

Chapter 7.3

Particulate matter

Introduction

In the 1987 edition of *Air quality guidelines for Europe (1)*, sulfur dioxide and particulate matter (PM) were treated jointly. Short-term (24-hour average) guideline values were derived for combined exposure to sulfur dioxide and particulate matter, expressed in “black smoke”, “total suspended particulates” and “thoracic particles”. Long-term (one-year average) guideline values were derived only for sulfur dioxide and black smoke. At the time, published studies were inadequate to develop a guideline for thoracic particles *per se*. Therefore, the guideline value for thoracic particles was based on site-specific ratios for total suspended particulates to thoracic particles, and on a single study that also involved exposure to sulfur dioxide. In recent years, several studies have been published that permit direct evaluation of the health effects of thoracic particles, because PM₁₀ (particulate matter in which 50% of particles have an aerodynamic diameter of less than 10 µm), which is essentially equivalent to thoracic particles, was actually measured in such studies. Also, studies have been published that permit evaluation of the health effects of PM₁₀ alone, either because exposure to other pollutants was low or because adequate adjustment was possible. This chapter focuses on evaluation of the health effects of suspended particles in air, emphasizing studies that permit direct evaluation of associations with PM₁₀, sulfate ion (SO₄²⁻), PM_{2.5}, and hydrogen ion (H⁺). The need to revise existing air quality guidelines and standards is widely felt, as many of the recent studies have suggested that significant effects on health occur at levels below those that were seen as “thresholds” in the recent past (2).

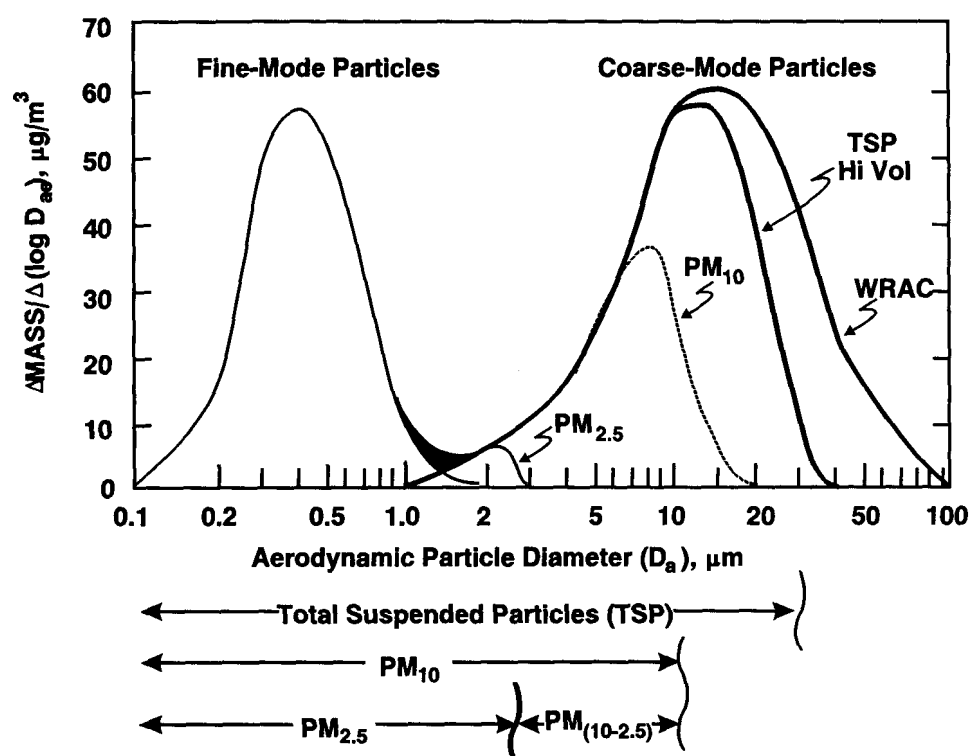
General description

Airborne particulate matter represents a complex mixture of organic and inorganic substances. Mass and composition tend to divide into two principal groups: coarse particles mostly larger than 2.5 µm in aerodynamic diameter, and fine particles mostly smaller than 2.5 µm in aerodynamic diameter (PM_{2.5}). The smaller particles contain the secondarily formed aerosols (gas-to-particle conversion), combustion particles and recondensed organic and metal vapours. The larger particles usually contain earth crust materials and fugitive dust from roads and industries. The fine fraction contains most of the acidity (hydrogen ion) and mutagenic activity of particulate matter, although in fog some coarse acid droplets are also present (3). An idealized distribution of ambient particulate matter is shown in Fig. 1.

Particulate air pollution is a mixture of solid, liquid or solid and liquid particles suspended in the air (5). These suspended particles vary in size, composition and origin. It is convenient to classify particles by their aerodynamic properties because: (1) they govern the transport and removal of particles from the air; (2) they also govern their deposition within the respiratory system; and (3) they are associated with the chemical composition and sources of particles. These properties are conveniently summarized by the aerodynamic diameter, that is the size of a unit-density sphere with the same aerodynamic characteristics. Particles are sampled and described on the basis of their aerodynamic diameter, usually called simply the particle size.

The size of suspended particles in the atmosphere varies over four orders of magnitude, from a few nanometres to tens of micrometres (Fig. 1). The largest particles, called the coarse

Fig 1. Schematic representation of the size distribution of particulate matter in ambient air (USEPA 1996)



fraction (or mode), are mechanically produced by the break-up of larger solid particles. These particles can include wind-blown dust from agricultural processes, uncovered soil, unpaved roads or mining operations. Traffic produces road dust and air turbulence that can re-entrain road dust. Near coasts, evaporation of sea spray can produce large particles. Pollen grains, mould spores, and plant and insect parts are all in this larger size range. The amount of energy required to break these particles into smaller sizes increases as the size decreases, which effectively establishes a lower limit for the production of these coarse particles of approximately 1 μm . Smaller particles, called the fine fraction or mode, are largely formed from gases. The smallest particles, less than 0.1 μm , are formed by nucleation, that is, condensation of low-vapour-pressure substances formed by high-temperature vaporization or by chemical reactions in the atmosphere to form new particles (nuclei). Particles in this nucleation range or mode grow by coagulation, that is, the combination of two or more particles to form a larger particle, or by condensation, that is, condensation of gas or vapour molecules on the surface of existing particles. Coagulation is most efficient for large numbers of particles, and condensation is most efficient for large surface areas. Therefore the efficiency of both coagulation and condensation decreases as particle size increases, which effectively produces an upper limit such that particles do not grow by these processes beyond approximately 1 μm . Thus particles tend to "accumulate" between 0.1 and 1 μm , the so-called *accumulation range*.

