{10-2.5}$. Recent epidemiologic studies strengthen the evidence for health effects associated with acute exposure to thoracic coarse particles. Several Canadian studies report respiratory morbidity in cities with low $PM_{10-2.5}$ concentrations. Many studies do not show statistically significant associations with mortality with the exception of a recent study showing a link with cardiovascular mortality in Vancouver. New toxicology studies have demonstrated inflammation and other health endpoints as a result of exposure to thoracic coarse particles. Clinical exposure studies show changes in heart rate and heart rate variability measures among exposed healthy and asthmatic adults. It appears that the observed responses may be linked to endotoxins and metals.

2.5 Conclusions

1. Expanded analyses of ongoing cohort studies continue to provide evidence of associations between of long term exposures to fine particles and mortality (10 ug/m^3 $PM_{2.5}$ is associated with approximately a 6 to 17% increase in relative risk of mortality with some outliers). Mixed results have been seen in the AHSMOG study and VA cohort study and 11 California ACS study. Across the range of particulate air pollution observed in recent studies, the concentration response relationship can reasonably be modeled as linear with no threshold.
2. Previous cohort studies may have underestimated the magnitude of mortality risks. PM mortality effects estimates tend to be larger when exposure estimates are based on more focused spatial resolution and/or when local sources of exposure, especially traffic sources, are considered.
3. The available evidence suggests a small increased lung cancer risk due to combustion-related ambient PM air pollution. The extended follow-up of the ACS and Harvard Six Cities cohort studies both observed PM lung cancer associations which were statistically significant in the ACS study. Outdoor air pollution typically includes combustion-generated respiratory carcinogens.
4. Multi-city time series studies in North America and a meta-analyses of European time series studies support single-city study evidence of an adverse effect of daily PM_{10} exposures on short term mortality at current concentrations (a 10 $\mu g/m^3$ $PM_{2.5}$ or 20 $\mu g/m^3$ PM_{10} increase is associated with a 0.4% to 1.5% increased in relative risk of mortality).
5. While earlier studies focused on evidence of respiratory effects, studies emerging over last 10 years have found a link between both short term and long term exposure to particulate matter and risk of cardiovascular disease and death.
6. Understanding the shape of the concentration-response function and the existence of a no-effects threshold level has played a key role in setting air quality standards. Recent empirical evidence concerning the shape of the PM concentration-response function is not consistent with a well-defined no effect threshold.
7. With respect to acute or short term exposures to moderately elevated PM concentrations, persons with chronic cardiopulmonary disease, influenza, and asthma, especially the elderly or very

young, are most susceptible. A number of indicators of susceptibility have been identified including pre-existing respiratory or cardiovascular disease, diabetes, socio-economic status and educational attainment.

8. PM exposure impacts the health of children including deficits in lung function and lung function growth, increased respiratory illness and symptoms, increased school absences, and hospitalizations for respiratory disease. Several recent reviews generally conclude that PM exposure is most strongly and consistently associated with postneonatal respiratory mortality with less compelling evidence of a link between PM and SIDS, fetal growth, premature birth and related birth outcomes.
9. Recent research has increased confidence that cardiopulmonary health effects observed in epidemiologic studies are biologically plausible. While a single definitive mechanism was not been identified four interrelated pathways involving i) accelerated progression and exacerbation of COPD, ii) pulmonary/systemic oxidative stress, inflammation leading to accelerated atherosclerosis; iii) altered cardiac autonomic function; and iv) vasculature alterations have been hypothesized.
10. There is little evidence of a single major component of PM or a single source or combination of sources that are most responsible for observed health effects, however epidemiological, physiological and toxicological evidence suggests that fine particles play a substantial role in affecting human health. The roles of coarse particles and ultrafine particles are yet to be fully resolved, as are the roles of atmospheric secondary inorganic PM. Other characteristics of PM pollution that are likely related to relative toxicity include solubility, metal content and surface area and reactivity.
11. Despite continuing uncertainties, the evidence overall tends to substantiate that PM effects are at least partly due to ambient PM acting alone or in the presence of other covarying gaseous pollutants.

2.6 Issues for Risk Management

The lack of evidence of a threshold concentration for health effects suggests that continued reductions in ambient pollutant levels will result in public health benefits. It further suggests that the target for reduction should be the background concentration. In view of the potentially large costs associated with further abatement measures to achieve cleaner air, questions arise concerning tradeoffs between expenditures on air quality management and other measures to achieve public health benefits. In air pollution hot spots and areas where standards have been achieved, air quality risk management becomes more complex. Chapter 5 examines these issues and describes innovative air quality risk management approaches intended to compliment the traditional regulatory approach focused on the attainment of national ambient air quality standards.

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