# Health Risks of Urban Airborne Particles

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## 1 Introduction

Adverse health effects of ambient airborne particles are of major concern to environmental health regulators. In recent years a tremendous amount of research on health effects of airborne particles has been published and evidence is well established, that even small concentrations of fine particles in air breathed by humans contribute significantly to their morbidity and mortality. These data prompted the European Parliament and Council to strengthen the limit values for particular matter with their new directive 2008/50/EC of 21 May 2008 on ambient air quality and cleaner air for Europe.

Extended reviews of the scientific evidence collected so far have been published amongst others by the World Health Organization (WHO-Europe 2005) and by the US Environmental Protection Agency (US-EPA 2004). A more recent review by the latter is in the process of external reviewing (US-EPA 2008[1]). This chapter draws extensively from these comprehensive syntheses.

Most evidence about the effects of airborne particular matter on human health has been produced by epidemiology. Additionally laboratory studies have been published, that involved both animals and human volunteers using concentrated ambient particles (CAPs). Toxicological studies on animals using instilled particles in high concentrations complete our knowledge on health effects of particular

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[1] A second external review paper is available since May 2009 via Internet: http://oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=491199. Accessed Oct 12, 2009.

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matter (PM). The toxicological evidence is complementary to the observational findings of epidemiological studies, providing the framework for assessing the biological plausibility of epidemiologically observed associations.

Epidemiological and clinical studies have linked particular matter (PM) to the following adverse health effects (WHO-Europe 2005):

- Mortality and hospital admission in patients with chronic obstructive pulmonary disease (COPD) or cardiovascular diseases (CVD)
- Exacerbation of symptoms and increased use of therapy in asthma
- Mortality and hospital admission in diabetes mellitus
- Increased risk for myocardial infarction
- Development of atherosclerosis
- Increased incidence of infection
- Increased risk for lung cancer.

In this chapter only effects of major relevance for public health will concisely be reviewed. For more details and completeness refer to the comprehensive reviews mentioned above.

## 2 Deposition of Airborne Particles in the Respiratory Tract

Airborne particles in order to have an effect on human health have to come into contact with cells and tissues of the human body. The main route of intake is inhalation. To a certain amount inhaled particles will be deposited at the surface of the extra- and intra-thoracic airways and in the alveoli of the lung. The amount and site of deposition depends on the aerodynamic and thermodynamic properties of the particles inhaled, particularly on their size and shape. On the contrary the interaction of the particle with the cells and tissues of the body is determined by its physical, chemical and biological properties. During their passage through the airways small hydrophilic particles adsorb immediately water vapour and grow significantly in size.

The probability of deposition and retention of particles at the surface of the different parts of the respiratory tract depends on their physical properties but also on the breathing pattern at inhalation and on the anatomic features of the respiratory tract. Figure 1 illustrates schematically the airway anatomy with distal progression into the lower respiratory tract. Natural growth in childhood, age and thoracic diseases, like asthma or chronic obstructive bronchitis, may influence the anatomy of the respiratory tract and as a consequence the deposition and retention of inhaled particles. In a healthy adult breathing through the mouth most of the larger particles with an aerodynamic diameter of more than 5 μm are deposited in the extra-thoracic airways (mouth, larynx and pharynx) and the large bronchi. Smaller particles reach the periphery of the lung where they might settle at the surface of the small bronchi, the respiratory bronchioli and the alveoli. Breathing through the nose notably changes the deposition pattern. The nose filters most of the particles larger

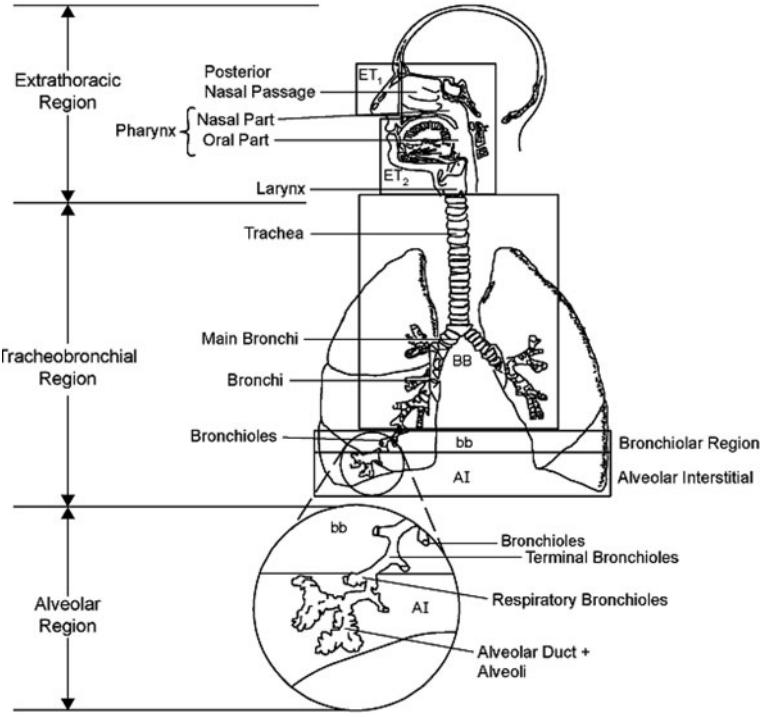


**Fig. 1** Schematic depiction of the human respiratory tract (based on ICRP 1994; US-EPA 2004). $ET_1$ anterior nasal passages, $ET_2$ oral airway and posterior nasal passages, *BB* bronchi, *bb* bronchioli, *Al* alveoli

than 2.5 μm and a relevant part of the particles with an aerodynamic diameter of 1–2.5 μm and in this way fewer particles of those sizes reach the deeper regions of the lung reducing the exposure of the bronchioli and alveoli (Heyder et al. 1986).

Figure 2 shows the deposition of particles of different sizes in the various regions of the respiratory tract during quiet breathing. The data presented in Fig. 2 are calculated on the basis of a theoretical model developed by the International Commission on Radiation Protection (ICRP 1994). It takes into account that particle deposition in the lung is predominantly governed by three physical processes: impaction, sedimentation and diffusion. The model reproduces quite well the available experimental data[2]. The efficiency of deposition in the respiratory tract may generally be described as a "U-shaped" curve on a plot of deposition efficiency versus the of log particle diameter as in Fig. 2. Total deposition shows a minimum for particle diameters in the range of 0.1 to 1.0 μm, where particles are small enough to have minimal sedimentation or impaction and sufficiently large so

[2] For a detailed discussion of the model and its limitations refer to the original ICRP-report or to US-EPA (2004).