Submicrometre-sized particles can be produced by the condensation of metals or organic compounds that are vaporized in high-temperature combustion processes. They can also be produced by condensation of gases that have been converted in atmospheric reactions to low-vapour-pressure substances. For example, sulfur dioxide is oxidized in the atmosphere to form sulfuric acid (H_2SO_4). Nitrogen dioxide (NO_2) is oxidized to nitric acid (HNO_3), which in turn

reacts with ammonia (NH_3) to form ammonium nitrate (NH_4NO_3). The particles produced by the intermediate reactions of gases in the atmosphere are called *secondary particles*. Secondary sulfate and nitrate particles are the dominant component of fine particles in the USA. Combustion of fossil fuels such as coal, oil and petrol can produce coarse particles from the release of noncombustible materials, i.e. flyash, fine particles from the condensation of materials vaporized during combustion, and secondary particles through the atmospheric reactions of sulfur oxides and nitrogen oxides initially released as gases.

Chow et al. (6) studied the composition of fine particles ($\text{PM}_{2.5}$) and PM_{10} in California's San Joaquin Valley. The fine particles were found to consist primarily of nitrate, sulfate and ammonium ions which, together with elemental and organic carbon made up 70–80% of the total $\text{PM}_{2.5}$ mass. In contrast, these components made up only about 10–20% of the coarse fraction between 2.5 and 10 μm . The coarse fraction was dominated by aluminium, silicon, sulfur, potassium calcium and iron, which made up 40–50% of its mass. In this particular study, fine and coarse particle mass were about equal. Israel et al. (7) studied the composition of $\text{PM}_{2.5}$ and PM_{10} in Berlin, Germany and at a rural control site. The average $\text{PM}_{2.5}$ concentration was 39 $\mu\text{g}/\text{m}^3$, the average PM_{10} concentration was 58 $\mu\text{g}/\text{m}^3$. For the fine fraction, 78% was found to consist of the same components as in the California study, while for the coarse fraction, the proportion was 50%. Similar airborne particle composition data have been reported from the United Kingdom (8).

Because of its complexity and the importance of particle size in determining exposure and human dose, numerous terms are used to describe particulate matter. Some are derived from and defined by sampling and/or analytic methods, e.g. “suspended particulate matter”, “total suspended particulates”, “black smoke”. Others refer more to the site of deposition in the respiratory tract, e.g. “inhalable particles”, which pass beyond the upper airways (nose and mouth), and “thoracic particles”, which deposit within the lower respiratory tract. Other terms, such as “ PM_{10} ”, have both physiological and sampling connotations.

Methods for sampling and analysing suspended particulate matter have been discussed by WHO (9) and the US Environmental Protection Agency (4,10). These methods included black smoke measurements, which represent the darkness of a stain obtained on a white filter-paper through which air has been passed (according to the British smoke method, sometimes referred to as the black smoke method), and also total suspended particulate measurements (gravimetric measurement of particulates with an ill-defined, wind speed and sampler orientation dependent cut-off point, and collected on a glass-fibre filter by a high-volume sampler according to the method of the US Department of Health, Education, and Welfare (11), as well as by several other methods).

The inlet system of a black smoke sampler (11) typically has a 4.5- μm aerodynamic diameter (50% cut-off point); some particles up to 7–9 μm in diameter are also collected.

Methods to measure total suspended particulates (by high-volume sampler) were used extensively in the USA until the late 1980s. However, the size range sampled extends well beyond those particles that are able to penetrate the upper respiratory tract and, in arid regions, the method is liable to sample wind-entrained soil dust of large aerodynamic diameter. This problem has been recognized by the US Environmental Protection Agency, which specified that particulate matter with a median cut-off point of 10 μm aerodynamic diameter (PM_{10}) be measured for measuring compliance with the revised particle standard promulgated in 1987, and

as a better indicator of health-related particles.

Recommendations have been made by the International Organization for Standardization (ISO) regarding the aerodynamic particle size range corresponding to thoracic penetration (12), and samplers with acceptance characteristics that approximate that curve are increasingly being used. Such thoracic particle measurements according to the ISO standard are roughly equivalent to the sampling characteristics for PM10.

Soderholm proposed modified particle-size-selective sampling criteria for adoption by ISO, the American Conference of Governmental Industrial Hygienists (ACGIH) and the European Committee for Standardization (CEN) of the European Community, with the objective of international harmonization (13). In effect, the proposed criteria split the difference between the original ACGIH and ISO criteria consistent with matching the best available total and regional human deposition data. His initiative was well received by the interested parties, and is being implemented by all concerned (14–16). Particulate mass fractions were (re)defined according to the following equations:

- *Inhalable* particulate mass consists of those particles that are captured according to the following collection efficiency regardless of sampler orientation with respect to wind direction:

$$SI(d_a) = 50\% \times (1 + \exp(-0.06d_a))$$
for $0 < d_a \leq 100 \mu\text{m}$
where:
 $SI(d_a)$ = the standardized collection efficiency for particles with an aerodynamic diameter of d_a in μm for inhalable particulate mass.
- *Thoracic* particulate mass consists of those particles that are captured according to the following collection efficiency:

$$ST(d_a) = SI(d_a)[1 - F(x)]$$
where:
 $ST(d_a)$ = the standardized collection efficiency for particles with an aerodynamic diameter of $d_a \mu\text{m}$ for thoracic particulate mass.
 x = $\ln(d_a / G) / \ln(S)$
 G = $11.64 \mu\text{m}$
 S = 1.5
 $F(x)$ = the cumulative probability function of a standardized normal variable, x
- *Respirable* particulate mass consists of those particles that are captured according to the following collection efficiency:

$$SR(d_a) = SI(d_a)[1 - F(x)]$$
where: $SR(d_a)$ = the standardized collection efficiency for particles with an aerodynamic diameter of $d_a \mu\text{m}$ for respirable particulate mass.
 $F(x)$ has the same meaning as above with $G = 4.25 \mu\text{m}$
 $S = 1.5$

Collection efficiencies representative of several sizes of particles in each of the respective mass fractions are shown in Fig. 2 (4).

The most significant change in this proposal is the change in the median cut-off point for a

respirable dust sampler to 4.0 μm ; this is in accord with the ISO/CEN protocol (14,15) which has been recommended to the European Economic Community. For some particle size distributions, the revised criterion is expected to register a larger dust concentration (17).