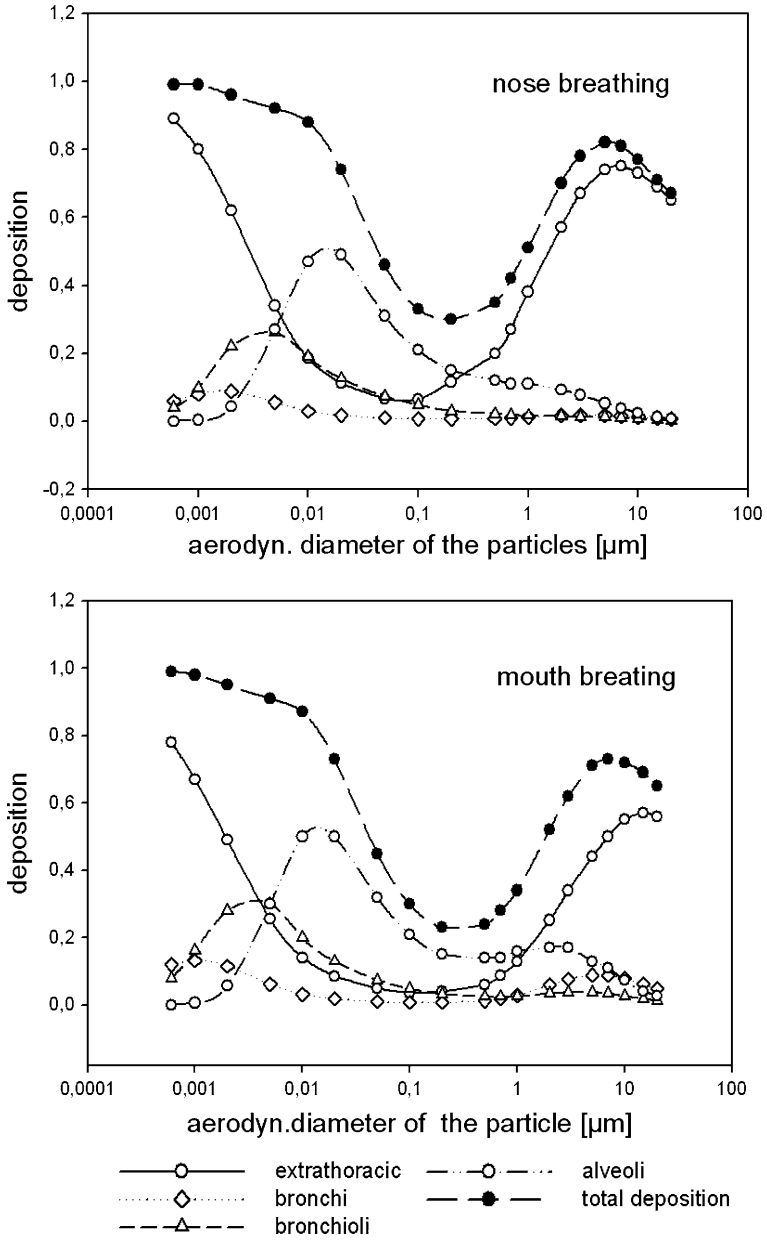


**Fig. 2** Total and regional deposition of particles in the respiratory tract dependent on log particle size (aerodynamic diameter) during quite breathing of an healthy individual (based on ICRP 1994)

as to have minimal diffusive deposition. Total deposition does not decrease to zero for any sized particle because of mixing between particle laden tidal air and residual lung air. The particles mixed into residual air remain in the lung following a breath and are removed on subsequent breaths or gradually deposited. Total deposition of ultrafine particle increases with falling diameter nearly up to 100 % due to their rising diffusivity (see left side of Fig. 2). In contrary alveolar deposition exhibits a maximum at approximately 20 nm. Yet smaller particles settle increasingly in the upper airways due to their specific diffusion characteristics and will not reach the periphery of the lung anymore.

In the various regions of the respiratory tract different physiological mechanisms exist to remove foreign material. In the extra-thoracic airways, the trachea and the bronchi there is a thick liquid lining and the synchronous movement of microscopic hairy cila at the surface of the bronchial epithelial cells rapidly moves deposited particles toward the larynx, where they are swallowed (mucociliary clearance). Normally this takes 1–3 days. Only highly soluble material moving from the air into the liquid layer will have systemic access via the blood.

With distal progression, the protective liquid lining diminishes and clearance rates slow down. Soluble compounds as well as some poorly soluble ultrafine particles may cross the air–liquid interface to enter the tissues and the blood especially in the alveolar region. Depending on the solubility of the particle retention may take years. Alveolar clearance is not a linear process and half live increases with the elimination time.

Macrophages on the alveolar epithelium may recognize foreign particles and phagocyte them, determining their further kinetic fate. Phagocytosis is rather effective for particles between 0.3 and 5 μm with an optimal rate for particles of 1–2 μm. The removal rate is much slower for smaller particles (overview in WHO-Europe 1997). If the macrophage moves toward the bronchi, the particle will be removed by the mucociliar clearance. During one year approximately one third of insoluble particles in the human alveoli will be removed by this way (Kreyling et al. 1990). The remaining two thirds stay on the alveolar epithelium or are kept in the interstitial space of the lung, under the pleura or in the lymphatic system of the thorax. According to their larger number ultra fine particles are distributed more evenly on the epithelium of the alveoli than larger particles. Ultra fine particles are less frequently phagocytized by alveolar macrophages and are present as well in the epithelium as in the interstitial lung tissue (Ferin et al. 1992). The incorporated particles may stay there or be transported toward the connective tissue or in to the bloodstream.

## 3 Short-Term Effects of Airborne Particles on Human Health

Most of the current body of evidence about short-term effect of particulate air pollution arises from epidemiological studies examining the association

between exposure to airborne particular matter (PM) of various size fractions (e.g. $PM_{10}$, $PM_{2.5}$ or ultra fine particles) and the health effect in question or outcome (e.g. various symptoms or diseases, medication use, hospital admissions or visits to an emergency department, additional deaths). The methods used include time series studies, "panel studies" or short-term cohort studies of susceptible groups, and cross-sectional studies. In time-series analysis the investigators observe the health indicator (e.g. the daily number of death) in a city or region and correlate them with the simultaneous registered indicator of the concentration of PM at the same location. An other type of studies follows a panel of selected subjects (e.g. asthmatic children or patients with chronic obstructive bronchitis) over a certain time period and evaluate the health indicator of interest (e.g. daily deaths, hospital admissions, lung function and/or respiratory symptom) in relation to changes in ambient PM. In some recent studies the risk for acute events, including myocardial infarction and stroke, has been assessed using the case-crossover design. In this design, the individual bearing the event 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 matching event-free "control" periods. The time series analysis study designs applied aim to disentangle the PM-health effect through complex modeling, the case crossover design by appropriate matching strategies.

## *3.1 Short-Term Mortality*

Various health effects have been reported from short-term studies. Increased mortality associated with short-term exposure is the most important health outcome in these studies. A multiplicity of studies from various settings in the US, Canada and Europe attest the association of different metrics of particular matter ($PM_{10}$, $PM_{2.5}$, $PM_{10–2.5}$ or ultrafine particles) with general and cause specific human mortality. In the first line are daily time series studies from single cities (e.g. Schwartz 1991). More relevant are analyses that pool data from several locations, using a common protocol for analysis of the within-city data and then combining estimates from various locations in order to gain precision and to evaluate the heterogeneity of the effect of particulate matter across the cities.

The APHEA (Air Pollution and Health—An European Approach) project studied air-pollution effects in 15 and later with the APHEA 2 project in 34 European cities (Katsouyanni et al. 1995, 1997, 2001). The NMMAPS (National Morbidity, Mortality, and Air Pollution Study) project in the United States focused on time-series analyses of $PM_{10}$ effects on mortality during 1987–1994 in the 90 largest US cities (Samet et al. 2000a, b, c), and in the 20 largest US cities in more detail (Dominici et al. 2000a, b). These data have been summarized in the US-EPA's particulate matter criteria document (US-EPA 2004) and in a met analysis carried out by a WHO-Europe task group (Anderson et al. 2004).

The WHO task group used the updated estimates for those studies with reanalyzed data. Estimates of the effect of $PM_{10}$ on all-cause mortality were taken from 33 separate European cities or regions. The summary relative risks of all cause deaths, deaths from cardiovascular and from respiratory causes for these 33 results is shown in Fig. 3. 21 of theses estimates were taken from the APHEA 2 study (Katsouyanni et al. 2001) and hence the summary estimate derived from this review is dominated by this multicity study. There were no cause specific mortality data available from the APHEA project at the time of met analysis and the summary risk estimate for cause specific mortality was calculated on the basis of 17 multicity studies mainly conducted in France, Italy and Spain. Therefore care has to be taken interpreting the differences in the risk estimates. The estimates for all-cause mortality and cause-specific mortality taken from European studies are comparable to those reported from the NMMAPS based upon the 20 largest cities in the United States (Samet et al. 2000a) (Fig. 3). Air pollution risk estimates were relatively robust to different modeling approaches (Samoli et al. 2008).

All-cause mortality associated to $PM_{2.5}$ were reported only in three studies from Erfurt, Germany (Wichmann et al. 2000), the Czech Republic (Peters et al. 2000) and the West Midlands conurbation in the United Kingdom (Anderson et al. 2001). Evidence from Europe of an effect of fine particles on daily mortality is therefore sparse. Of the five estimates from three studies available, none showed a statistically significant positive association and one was significantly negative. The risk

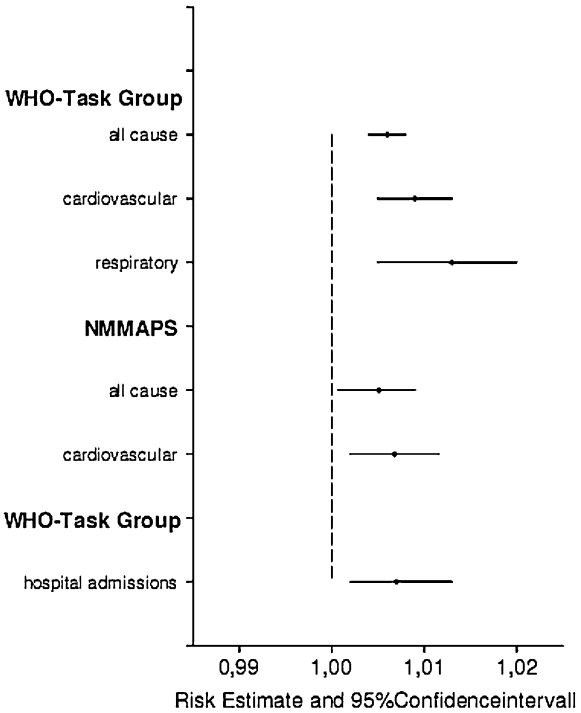


**Fig. 3** Risk estimates of short-term mortality for a 10 $\mu g/m^3$ increase of $PM_{10}$ from WHO-Task Group (Anderson et al. 2004) and US-National morbidity, Mortality, and Air Pollution Study—NMMAPS (Samet et al. 2000b)

estimates for North American cities were larger than those for Europe and their summary estimates were statistically significant, the cause-specific mortality for respiratory diseases being larger then the mortality for cardiovascular diseases or all-cause mortality (US-EPA 2008).

An analysis of the lag structures (time lag between change in concentration of PM and death) used in the studies found that the greatest effects were observed at lag 1 or lag 0–1 day, and the use of a distributed lag model resulted in slightly larger (by ~30%) risk estimates compared to single-day lags (Zeka et al. 2005).

It has been considered, that the associations between PM and daily mortality observed in the time series studies could reflect only a brief advance in the time of death, perhaps among those already frail because of underlying heart and lung disease. This possibility, referred to as "harvesting", implies that the associations observed in the daily time series studies are not indicating an effect of public health significance. Analytical approaches to assess the extent of "harvesting" have been developed and their results indicate that any advance of the time of death caused by PM is more than just a few days (Zeger et al. 1999; Schwartz 2000).

## *3.2 Short-Term Respiratory Morbidity*

A great variety of epidemiological studies investigated the association of different indicators of respiratory health with particulate mater (US-EPA 2004) specifically in asthmatic children (Roemer et al. 2000).