As the physical and chemical composition of airborne particulate matter varies in time and space, the various measures of airborne particulate matter can only be compared approximately (18). It is not clear to what extent such approximations can be used to interpret data from different countries. The conversion of black smoke data into PM₁₀ seems especially uncertain, owing to the completely different principles of measurement and the large variation of the contribution of “black” material to thoracic airborne particulate matter mass. Preliminary data from a study conducted on 28 European locations in the winter of 1993-1994 with co-located measurements of black smoke and PM₁₀ indicate location-specific black smoke: PM₁₀ ratios varying from less than 0.3 to about 1.4, with most of the measurements giving ratios well below 1 (19). Recent data from the US-Canadian 24-cities study have shown ratios of fine particles (2.1 μm aerodynamic diameter) to PM₁₀ varying from 0.30 to 0.70, depending on location of measurement, with the higher ratios generally observed in the Eastern states and provinces (20).

Sources

Suspended particulate matter is a term used to cover a range of finely divided solids or liquids that originate from a number of natural or man-made sources.

Particulate matter of thoracic size may be emitted from a number of sources, some of them natural (e.g. volcanoes and dust storms) and many others that are more widespread and more important to public health (e.g. power plants and industrial processes, vehicular traffic, domestic coal burning, industrial and municipal waste incinerators). The majority of these man-made sources are concentrated in limited areas, i.e. the urbanized areas, where populations are also concentrated (21).

Hildemann et al. (22) showed that industrial-scale boilers, fireplaces, cars with and without catalytic converters, diesel trucks and meat cooking operations all emit particles primarily in the range 0.1–0.2 μm . Petrol fuelled cars with catalytic converters emitted much lower particle masses than those without, while diesel trucks emitted about 100 times the particle mass, per kilometre driven, of a passenger car with a catalytic converter. Diesel particulate matter is almost pure carbon and exists as submicrometre-sized aggregates of ultrafine carbon spheroids with aerodynamic diameters of around 0.1 μm .

By measuring the chemical composition of particles in the air, the particle mass can be apportioned to various sources that emit particles of known composition. However, compositions may change over time, as with motor vehicle emissions with the phasing out of lead from petrol. As an example, Huang et al. (23) have suggested that for current motor vehicle emissions, zinc, bromine and antimony may serve as markers in airborne particles, given their relatively high concentrations in tailpipe emissions, and their relatively high fine:coarse particle ratios. In areas where leaded petrol is still being used on a large scale, lead is still a good marker for petrol exhausts.

On the basis of a detailed chemical analysis of collected airborne particles and of source emissions, Chow et al. (24) estimated the annual average source contributions for six sites in the California San Joaquin valley to PM_{2.5} and PM₁₀. Secondary ammonium sulfate, secondary ammonium nitrate and motor vehicle exhausts were found to be major contributors to PM_{2.5},

explaining 50–70% of the mass. About 40–60% of the coarse particles were found to originate from geological contributions (fugitive dust from tilling, roadways, construction). A similar study was conducted in Sao Paulo (25), showing that emissions from residual oil and diesel (41%) and resuspended soil dust (28%) contributed most to PM_{2.5}. Soil dust (59%) and industrial emissions (19%) contributed most to the coarse fraction (2.5–15 µm).

Occurrence in air

In the past decade, extensive measurements of PM₁₀ and, to a lesser extent, PM_{2.5} have been carried out in the USA. Data collected in six US cities over a 6-year period indicated annual mean PM₁₀ (or, in earlier years, PM₁₅) concentrations ranging from 18 µg/m³ (Portage, WI) to 47 µg/m³ (Steubenville, OH), with little change over the years (26). PM_{2.5} ranged from 11 to 30 µg/m³, and PM_{2.5}:PM₁₀ ratios varied from 0.47 to 0.64. Recent data from other US cities rarely show annual average PM₁₀ concentrations of more than 50 µg/m³. In contrast, mean PM₁₀ concentrations measured in the wintertime in 5 Chinese cities were found to range from 186 µg/m³ to as high as 494 µg/m³ (27). Preliminary data from a study conducted in 28 European locations in the winter of 1993–1994 indicated low PM₁₀ concentrations in Northern Europe, with mean urban values of around 20 µg/m³; higher concentrations were found in areas with high population and traffic density such as Amsterdam, Netherlands and Berlin, Germany (45–50 µg/m³), central European cities such as Budapest, Hungary (57 µg/m³); and even higher concentrations in southern European cities such as Pisa, Italy (61 µg/m³) and Athens, Greece (98 µg/m³). The comparability of measurement locations and procedures was ensured by detailed protocols, site visits and interlaboratory comparisons. Urban/rural contrasts within countries were often small to negligible, even at distances of up to 100 km, unless mountains or hills separated the urban from the rural locations, as in Greece (19).

Data on exposures to acidic aerosols in North America have been summarized by Spengler et al. (28), showing peak daily hydrogen ion concentrations above 500 nmol/m³. Annual average hydrogen ion measurements in 16 US and Canadian cities in north-eastern North America (1988–1991) were in the range 19–52 nmol/m³, while summer-time means were 29–88 nmol/m³ (20).

Routes of exposure

Inhalation is the only route of exposure that is of concern in relation to the direct effects of suspended particulate matter on human health. Where relevant, chapters in this publication on other components, such as lead, discuss multiple routes of exposure.

Humans in developed countries spend much more time indoors than outdoors, so it is of obvious interest to know to what extent outdoor particles penetrate into homes and other indoor spaces. Smoking is an important source of indoor airborne particles, so that the penetration of outdoor particles into indoor spaces should preferably be studied in locations without smokers. Colome et al. (29) found an indoor:outdoor ratio of 0.70 for median PM₁₀ concentrations measured in 10 homes of nonsmokers living in southern California. The ratio for a finer size fraction (PM₅) was 0.79. The correlation between indoor and simultaneously measured outdoor concentrations was better for PM₅ (correlation coefficient: $R = 0.75$) than for PM₁₀ ($R = 0.58$). Clayton et al. (30) conducted a large-scale study on indoor and outdoor PM₁₀ and PM_{2.5} concentrations in California. Personal exposure to PM₁₀ was also measured, in a population of well over 100 subjects, including smokers and nonsmokers. The inter-subject correlation between personal daytime exposure measurements and ambient concentrations was relatively poor ($R = 0.60$). Personal concentrations were also found to exceed indoor as well as outdoor

concentrations by a factor of about 1.5. To what extent this is attributable to personal activities, creating a “personal cloud” of inhalable particles, or to other factors is not yet clear. Buckley et al. (31) repeatedly measured personal exposure to PM₁₀ in 13 subjects. The correlation between personal and ambient measurements ranged from 0.14 to 0.90, indicating large differences between subjects in the predictability of personal exposure from outdoor measurements alone. When the time-activity patterns and occupational exposures of the subjects were taken into account the correlation improved to 0.58–1.00. Wallace (32) has recently argued that the correlation in time between personal and ambient exposure to fine particles is fairly high, supporting the use of ambient fine particle concentrations as a valid measure of exposure in time-series studies of the association between ambient particulate matter and mortality, hospital admissions and other health endpoints.