### 3.2.1 Deterioration of Respiratory Disease

Investigators discovered significant associations of $PM_{10}$ and to a lesser extent of $PM_{2.5}$ and $PM_{10-2.5}$ with hospital admissions for pneumonia (Ito 2003), for chronic obstructive pulmonary disease (Zanobetti and Schwartz 2003; Moolgavkar 2003), for asthma (Nauenberg and Basu 1999; Sheppard 2003) and general for all respiratory diseases (Burnett et al. 1997). Significant associations of PM with exacerbations and emergency department visits for asthma (Choudhury et al. 1997; Sheppard 2003) and for respiratory diseases in general (Stieb et al. 2000; Burnett et al. 1997) were also reported.

According to the WHO-met analysis (Anderson et al. 2004) the risk for hospital admissions with respiratory diseases in individuals age 65 years and older for a 10 $\mu g/m^3$ increase in $PM_{10}$ increased by 0.7% (see Fig. 3) based upon 8 estimates mostly provided by the APHEA 2 project (Atkinson et al. 2001). A re-analysis of the APHEA 2 data confirmed the robustness of the original results (HEI 2003b). For the other two age categories, ages 0–14 and 15–64 years, the

met analysis indicated a trend of increased frequency for hospital admission, which was not significant. For fine ($PM_{2.5}$) and coarse ($PM_{10–2.5}$) particles only the West Midlands study (Anderson et al. 2001) provided results for the respiratory hospital admissions. There was a trend for an association of hospital admissions in the youngest age group with $PM_{2.5}$, but it was not statistically significant too.

### 3.2.2 Lung Function and Respiratory Symptoms

Numerous studies report short-term PM exposure effects on lung function and respiratory symptoms. Lung function was usually measured daily, both in the morning and afternoon. Most studies included forced expiratory volume in one second ($FEV_1$), forced vital capacity (FVC) and peak expiratory flow rate (PEF), which are indicators of bronchial obstruction. Additionally various respiratory symptoms were registered, including cough, phlegm, difficulty breathing, wheeze, and medication use. Detailed summaries of these studies are presented in US-EPA (2004).

The results for asthmatic children tend to show small decrements of lung function associated with $PM_{10}$ and $PM_{2.5}$ as seen in studies by Gielen et al. (1997), Peters et al. (1997), and Pekkanen et al. (1997). For $PM_{10}$, the available point estimates for morning PEF showed decreases lagged one day, but the majority of the studies were not statistically significant. $PM_{10}$ and $PM_{2.5}$ both appear to affect lung function in asthmatics, but there is only limited evidence for a stronger effect of fine versus coarse fraction particles; ultrafine particles do not appear to have any notably stronger effect than other larger-diameter fine particles. Of the studies provided, few if any analyses were able to clearly separate out the effects of PM from other coexisting pollutants.

The effects of $PM_{10}$ on respiratory symptoms in asthmatics tended to be positive, although they are somewhat less consistent than $PM_{10}$ effects on lung function. Most studies showed increases in cough, phlegm, difficulty breathing, and bronchodilator use, although these increases were generally not statistically significant for $PM_{10}$. For example, Vedal et al. (1998) reported that increases in $PM_{10}$ were associated with increased reporting of cough, phlegm production, and sore throat. Children with diagnosed asthma were more susceptible to the effects than were healthy children. Similarly Gielen et al. (1997) studied a panel of children, most of whom had asthma. Low levels of PM increased symptoms and medication use. Ostro et al. (2001) studied a panel of inner-city African American children using a model with several measures of PM, including $PM_{10}$ (both 24-h average and 1-h max.) and $PM_{2.5}$, demonstrating positive associations with daily probability of shortness of breath, wheeze, and cough.

The effects on respiratory symptoms in non-asthmatics were similar to those in asthmatics. Most studies showed that $PM_{10}$ increases cough, phlegm, difficulty breathing, although these were generally not statistically significant. Vedal et al. (1998) reported no consistent evidence for adverse health effects in their non-asthmatic control group.

Several recent panel studies conducted in Europe have examined effects of daily exposures to air pollution on adults with asthma, chronic bronchitis or cardiovascular diseases. As part of the multicenter ULTRA (Exposure and Risk Assessment for Fine and Ultrafine Particles in Ambient Air) study (de Hartog et al. 2003) enrolled 131 older adults with coronary artery disease in three cities [Amsterdam, Erfurt (Germany), and Helsinki]. Pooling data from all three cities, significant associations were observed between $PM_{2.5}$ and shortness of breath and phlegm. In a study from Erfurt, Germany (von Klot et al. 2002), examined daily, winter time exposure to ambient $PM_{10–2.5}$, $PM_{2.5–0.01}$ and $PM_{0.1–0.01}$ and respiratory health effects in 53 adult asthmatics. The authors examined associations between wheeze, use of inhaled short-acting $\beta_2$-agonists or inhaled corticosteroids and exposure to particles in single and multipollutant models. Particle exposure metrics examined included same-day, 5-day and 14-day averages. No significant effects were observed for wheeze and exposure to $PM_{10–2.5}$ or $PM_{2.5–0.01}$ for any averaging time. The strongest association between wheeze and exposure to ultrafine particles was for a 14-day average: each 7,700 increase in the number count (NC) increased the risk of wheeze by 27% (RR 1.27, 95% CI: 1.13–1.43). The effect was attenuated in co pollutant models that also included $PM_{2.5–0.01}$.

In Paris, Segala et al. (2004) recruited 78 adults from an otolaryngology clinic and followed them for three months. Both $PM_{10}$ and Black Smoke [which were very highly correlated ($r = .88$)] were associated with cough. Also in Paris, 60 severe asthmatics were followed for 13 months and the relationship between daily air quality (including 24-h $PM_{10}$ as measured at the site nearest to the subject's home) and asthma attack (defined as the need to increase rescue medication use and one or more positive signs of obstruction on clinical examination) were examined (Desqueyroux et al. 2002). Each 10 $\mu g/m^3$ increase in $PM_{10}$ increased the risk of asthma attack, but only after lags of 3 to 5 days. Boezen et al. (2005) enrolled 327 elderly adults in the Netherlands. For subjects with both airways hyperreagibility and high total immunoglobulin E (IgE $>$ 20 kU/L) an indicator of atopic disposition, each 10 $\mu g/m^3$ increase of $PM_{10}$ was significantly associated with an increased risk of upper respiratory symptoms for males and cough for females with different lags. The strongest association in both cases was for the 5-day mean. The authors suggest that the sex differences of the lag observed may be explained by differential daily exposure to traffic exhaust experienced by men compared to women.