Toxicokinetics

As discussed elsewhere (33–35), a portion of the inhaled aerosol is deposited by contact with airway surfaces and the remainder is exhaled. In inhalation toxicology, the term “deposition” refers to removal from inspired air of inhaled particles. “Clearance” refers to the subsequent removal of deposited material from the respiratory tract. Within a species, deposition of inhaled particles in the respiratory tract depends mainly on breathing pattern and aerodynamic particle size. Larger particles ($> 10\ \mu\text{m}$) are mainly deposited in the extrathoracic part of the respiratory tract (above the larynx) and the main proportion of particles of 5–10 μm in aerodynamic diameter are deposited in the larger conductive airways. Particles of between $\sim 2.5\ \mu\text{m}$ and 5 μm are deposited in the smaller conductive airways in proximity to the fine airways (respiratory bronchioles), with normal nasal breathing. With mouth breathing, the regional deposition pattern changes markedly, extrathoracic deposition being reduced and tracheobronchial and pulmonary deposition enhanced. The proportion of mouth breathing to nose breathing increases with exercise and conversation (36).

During mouth breathing, fine particles ($< 2.5\ \mu\text{m}$ aerodynamic equivalent diameter D_{ae}) are deposited primarily in the pulmonary region; between about 3 and 5 μm D_{ae} significant deposition in both the pulmonary and the tracheobronchial regions occurs; at larger sizes (about 7–15 μm D_{ae}), thoracic deposition is predominantly in the tracheobronchial region as opposed to the pulmonary region (37).

The deposition of particles in the lung is governed by particle characteristics, anatomy of the respiratory tract, tidal volume and breathing pattern (38,39). Among the important particle characteristics are size, shape, electrical charge, density and hygroscopicity. Lung size, airway branching pattern, airway diameters and lengths as well as frequency, depth and flow rate of breathing also influence particle deposition. Particle size is often characterized in terms of the “aerodynamic” diameter, the diameter of a spherical particle having unit density and the same settling velocity from an airstream as the particle under study (39). There are large differences between species in respiratory tract anatomy, making the extrapolation of particle deposition data from animal experimental results to humans difficult. Differences in breathing patterns exist both within and between species. In humans, the effect of differences in activity levels (and hence, breathing patterns) on total lung deposition of particles of various aerodynamic diameters seems to be slight, but in rats, the difference may be two-fold or more (40). In humans, a much larger fraction of particles penetrating the upper respiratory tract is deposited in the lung than in rats. Total lung deposition of such particles in humans is about 60% for particles with aerodynamic diameters of $< 0.1\ \mu\text{m}$, decreasing to about 20% for particles of 0.1–

1 μm and increasing to about 80% for particles of 5 μm . Nasal deposition of particles 1–3 μm has been reported to be about 20% in adults at rest, increasing to 30–40% during exercise, with lower values between 10 and 20% in children aged 5–15 years (41).

An important observation is that large particles ($> 2 \mu\text{m}$ aerodynamic diameter) are not deposited uniformly in the airways, but that there are prominent deposition “hot spots” at airway bifurcation and other airway surfaces directly downstream of high-velocity air flows. Studies have shown that smaller particles that penetrate deeply into the lung also tend to be deposited preferentially near airway bifurcation (38).

Once deposited in the lung, most particles are removed by the various clearance mechanisms. Insoluble particles deposited on ciliated airways are generally cleared from the respiratory tract by mucociliary activity in 24–48 hours (38,42). Clearance from the pulmonary region may occur through the action of alveolar macrophages or alternative mechanisms. Uptake of deposited particles by macrophages is rapid, but removal of these macrophages from the lungs takes several weeks. Overall, clearance of insoluble particles deposited in the pulmonary region of the lung has half-times that are measured in weeks to months or even years. Experiments conducted on rats have suggested that the retention of insoluble ultrafine particles (diameter about 20 nm) is much greater than that of fine particles with a diameter of about 250 nm (43), probably owing to better access of these ultrafine particles to the pulmonary interstitium. Clearance mechanisms themselves may be adversely affected by inhaled toxicants, so that clearance may take even longer because of the influence of the particles and co-pollutants such as ozone on the clearance mechanisms themselves. There are large differences between species in the clearance rates of particles from the lung. The clearance rates in dogs and humans seem to be comparable, but clearance of a variety of particles from the lung of rats was shown to be much faster than from either humans or dogs (44). As a result, the long-term retention of particles deposited in the lung can be much greater in humans than in rats, with obvious consequences for the extrapolation of long-term inhalation studies in rats to humans (45).

The deposition of particles in the lungs of either experimental animals with induced mild airway obstruction or in human patients with poor lung function, asymptomatic smokers or mild bronchitics with normal spirometry has been shown to be increased (46,47). This may put subjects with pre-existing airway obstruction at increased risk for the adverse effects of inhaled particles.

Health effects

Effects on experimental animals

The complexity of airborne particulate matter, both physical and chemical, makes it very difficult to conduct animal bioassays that will reliably predict what will happen to humans when they are exposed to airborne particles in various settings. Differences in particle deposition and clearance from the lung between different experimental animal species and humans, briefly discussed above, only add to the complexity. Much work has been devoted to elucidating the effects of acid aerosols on animals; these studies are reviewed in the next section. In this section, some examples will be given of experimental studies aimed at understanding the role of airborne particles (other than acid aerosols) in the causation of adverse effects in the human lung.

One approach has been to study whether particles of different sizes within the thoracic fraction

have different effects. Oberdörster et al. (48) found that ultrafine titanium dioxide (“nuisance”) particles with a diameter of ~ 20 nm had a higher pulmonary toxicity than particles with a diameter of ~ 200 nm. The smaller particles enter the lung interstitium more easily, leading to an increased inflammatory response. This response seemed to be related more to the total surface area of the particles (greater in the smaller particles) than to the total mass. Recent work by the same team of investigators has suggested that ultrafine thermovolatilization products of polytetrafluoroethylene (PTFE) exhibited a very high toxicity to rats at mass concentrations of these ~ 20 -nm particles of about $4\text{--}8 \mu\text{g}/\text{m}^3$, resulting in acute haemorrhagic pulmonary inflammation and death after 20–30 minutes of exposure (49). To what extent such observations help to explain the observed relationship between daily variations of PM₁₀ and mortality in epidemiological studies (see below) is still unclear.

Another approach has been to study the acute and chronic effects of major components of airborne particulate matter such as nitrates and sulfates. There is little, if any, evidence that nitrate and sulfate ions influence the lung mechanics of experimental animals at ambient or near-ambient concentrations (50). An exception is sulfuric acid coated on ultrafine zinc oxide particles; these have been shown to influence the vital capacity of guinea pigs at exposure concentrations (as sulfuric acid) of $20 \mu\text{g}/\text{m}^3$ for 3 hours/day for 3–5 days (51).