## *3.3 Short-Term Cardiovascular Morbidity*

Surprisingly a number of epidemiology studies in the early nineties showed associations between ambient particulate matter and increases in cardiac-related deaths and/or morbidity indicators and that the risk of PM-related cardiac effects may be so great or greater than those attributed to respiratory causes. These effects appear to be induced via direct particle uptake into the blood and/or via mediation by the nervous system. Such effects may be especially deleterious to individuals

compromised by diseases such as ischemic heart disease, cardiac arrhythmias, and chronic obstructive pulmonary disease (COPD).

### 3.3.1 Hospital Admissions

The US-EPA-Air Quality criteria document (US-EPA 2004) quotes more than twenty studies relating daily hospitalizations with primary discharge diagnoses of cardiovascular diseases (CVD) to the effect of urban particulate matter. The NMMAPS study evaluated the effect of daily changes in ambient PM levels on total CVD hospitalizations among elderly Medicare beneficiaries in 14 US cities and found a $\sim$1% excess risk per 10 $\mu g/m^3$ increase in $PM_{10}$ (Samet et al. 2000b; Zanobetti and Schwartz 2003). Recent large studies conducted in the US (Dominici et al. 2006; Bell et al. 2008) and Europe (Host et al. 2008; von Klot et al. 2005) have confirmed these findings for $PM_{10}$, and have also observed consistent associations between $PM_{2.5}$ and cardiovascular hospitalizations. It is apparent from these studies that the observed increases in cardiovascular hospitalizations are largely due to admissions for ischemic heart disease and congestive heart failure rather than for stroke.

### 3.3.2 Heart Rate, Heart Rate Variability, Arrhythmia, Blood Pressure

Heart rate (HR), heart rate variability and blood pressure are regulated, in part, by the sympathetic and parasympathetic nervous systems. Changes in one or more may increase the risk of cardiovascular events (e.g. arrhythmias, myocardial infarction). Decreases in heart rate variability have been associated with cardiovascular mortality/morbidity in older adults and those with significant heart disease. Fine particles in ambient concentrations have recently been implicated in decreases of heart rate variability (Timonen et al. 2006), increased risk of arrhythmias (Metzger et al. 2004; Lanki et al. 2006) and increased blood pressure (Timonen et al. 2006) in particular in older subject with compromised health. Additionally inhaled particles seem to enhance blood coagulation (Rückerl et al. 2007a, b).

## 4 Long-Term Effects of Airborne Particles on Human Health

### *4.1 Mortality*

Long-term exposure to urban airborne particles over many years or decades implies serious consequences for human health. These include shorter life

expectancy caused by higher mortality for cardiovascular diseases and lung cancer as well as increased infant mortality in polluted regions. The influence of PM on human mortality was investigated by several large and expensive cohort studies first published in the late eighties and nineties of the last century. Most of our knowledge is based on these. They were supplemented and extended by more recent studies and the data reanalysed with more sophisticated modelling.

The Harvard Six Cities Study (HSC) (Dockery et al. 1993) monitored approximately 8,000 adults over 14–16 years in six US-Cities with varying air pollution. The study investigated the influence of TSP, $PM_{2.5}$, $SO_4^-$, $H^+$, $SO_2$ and ozone on different health indicators. The strongest association of mortality was found with sulfate and $PM_{2.5}$. In the city with the highest $PM_{2.5}$ the mortality exceeded the mortality in the city with the lowest $PM_{2.5}$ by 26%. The results were confirmed by reanalysis of the data (Krewski et al. 2000). Laden et al. (2006) studied the effect of improvements in particle exposure with the methodology oft the HSC. They extended the mortality follow-up for 8 years in a period of reduced air pollution concentrations. From their data they found a decrease in overall mortality, cardiovascular and lung cancer deaths associated with decrease in $PM_{2.5}$ modelled either as the overall mean or as exposure in the year of death.

The Study of the American Cancer Society (ACS) (Pope et al. 1995) included approximately 550,000 adults in 154 North American cities for a time period of 8 years, later extended to 16 years of follow up (Pope et al. 2002). An association of mortality with sulfate was found but where measurements of $PM_{2.5}$ were available, this parameter exhibited the strongest association with mortality. These data were extended with better PM-data and reanalyzed by Krewski et al. (2005).

Eftim et al. (2008) extended the HSC and ACS studies using US-Medicare data for the period 2000–2002. They assessed the association of $PM_{2.5}$ with mortality for the same locations included in the HSC and ACS studies. The adjusted risk estimates are somewhat higher than those reported by the original investigators (Fig. 4).

The Adventist Health Study of Smog (AHSMOG) (Abbey et al. 1999; McDonnell et al. 2000) included 1977 6300 non-smoking white Seventh Day Adventists age 27–95 years living in California. Mortality was followed up 15 years. $PM_{10}$ showed a strong association with mortality for any mention of non-malignant respiratory disease or lung cancer on the death certificate, adjusting for a wide range of potentially confounding factors, including occupational and indoor sources of air pollutants. The risk estimates for a change in $PM_{2.5}$ of 10 $\mu g/m^3$ of the three US long-term studies cited above are depicted in Fig. 4.

The Veterans' Administration Cohort Mortality Study (VA) (Lipfert et al. 2000) studied 70,000 men with light to medium elevated blood pressure and age 39–63. The investigators did not find any significant correlation of mortality with any PM-metric. $PM_{2.5}$ exhibited a negative association with mortality. On the contrary a positive, consistent and significant association with ambient concentrations of $NO_2$ and ozone was found.

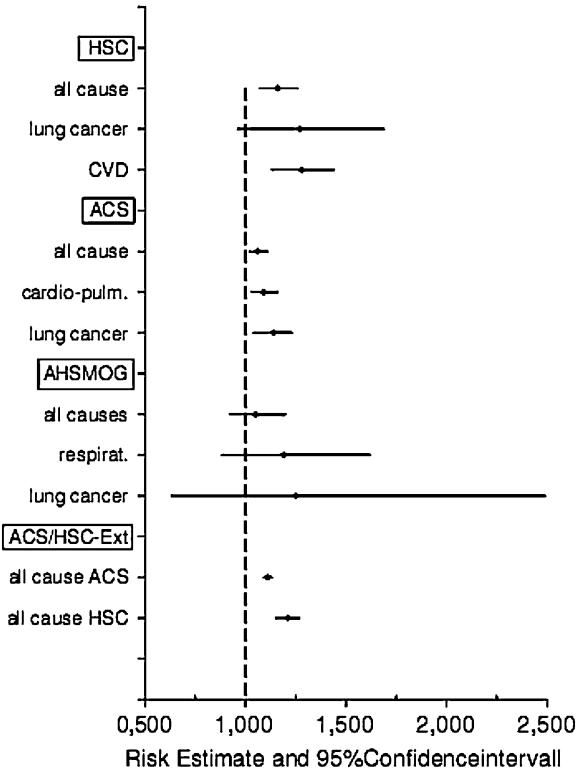


**Fig. 4** Risk estimates for long-term mortality associated with a 10 μg/m$^3$ increase in $PM_{2.5}$ HSC refers to the extended Harvard Six Cities Study (Laden et al. 2006), ACS to the American Cancer Society Study (Pope et al. 2002), AHSMOG to the Adventist Health Study of Smog (McDonnell et al. 2000) and ACS/HSC Ext to the extended study of Eftim et al. (2008) at the same locations as ACS and HSC. *CVD* death caused by cardiovascular disease

In the Dutch Traffic Cohort Study (NL) (Hoek et al. 2002; Beelen et al. 2008) cardio-pulmonary mortality was significantly associated with living near a major road (relative risk 1.95, 95% CI: 1.09–3.52). Total deaths and lung cancer were not significantly associated with traffic exposure (RR 1.41, 95% CI: 0.94–2.12 and RR 1.03, 95% CI 0.88–1.20 respectively).

The Nurses' Health Study (Puett et al. 2008) examined the association of chronic particulate exposures with all-cause mortality, incident nonfatal myocardial infarction, and fatal coronary heart disease (CHD) in a prospective cohort of 66,250 women from the Nurses' Health Study in north-eastern US metropolitan areas. In an age- and season-of-the-year-adjusted models, 10 μg/m$^3$ increases in 12-month average exposures to $PM_{10}$ were associated with increased all-cause mortality (RR 1.16, 95% CI: 1.05–1.28) and fatal CHD (1.43, 95% CI: 1.10–1.86).

The North Rhine-Westphalia State Environment Agency studied a cohort of approximately 4800 women and assessed whether long-term exposure to air pollution originating from motorized traffic and industrial sources was associated with total and cause-specific mortality (Gehring et al. 2006). Cardiopulmonary mortality was associated with living within a 50-meter radius of a major road (adjusted RR = 1.70; 95% CI: 1.02–2.81), and with $PM_{10}$ concentrations

calculated from air monitoring station data (RR = 1.52 [95% CI: 1.09–2.15] per 10 μg/m$^3$ $PM_{10}$).

In spite of some inconsistencies in the relative strength of the associations of mortality with fine ($PM_{2.5}$) or coarse ($PM_{10}$) particles and the negative results of the VA study the overwhelming evidence speaks for an causal relationship of long lasting exposure to respirable airborne urban particles and premature deaths specifically deaths due to cardiopulmonary diseases or lung cancer. The evidence for increased number of CVD deaths is much stronger than for lung cancer.

## *4.2 Cardiovascular Effects of Long-Term Exposure to Airborne Particles*

Künzli et al. (2005) were the first to report an association of an indicator of atherosclerosis with $PM_{2.5}$. They used data on 798 participants from two clinical trials to investigate the association between atherosclerosis and long-term exposure to ambient $PM_{2.5}$. For a cross-sectional exposure contrast of 10 μg/m$^3$ $PM_{2.5}$, the atherosclerosis indicator used in the study (carotid intima-media thickness or CIMT) increased by 5.9% (95% CI: 1–11%). Several recent studies showed comparable results with other indicators of atherosclerosis (Diez Roux et al. 2008; Hoffmann et al. 2007).

Zanobetti and Schwartz (2007) studied 196,000 persons from 21 US cities discharged alive following an acute myocardial infarction (MI), using within-city between-year exposure to PM. They constructed city-specific cohorts of survivors of acute MI using Medicare data between 1985 and 1999, and defined three outcomes on follow-up: death, subsequent MI, and a first admission for congestive heart failure. Yearly averages of $PM_{10}$ were merged to the individual annual follow-up in each city. Significant associations were found with adjusted risk of 1.3 [95% CI: 1.2–1.5] for mortality, of 1.4 (95% CI: 1.2–1.7) for a hospitalization for congestive heart failure, and of 1.4 (95% CI: 1.1–1.8) for a new hospitalization for myocardial infarction per 10 μg/m$^3$ $PM_{10}$.

Baccarelli et al. (2008) studied in a case–control study 870 patients with deep vein thrombosis (DVT) and 1210 healthy controls from the Lombardy region in Italy, who were examined between 1995 and 2005. They estimated exposure to $PM_{10}$ in the year before DVT diagnosis (cases) or examination (controls) through area-specific mean levels obtained from ambient monitors. Each increase of 10 μg/m$^3$ in $PM_{10}$ was associated with a 70% increase in DVT risk (OR 1.70; 95% CI: 1.30–2.23).

Miller et al. (2007) examined the association of long-term exposure to particulate $PM_{2.5}$ with cardiovascular events. They studied 65,893 postmenopausal women without previous cardiovascular disease in 36 US metropolitan areas from 1994 to 1998, with a median follow-up of 6 years and assessed the women's exposure to air pollutants using the monitor located nearest to each woman's residence. 1816 women had one or more fatal or nonfatal cardiovascular events,

including death from coronary heart disease or cerebro-vascular disease, coronary revascularization, myocardial infarction, and stroke. Each increase of 10 μg/m$^3$ $PM_{2.5}$ was associated with a 24% increase in the risk of a cardiovascular event (CI: 9–41%) and a 76% increase in the risk of death from cardiovascular disease (95% CI: 25–147%). The risk of cerebro-vascular events was also associated with increased levels of $PM_{2.5}$ (OR 1.35; 95% CI: 1.08–1.68).