Yet another line of research is to expose experimental animals to well-characterized environmental particle samples, either by intratracheal instillation or by aerosolizing the dust in exposure chambers. Hatch et al. (52), for example, studied the effects of various particles on pulmonary host defences *in vitro* as well as *in vivo*. Among the studied dusts were coal flyash, particles collected from ambient air, diesel exhaust particles and volcanic ash. There was a large range in the extent to which the viability of alveolar macrophages was found to be reduced, and to which mice were found to be susceptible to bacterial infection after exposure. Coal flyash and some ambient air particles were found to be particularly toxic. Toxicity seemed to be related to small particle size and high metal content of the particles. Another example is a study by Ziegler et al. (53), who demonstrated that resuspended road dust at $360 \mu\text{g}/\text{m}^3$ impaired the immune response of exposed rats relative to either clean air or ammonium nitrate exposure, leading to a lowered resistance to respiratory infection. Exposure duration was 4 hours/day for 4 days/week for 8 weeks. The mass median aerodynamic diameter of the road dust particles was $5 \mu\text{m}$ with a geometric standard deviation of 2.0. Other investigators have suggested that surface-complexed iron on particles such as silicates and coal flyash is related to the generation of reactive oxygen species and, consequently, inflammation in the lung (54,55).

Yet another approach has been to expose laboratory animals outside the laboratory to polluted (urban) and clean (rural) ambient air. A series of such studies was conducted in Sao Paulo, Brazil, documenting that rats exposed for 6 months to the urban air pollution mixture had significantly greater lung damage than rats kept at a rural control location (56). Such studies have the advantage that they exclude the confounders that plague comparisons of human populations exposed to different levels of air pollution (active and passive smoking, occupational exposures, domestic pollution, dietary habits, etc.). However, they face the same problems as human epidemiological studies in disentangling the effects of the multiple contaminants present in the mixture.

These are just a few examples of approaches used to investigate effects of airborne particulate matter on experimental animals. The examples mainly serve to indicate that on the basis of currently available animal data on particles other than acidic aerosols, it is difficult to estimate

precisely the risks of human exposure to the airborne particulate matter mixture.

Animal studies with acid aerosols

Guinea pigs have been shown to be particularly sensitive to sulfuric acid, and increased airway resistance has been observed on exposure to low concentrations. Aerosols with a mass median diameter (MMD) of 7 μm produce only a small increase in airway resistance even at concentrations as high as 30 $\mu\text{g}/\text{m}^3$, whereas with MMD 2.5 μm there is a response that develops slowly and is accompanied by a decrease in compliance. Particles of less than 1 μm MMD produce a swift response. At concentrations below 1 $\mu\text{g}/\text{m}^3$ effects appear to be inversely related to particle diameter (57).

Acute studies at realistically low levels of sulfuric acid have demonstrated changes in airway resistance and particle clearance. A dose-related increase in airway resistance has been demonstrated in guinea pigs exposed to 100–1000 $\mu\text{g}/\text{m}^3$ for one hour. Particle sizes of 0.3–1.0 μm MMD were used, with the smaller particles producing the greater increases in resistance (58).

Altered mucociliary particle clearance was reported in donkeys exposed to sulfuric acid at concentrations of 194–1364 $\mu\text{g}/\text{m}^3$, with particle sizes of 0.3–0.6 μm , for one hour (59). In rabbits exposed via oral tube, for one hour mucociliary clearance was slowed at concentrations of 500 $\mu\text{g}/\text{m}^3$ and greater and accelerated at concentrations of 100–500 $\mu\text{g}/\text{m}^3$ (60).

Subchronic and chronic studies with similar levels of exposure have reported similar effects. In rabbits repeatedly exposed to 250 $\mu\text{g}/\text{m}^3$, MMD 0.3 μm , baseline pulmonary resistance did not change, but bronchial responsiveness was found to increase from 4 months onwards, with accompanying changes in bronchial reactivity (61). In addition, mucociliary particle clearance was slowed during the exposures, and became even slower in the months after the 12-month exposures ended. Repeated exposure of donkeys for 1 hour/day, 5 days/week for 6 months to 100 $\mu\text{g}/\text{m}^3$, MMD 0.5 μm , resulted in variable effects on clearance. In two of the four animals examined, clearance did not return to baseline values during a 3-month follow-up period (62).

Acid sulfate exposures have also been used in a number of studies, with ammonium sulfate generally being found to be less toxic than sulfuric acid. In a series of experiments with guinea pigs (63), the percentage change in airway resistance per milligram of sulfate decreased in the order ammonium sulfate > ammonium bisulfate > cupric sulfate. All the sulfate salts examined were less irritant than sulfuric acid.

Schlesinger (50) has observed that toxicological data support the available epidemiological data to the extent that airborne ambient particulate matter has been shown to be able to produce adverse biological responses that are consistent with the human morbidity findings. However, the exposure concentrations or doses needed to produce such effects in animal experiments have generally been well above those to which humans are exposed, so that there is still a quantitative gap between the epidemiological and the toxicological research findings. As for effects on mortality, Schlesinger has observed that there are very few animal data to support the relationships seen in epidemiological studies. However, animal studies, almost all conducted on healthy young animals, have generally failed to take the large range of susceptibilities present in human populations into account. The importance of this was recently underlined when preliminary data from an animal model of pulmonary disease showed that 37% of rats in which chronic bronchitis had been induced died after only 18 hours of exposure (distributed over three

6-hour periods on three consecutive days) to concentrated ambient airborne particles at an average concentration of $288 \mu\text{g}/\text{m}^3$ (64).

Effects on humans

Controlled human inhalation experiments

The data regarding controlled human exposure to particulate matter has been limited to sulfuric acid and acid sulfates in normal and asthmatic subjects. There are, however, a number of complicating factors that lead to differences in exposure which can produce inconsistent findings. These include technical difficulties in controlling both particle size and concentration adequately, and the hygroscopic properties of the particles. Fine hygroscopic particles can penetrate deeply into the respiratory tract but they grow in size and become dilute in the process. Larger particles having diameters from a few micrometres upwards are more likely to affect the upper respiratory tract. Neutralization and buffering of sulfuric acid are liable to occur on inhalation depending on a number of factors including gaseous ammonia released by ammonia-producing bacteria in the mouth and endogenous ammonia sources, the buffering capacity of airway mucus and the partitioning of airflow between the nose and the mouth.

Most studies in normal subjects have focused on sulfuric acid. There is general agreement that inhalation of sulfuric acid mists in concentrations of up to $100 \mu\text{g}/\text{m}^3$ (MMD $1 \mu\text{m}$ or less) does not cause any change in lung function even when subjects are exposed for several hours, with intermittent exercise (65–67). Little response has been reported for mists of this size at concentrations of up to $1500 \mu\text{g}/\text{m}^3$, though some subjects at that level developed cough (68). One study showed a small (1.5%) change in forced expiratory volume in 1 second (FEV_1), with cough and throat irritation in subjects exposed to $950 \mu\text{g}/\text{m}^3$ with intermittent exercise (69), and another showed a small fall in maximum mid-expiratory flow but not FEV_1 in subjects exposed to $1000 \mu\text{g}/\text{m}^3$ for 2 hours with intermittent light exercise (70). No change in lung function was seen in chamber exposures of $450 \mu\text{g}/\text{m}^3$ for 4 hours, but bronchial reactivity was increased 24 hours after cessation of exposure. The effects of 16-minute exposures to sulfuric acid, ammonium sulfate, ammonium bisulfate and sodium bisulfate at concentrations of $1000 \mu\text{g}/\text{m}^3$ were also compared in this study. The only change in lung function was seen with sulfuric acid and ammonium sulfate, and showed some relation to acidity (71).

It has been suggested that asthmatic subjects are more sensitive to sulfuric acid than normal subjects, though the findings in different studies vary considerably and the range of responses overlaps those of normal subjects. Several studies in asthmatic patients have found no change in mean values of lung function after exposures to concentrations of sulfuric acid of up to $3000 \mu\text{g}/\text{m}^3$ (65, 72–74). Other studies have, however, detected bronchoconstriction at concentrations of $< 1000 \mu\text{g}/\text{m}^3$. In one of these (75), FEV_1 fell 4.5% after exposure to $1000 \mu\text{g}/\text{m}^3$ and there was a 20% reduction in specific airway conductance after exposure to both $1000 \mu\text{g}/\text{m}^3$ and $450 \mu\text{g}/\text{m}^3$. In a study involving both normal and asthmatic subjects (68) with intermittent heavy exercise, the asthmatics showed reductions in FEV_1 after exposure for one hour to 1000 and $1500 \mu\text{g}/\text{m}^3$ but not $380 \mu\text{g}/\text{m}^3$, whereas the normal subjects showed no changes in lung function. The greatest apparent sensitivity reported was in a study of adolescent asthmatics, who showed no change in lung function following exposure at rest to $100 \mu\text{g}/\text{m}^3$ for 30 minutes, but a fall in maximum expiratory flow and FEV_1 after a further exposure of 10 minutes with moderate exercise (76).

Interpretation of the results from studies in which asthmatic patients have been exposed to

sulfuric acid is difficult because the changes, when they have occurred, have been small (maximum change in FEV₁, 0.2 litre), and there is a large variation in sensitivity to sulfuric acid in the different studies. The mode of delivery and the particle size of the acid aerosol has varied between studies, but comparison of the MMD of the particles does not provide an obvious explanation of the diverse results obtained.

There have also been some studies examining effects of inhalation of sulfuric acid on particle clearance in humans. In exposures of healthy nonsmoking adult volunteers at rest to 0.5- μ m sulfuric acid mist at 100 μ g/m³ for one hour there was an acceleration of bronchial mucociliary clearance of particles, which deposited primarily in the large thoracic airways, and a slowing down of clearance when the exposure was raised to 1000 μ g/m³. For particles that were deposited primarily in medium-sized and small airways there was a small but significant slowing of clearance at 100 μ g/m³ and a greater slowing at 1000 μ g/m³. These changes are consistent with the greater deposition of the acid in medium-sized to smaller airways. Exposures to 100 μ g/m³ for 2 hours produced slower clearance than the same exposure for one hour, indicating a cumulative dose-response relationship (77).

Epidemiological studies

Epidemiological studies have traditionally played an important role in deriving guideline values for airborne suspended particulate matter. Current concerns about the health effects of airborne particles are largely based on the results of recent epidemiological studies suggesting effects on mortality and morbidity at very low levels of exposure. This section provides a brief review of epidemiological studies relating airborne particulate matter exposure to various health endpoints. In view of the uncertainty of the current relationships of black smoke and total suspended particulates to mortality and morbidity, no studies with measurements of these components alone will be included. The emphasis is on studies with measurement data on PM₁₀, PM_{2.5} and/or sulfate and acid aerosol fractions, and on studies that permit some separation of the effects of particulate matter from those of other pollutants in the mixture. Not surprisingly, the effects of particulate matter on health have been reviewed repeatedly in the past few years (18,78–81). The information given here is based on the recent reviews as well as on an evaluation of the original papers themselves.

A. Time-series studies

The use of time-series studies to document the acute effects of particulate matter on health has increased substantially since the 1987 edition of *Air quality guidelines for Europe* (1). Time-series studies relate the development in time of air pollution and some health variable such as daily mortality, hospital admissions, etc. Usually, routinely collected data on air pollution levels are used as exposure variables, although in some instances, air pollution monitoring programmes have been implemented specifically for use in time-series studies. The sources of health data are more varied: for mortality, routine statistical data are usually used; for hospital admissions, data are sometimes available in central registries covering large areas, but sometimes have to be obtained from individual hospitals; when “panels” of healthy or diseased subjects are being studied, the health data are usually obtained by the investigators from the participants in the study using diaries, lung function measurements, etc.

There are several methodological problems involved in the analysis of time-series studies. One is that the health variables usually exhibit some pattern over time (e.g. higher mortality in winter or during heat waves) which needs to be accounted for before air pollution effects can be studied. In some long time-series studies (spanning several years), long-term time trends in health data have been observed in addition to seasonal cycles. As the weather may affect both

air pollution concentrations and health, the most appropriate way to adjust associations between air pollution and health for weather influences has been a matter of some debate. The great advantage of time-series studies is that they focus on variation with time over relatively short periods of days to weeks at most. Over such short periods, many personal characteristics such as age, smoking habits, etc. do not change, so that they can be ignored as potential confounders. Also, the variation in time of short-term average air pollution concentrations is often much greater than the variation in space of the long-term average pollution concentrations that form the basis of studies of long-term effects of air pollution on health (82). This is important because sufficient variation in exposure is a prerequisite in any analytical epidemiological study.

B. Mortality: acute effects as suggested by time-series studies

Many recent studies have addressed the relationship between daily variations in particulate air pollution and mortality at low levels of exposure.