Hoffmann et al. (2006) studied the relationship between the long-term residential exposure to traffic and prevalence of coronary heart disease (CHD). For 3,399 participants from two German cities they assessed the long-term personal traffic exposure and background air pollution, comparing residents living within 150 m of major roads with those living further away. The principal outcome variable studied was clinically manifest coronary heart disease (CHD). 242 (7.1%) had CHD. The odds ratio (OR) of CHD after adjusting for cardiovascular risk factors and background air pollution at high traffic exposure was significantly elevated (OR 1.85, 95% CI 1.21–2.84). Subgroup analysis showed stronger effects for men (OR 2.33, 95% CI 1.44–3.78), participants younger than 60 years (OR 2.67, 95% CI 1.24–5.74) and never-smokers (OR 2.72, 95% CI 1.40–5.29).

## *4.3 Respiratory Effects of Long-Term Exposure to Airborne Particles*

Children living in communities with higher particulate air pollution exhibit higher frequencies of respiratory symptoms and bronchitis (McConnell et al. 1999); specifically children with asthma (McConnell et al. 2003). Declining levels of $PM_{10}$ in Switzerland were associated with declining prevalence of chronic cough, bronchitis, common cold, nocturnal dry cough, and conjunctivitis symptoms in school children (Bayer-Oglesby et al. 2005). Brauer et al. (2007) assessed the development of asthma, allergic symptoms, and respiratory infection in relation to long-term traffic related air pollution at the home address. $PM_{2.5}$ was associated with doctor-diagnosed asthma, respiratory infections and some measures of allergy during the first 4 years of life.

Longitudinal cohort studies have evaluated the relationship between long-term exposure to PM and changes in measures of pulmonary function (FVC and $FEV_1$, and measures of expiratory flow). Lung function increases in healthy subjects continually from infancy to early adulthood with growth and development, then declines with aging. Within the Children's Health Study of 1,600 Californian school children (Gauderman et al. 2002) found that the estimated growth rate for children in the most polluted communities as compared with the least polluted was reduced: 3.4% for the $FEV_1$ (forced expiratory volume in 1 s) and by 5.0% for MMEF (maximal midexpiratory flow) over the 4-year study period. The estimated deficits were generally larger for children spending more time outdoors.

Nordling et al. (2008) examined the relationship between estimated PM exposure levels and respiratory health in a Swedish birth cohort (n = 4,089) of

preschool children. Persistent wheezing (cumulative incidence up to age 4) was associated with exposure to traffic-generated $PM_{10}$ (OR 2.28, 95% CI: 0.84–6.24 per 10 μg/m$^3$ increase). Peak expiratory flow (PEF) at age 4 was associated with exposure to traffic-$PM_{10}$ too. PEF was 8.93 L/min lower in children with the higher PM exposure [95% CI: −17.78 to −0.088].

Gotschi et al. (2008) examined the relationship between air pollution and lung function in adults within the European Community Respiratory Health Survey (ECRHS). $FEV_1$ and FVC were assessed at baseline and after 9 years of follow-up from 21 European centers (followed-up sample n = 5610). $PM_{2.5}$ was measured in 2000–2001 using central monitors. Despite sufficient statistical power no significant associations were found between city-specific annual mean $PM_{2.5}$ and average lung function levels in adults.

### *4.4 Lung Cancer*

A limited number of epidemiologic studies evaluated associations between long-term exposure to PM and the incidence of cancer. Though several studies have reported an association between lung cancer mortality and long-term PM exposure (e.g. Dockery et al. 1993; Beelen et al. 2008), the single study that looked at lung cancer incidence found no association with $PM_{2.5}$ (Beelen et al. 2008). There are known constituents of PM that have varying levels of toxicity, including some that have been classified as possible or probable carcinogens. An epidemiologic study looked at PM (using TSP as a surrogate for PAHs) and found a positive association (Bonner et al. 2005). Overall, there is limited evidence available to evaluate the relationship between relevant PM exposures and cancer incidence.

### *4.5 Low Birth Weight*

Parker et al. (2005) investigated the associations between birth weight and air pollution among full-term infants in California. They found a significantly increased odds ratio of neonates small for gestational age and a small difference in birth weight with increased $PM_{2.5}$ at mother's residence at pregnancy after controlling for CO. Similar results were obtained in other studies in the US (Wilhelm and Ritz 2005; Chen et al. 2002), in Munich (Slama et al. 2007) and in the Czech Republic (Dejmek et al. 1999).

## 5 Limitations of Epidemiological Studies

The limitations of the epidemiological studies have been carefully considered. Issues in interpreting the findings have been those relevant to any body of

observational evidence, which are exposure misclassification and the potential for uncontrolled confounding.

Exposure misclassification is a far reaching concern. In general, this type of misclassification tends to reduce estimates of effect towards the null, i.e. finding no effect. A detailed analysis for daily time series studies led to the conclusion that measurement error would lead to an underestimation of effect under most conditions (Zeger et al. 2000). One critical uncertainty in interpreting the epidemiological studies is the question of the contribution of particles in outdoor air to total personal (and population) exposure. In moderate climate, where the studies were predominantly conducted most time is spent indoors. Ambient particles would make a substantial contribution to personal exposure only if they penetrated into the indoor spaces. Personal exposure studies carried out in the United States and Europe showed that particles in outdoor air contributed substantially to personal exposures and to temporal variation in personal exposures (NRC 2004). These findings provide support for using central site measurements of ambient particle concentrations as a surrogate for changes in personal exposures in epidemiological studies.

Confounding is always of concern in interpreting the findings of observational studies. Confounding arises when the effect of a factor other than that being studied biases the effect of the factor under study; for confounding to occur, the potential confounding factor needs to be both associated with the outcome of interest and the factor under investigation (Rothmann and Greenland 1998). In carrying out studies, epidemiologists use both design and analytical strategies to control for any bias from confounding. The potential for confounding to have biased the findings of the daily time series studies has been explored in a number of ways. Temperature and humidity, along with season, have been controlled in the daily time series studies with approaches that involve inclusion of temperature (and relative humidity) variables in the models and the use of temporal smoothing methods that account for the well-known seasonality of mortality. Because influenza epidemics, are a particular concern, models have been used that incorporate this factor and also temporally smooth its effects. The sensitivity of findings to the degree of smoothing provides one indication of potential confounding. Even with very sophisticated models it is some times difficult or impossible to separate the effects of particulate matter from the effects of other concomitant and heavily correlated pollutants like $NO_2$, ozone or sulfate.