Pope et al. studied daily mortality in relation to PM₁₀ pollution in Utah Valley for the period from April 1985 to December 1989 (83). A local steel mill is a major source of particulate air pollution in the area, in which concentrations of ozone, sulfur dioxide and nitrogen dioxide are generally low. Total, respiratory and cardiovascular mortality were found to be related to the 5-day moving average PM₁₀ concentration, including the concurrent day. The 24-hour average concentrations ranged up to 365 µg/m³, with 5-day moving average concentrations of up to 297 µg/m³ in the observation period; a graphical and tabular analysis suggested that effects on mortality could be seen at levels of < 100 µg/m³. The estimated increase in total daily mortality was 16% for each 100 µg/m³ increase in the 5-day moving average PM₁₀ concentration (which would translate into a 13% increase per 100 µg/m³ when expressed for 24-hour average PM₁₀ concentrations).

Dockery et al. published an analysis of daily mortality in St Louis, MO, and the counties surrounding Kingston/Harriman, TN (82). During the period of observation (September 1985 to August 1986), 24-hour average PM₁₀ levels ranged from 1 to 97 µg/m³ in St Louis and from 4 to 67 µg/m³ in Kingston/Harriman. Even at these low levels, the relationship between PM₁₀ and mortality was statistically significant in St Louis. The estimated coefficient for Kingston/Harriman was not significant, but of similar magnitude. A number of gaseous air pollution components (sulfur dioxide, nitrogen dioxide, ozone) were also evaluated but none of these was found to be significantly associated with mortality. The relationship with PM₁₀ was stronger than with PM_{2.5}, which was stronger than with sulfates, which was stronger than with hydrogen ion. The estimated effect on total mortality was a 16% increase for each 100 µg/m³ increase in the 24-hour average PM₁₀ concentration on the previous day, and a 17-23% increase for each 100 µg/m³ increase in the 24-hour average PM_{2.5} concentration on the previous day.

Schwartz (85) studied the relationship between PM₁₀ and daily mortality in Birmingham, Alabama over the period 1985–1988. PM₁₀ averaged 48 µg/m³, and the highest 24-hour value was 163 µg/m³. Daily mortality was found to increase with increasing PM₁₀ concentrations. Relative risks for chronic lung disease and cardiovascular deaths were higher than for death from other causes. The relationship remained when all days with PM₁₀ values of > 150 µg/m³ were excluded. Data on other pollutants were not reported. The relative risk for total mortality was an 11% increase for each 100 µg/m³ increase in the PM₁₀ concentration, averaged over the previous 3 days. The published data do not permit estimation of the effect expressed per 24-hour average concentration.

In 1995 and 1996, a large number of additional analyses of the relationship between daily

fluctuations in PM₁₀ and daily fluctuations in mortality have been published. These include studies conducted in Los Angeles, CA (86), Chicago, IL (87), Amsterdam, Netherlands (88), the US cities Boston, MA, Knoxville, TN, St Louis, MO, Steubenville, OH, Madison, WI and Topeka, KS (89), Santiago, Chile (90), Lyon, France (91), Cologne, Germany (92), and Sao Paulo, Brazil (9r). In all of these studies, PM₁₀ was measured, or a closely related size fraction such as PM₁₃ (91) or PM₇ (92).

Several other studies have been reported using other measures of airborne particulate matter such as black smoke, total suspended particulates or the coefficient of haze (for reviews of studies published until about 1994 see Dockery and Pope (18) and Pope et al. (79)).

Recently, a European project entitled "Air Pollution and Health: a European Approach" (APHEA) has been completed. Following a standardized protocol for data analysis, a large European database has been analysed for relationships between day-to-day fluctuations in air pollution and daily fluctuations in mortality and hospital admissions (94). In addition to the studies by Zmirou et al. (91) and Spix and Wichmann (92), mortality has been associated with various air pollution components including sulfur dioxide and black smoke in Athens (95), Milan (96), Barcelona (97) and London (98). A study not related to the APHEA project that was reported from Switzerland (99) has documented significant associations between total suspended particulates and mortality in three different cities. Interestingly, studies conducted in Poland and the Slovak Republic using the APHEA protocol have failed to find significant associations between particulate air pollution and mortality (100,101).

A summary of the risk estimates from studies in which PM₁₀ (or a closely related fraction) was actually measured, is given in Table 1. The table shows relative risks that have all been scaled to represent the relative risk associated with a 10 µg/m³ change in PM₁₀. The method of calculation involved the back-calculation of logistic regression coefficients from reported relative risk estimates if the coefficients themselves had not been given, and using these back-calculated coefficients to estimate the relative risk over a 10 µg/m³ range. A pooled estimate has been obtained using the variance based method given in Petiti (102). As the results indicate, most of the studies have shown significantly increased mortality with increases in daily PM₁₀ concentrations, with a pooled estimate of 1.0074 (95% confidence limits 1.0062–1.0086), associated with a 10 µg/m³ increase in PM₁₀. The time lags at which these effects were observed were not the same in all studies, but generally, these effects were associated with exposure on the day of death, or on the few days leading up to it. The test of heterogeneity (Q-statistic) (102) just reaches statistical significance; the high estimate from St Louis (84) and the low estimate from Cologne (92) accounted for almost 50% of the heterogeneity. The joint estimate of the effect of PM₁₀ on daily mortality on the basis of these studies is a relative risk of 1.0074 (or a 0.74% increase) for each 10 µg/m³ increase in the 24-hour average PM₁₀ concentration. Although this seems to be a small relative increase, it is associated with an equally small increase in the daily average concentration of PM₁₀. The number of deaths estimated to be associated on a yearly basis with such relative risks can still be substantial, as will be argued later in this chapter. It is also noteworthy that all except one of the relative risk estimates were above unity, and that the large majority of individual studies were statistically significantly elevated. As a result, the joint estimate is highly significant with a narrow confidence band. Fig. 3 shows the effect estimates in graphic form.

Table 1. Summary of studies relating daily fluctuations in total mortality to daily fluctuations in PM₁₀, relative risks estimated per 10 µg/m³

Location and reference	Relative risk	95% Confidence limits
Utah Valley (83)	1.015	1.009–1.021
St Louis (84)	1.015	0.999–1.029
Kingston/Harriman (84)	1.016	0.987–1.046
Birmingham (85)	1.010	1.002–1.018
Los Angeles (86)	1.005	1.000–1.010
Chicago (87)	1.006	1.001–1.010
Amsterdam (88)	1.006	0.999–1.014
Boston (89)	1.012	1.007–1.017
Knoxville (89)	1.009	1.001–1.018
St Louis (89)	1.006	1.001–1.010
Steubenville (89)	1.009	1.001–1.016
Madison (89)	1.007	0.996–1.107
Topeka (89)	0.995	0.980–1.009
Santiago (90)	1.008	1.006–1.010
Lyon (91)	1.002	0.994–1.010
Cologne (92)	1.003	1.000–1.006
Sao Paulo (93)	1.012	1.007–1.017
Joint estimate	1.0074	1.0062–1.0086
Test of heterogeneity (Q)	29.04	
P value of Q	0.01 < P < 0.025	

Effects of PM_{2.5} on mortality.