Particularly with regard to the time series and other longitudinal studies, critics have questioned the statistical models used, both with regard to the selection of particular models and to the specification of the variables in the models. Various models have been used to assess the extent to which control of confounding is model-dependent (HEI 2003a). But in general the risk estimates presented turned out to be rather robust. Because of identification of the potential for bias from default settings in widely used statistical software a number of key data sets have been reanalyzed (HEI 2003b). The reanalysis gave similar results as the original analysis, but showed lower effect estimates and larger standard errors.

## 6 Toxicological Evidence of PM Health Effects

Considering the epidemiological evidence of the health effects of particulate matter, the main purpose of toxicological studies was to prove the plausibility of the statistical associations, to elicit the components of particulate matter responsible for the health effects and to analyze the mechanisms of action and the dose-effect relationship. A vast body of data has accumulated during the past 10 years (for an overview see, US-EPA 2004, 2008).

Evidence related to underlying mechanisms and the plausibility of the effects observed in epidemiological studies comes from a range of clinical studies on human volunteers and toxicological studies on animal models and cell systems. In principal, the toxicological in vitro and animal experiments give clear hints as to the mechanisms of the effects observed in the epidemiological studies but the exposures in these experiments are by up to two magnitudes higher than the exposures observed in epidemiology. Additionally it has to be considered that experimental studies only partly reproduce the year- or life-long exposure of populations in observational studies.

Inhalation or instillation of particles induces oxidative responses at the bronchial and alveolar surfaces and local inflammation. At least at higher concentrations (e.g. CAP or instillation) pulmonary injury may result. At concentrations lower than 100 $\mu g/m^3$ no morphological changes in the lung of the exposed animals were observed. Some constituents of the particles are more toxic than other. Instilled residual oil fly ash (ROFA) produces significant cell damage and inflammation in animal lungs depending on its content of transition metals (Fe, Ni, V, Zn) but in concentrations much higher than in ambient air (Dreher et al. 1997; Kodavanti et al. 1997). Water soluble components, rich on metals were most toxic (Dye et al. 2001; Ghio and Devlin 2001).

The production of reactive oxygen species (ROS) by particles in contact with epithelial and cellular surfaces in the bronchial tree and the lung is considered to be the first step in a cascade to generate inflammation and lung injury. Numerous studies have demonstrated the oxidative potential of PM in vitro assay systems (Ayres et al. 2008). Both redox active surface components such as metals and organic species and the surface characteristics of crystal structures have been shown to contribute to the oxidative potential (Warheit et al. 2007). In this way, PM may be a direct source of ROS in the respiratory tract. PM may also act as an indirect source of ROS in the respiratory tract by stimulating cells to produce ROS (Tao et al. 2003). Li et al. (2002) proposed a model in which at the beginning mild oxidative stress enhances antioxidant defenses by upregulating antioxidant enzymes. Subsequently further increase in oxidative stress induces inflammation and cell death.

Mechanisms underlying the extra-pulmonary cardio-vascular or systemic effects are incompletely understood. However, pulmonary inflammation can lead to systemic inflammation and pulmonary reflexes can activate the autonomic nervous system. Many animal studies confirm the systemic cardiovascular toxicity

of particles and give hints regarding the underlying mechanisms (Godleski 2006; Muggenburg et al. 2000; Salvi et al. 1999; Thomson et al. 2006). The hypothesis is that particles induce a reversible increase of coagulation and an inflammation reaction. Elemental composition seems to be an important factor influencing these effects (Costa and Dreher 1997). The experiments show effects mostly in older animals and in animals of impaired health supporting the epidemiological findings of increased mortality and morbidity predominantly of persons with respiratory or cardiovascular diseases.

Whether particles are capable of crossing the epithelial barrier and reaching capillary endothelial cells or the circulation is in question. To date, the evidence for ultrafine or other PM size fractions accessing the circulation by traversing this barrier is not convincing. The effects of ultra fine particles evoked special interest because of their large surface area per mass. Oberdörster et al. (1994) and Li et al. (1999) compared the effects of fine and ultra fine particles. At equal mass concentration ultra fine particles seem to be more toxic than fine particles producing oxidative stress reactions. The effects depend on the chemical composition of the particles, e.g. ZnO-particles being more toxic than MgO-particles (Kuschner et al. 1997). But the experimental evidence is insufficient for firm conclusions about the role of ultra fine particles regarding the health effects of particulate matter.

## *6.1 Allergic Responses*

Laboratory and toxicological studies have shown that PM can modulate immune reactivity in both humans and animals to promote allergic sensitization and exacerbate allergic responses (US-EPA 2004). Exposure to diesel exhaust particles for example was shown to increase the allergic response among atopic adults (Bastain et al. 2003). Numerous forms of PM, including inert materials, have been shown to function as adjuvants in laboratory studies. Although studies of relatively homogeneous materials demonstrate greater adjuvancy for smaller particles than for larger, this could not be reproduced by analyses of ambient PM. Particle composition might be more influential than size (Steerenberg et al. 2006; Gavett et al. 2003), but few if any studies have compared size fractions of well-characterized ambient PM for adjuvant activity in a direct, controlled fashion via inhalation exposure.

## *6.2 Host Defense*

Toxicological studies demonstrated increased susceptibility to infectious agents following exposure to PM. These studies evaluated the effect of high concentrations of particles inhaled (CAP) or of suspensions of particles instilled in rodents.

They observed e.g. an increase in susceptibility to influenza infection in mice (Ciencewicki et al. 2007). Similar effects of ambient particles may be partly responsible for the observed increase of hospital admissions with pneumonia cited above.

## 7 Conclusions

Evidence has grown over the last decade, that urban airborne particles at ambient concentration levels common in many cities in Europe, America and Asia exert adverse effects on human health. Short- or long-term exposure to particulate matter (measured as $PM_{10}$ or $PM_{2.5}$) is associated with an increase risk of cardiovascular and respiratory morbidity and mortality. Collectively the toxicological and epidemiological studies provide sufficient evidence that a causal relationship is likely to exist between exposure to ambient concentrations of $PM_{10}$ or $PM_{2.5}$ and specific human morbidity (exacerbation of chronic bronchitis, asthma or coronary heart disease) and premature deaths.

For various health outcomes of PM, there has not been any indication of a threshold below which adverse effects would not be anticipated. Anyways a reduction of present levels of urban air pollution by particulate matter seems to be warranted.

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