Recently, an analysis from the Harvard Six Cities study (a large, prospective study on the health effects of air pollution conducted in six different communities in the USA) was published addressing the question whether fine particulate mass (PM_{2.5}) is a better predictor of mortality than coarse particulate mass (the difference between PM₁₀ and PM_{2.5}) (89). The results indicate that mortality is strongly associated with PM_{2.5} but not with coarse mass. Because of the high correlation between PM_{2.5} and PM₁₀, mortality was also strongly associated with PM₁₀, and the results of this particular analysis suggest that the associations between PM₁₀ and mortality observed in other studies may very well be due to the effects of fine rather than coarse particulate mass. Table 2 provides a summary of this recent analysis. The pooled estimate was a relative risk of 1.015 (95% confidence limits 1.011–1.019) for each 10 µg/m³ increase in PM_{2.5}.

Estimated effects on mortality in these studies were generally greatest for deaths due to respiratory or cardiovascular causes. They were also generally greater among the elderly than among younger subjects. An in-depth analysis of mortality occurring on low- and high-pollution days conducted on the data from Philadelphia showed a disproportionate increase in mortality

among the elderly (103). Mortality due to chronic lung disease and cardiovascular disease was also disproportionately increased. Interestingly, respiratory conditions were also more often mentioned on death certificates as contributing causes to cardiovascular deaths on high-pollution days. An analysis of location of death revealed that deaths outside the hospital were disproportionately increased as compared to death of hospitalized patients. This pattern is very similar to the pattern of mortality seen during and following the 1952 London smog.

Table 2. Summary of relations between daily fluctuations in total mortality and daily fluctuations in PM_{2.5} as found in the Harvard Six Cities study (89), relative risks estimated per 10 µg/m³

Location	Relative risk	95% Confidence limits
Boston	1.022	1.015–1.029
Knoxville	1.014	1.002–1.026
St. Louis	1.011	1.004–1.017
Steubenville	1.010	0.999–1.021
Portage	1.012	0.997–1.028
Topeka	1.008	0.980–1.036

Particulate acid was a notable feature of the former London smogs but, with concentrations of sulfur dioxide and smoke also being high in such episodes it was not clear how far acid contributed to the sharp increases in mortality and morbidity observed. Recently there have been several re-analyses of daily mortality in London during non-episodic winters, from 1965 to 1972, linked with corresponding measurements of “net particulate acidity” at a single central site as well as with mean concentrations of sulfur dioxide and smoke at a set of seven sites distributed through the area (104). The authors reported that a model-based analysis showed a clear association between mortality and the pollution mixture, but could not attribute more of the mortality response to the acid than to other measured components, possibly owing to the poor representativity of the single-site acid measurements. In a further analysis of the same data set, Lippmann and Ito (105) took a different approach in order to separate the influences of temperature, season and ambient pollution levels on daily mortality. In each season between 1965 and 1972, the majority of days fell within one or two temperature ranges, within which the daily death rates also fell within narrow ranges. Within these restricted temperature and mortality ranges, preliminary analyses indicated that there were relatively strong associations between daily mortality and the daily logs of the concentrations of hydrogen ion and sulfur dioxide that were not confounded by temperature or seasonal variations. By contrast, the associations between the daily log of black smoke and daily mortality in these restricted ranges were weaker, especially in the winter and summer seasons. While a more comprehensive analysis of these London data and of other pollutant and mortality data sets is needed, these initial results suggest that this new approach can serve as a valuable complement to model-based approaches for studying associations between pollutant exposures and daily mortality.

Over the last few years, some controversy has been generated with respect to the interpretation of the time-series studies on mortality (e.g. 106,107). The debate has focused on the sensitivity of the results to the statistical models employed and on control for co-pollutants and weather variables. The debate has stimulated an independent re-assessment of the findings reported from

Philadelphia and some other US cities (108). The recent US Environmental Protection Agency criteria document for particulate matter (81) contains a detailed discussion of the reservations expressed by some investigators in the literature. It concludes that there is no evidence that the use of acceptable alternative statistical models for the analysis of the time-series studies will lead to fundamentally different results from those already published; there is also no evidence that the relative risks of death estimated to be associated with particulate matter exposure will change considerably after taking the role of other pollutants into account. Finally, alternative adjustments for weather variables have not been shown to change significantly the relative risk estimates for particulate matter (1).

Acute effects of particulate matter on mortality: old and new evaluations.

In the 1987 edition of *Air quality guidelines for Europe*, it was concluded that there was no solid evidence for the effects of particulate matter on mortality at 24-hour average levels below $500 \mu\text{g}/\text{m}^3$ for black smoke in combination with $500 \mu\text{g}/\text{m}^3$ (1). This illustrates that a dramatic change in the evaluation of effects of particulate matter on mortality has taken place since then, as there are now a large number of studies suggesting that effects on mortality are being observed at levels of PM₁₀ (or PM_{2.5}) alone of well below $100 \mu\text{g}/\text{m}^3$. Although a detailed discussion of the development of understanding over the past ten years is beyond the scope of this chapter, some arguments can be put forward that may help to explain the large difference between the current and the previous evaluation.

When comparing the results of recent and historic studies, a pattern as shown in Fig. 4 emerges. In past studies, particulate matter concentrations were often in the range $100\text{--}1000 \mu\text{g}/\text{m}^3$ as 24-hour averages. Nowadays, many situations are characterized by levels one order of magnitude lower, i.e. mostly between 10 and $100 \mu\text{g}/\text{m}^3$. Overall, exposure-response over a wide range can be described as curvilinear rather than linear, with small absolute changes in exposure at the low end of the curve having similar effects on mortality to large absolute changes at the high end. A re-analysis of the London data, for example, has shown that mortality increased by 14% over a range of black smoke concentrations of $20\text{--}300 \mu\text{g}/\text{m}^3$ with a similar increase in the range $300\text{--}1000 \mu\text{g}/\text{m}^3$ (110). Similar results have been reported for Erfurt in the former German Democratic Republic, over a particulate matter range spanning $15\text{--}650 \mu\text{g}/\text{m}^3$ (111).

In many studies of smog episodes, increased mortality during the episode was followed by a decrease shortly after the episode. When multiple episodes follow each other with brief time intervals, it could be expected that the air pollution effect would be related to the mortality observed just before the episode. An analysis from Germany has shown that air pollution episodes of similar pollution concentrations were associated with more mortality when mortality had been relatively low in the weeks preceding the episode, and less when mortality had been relatively high (112).

Furthermore, when air pollution was very high in western countries, some 30 or more years ago, life expectancy was lower than at present, and a much smaller proportion of the population was in the category of old, already diseased subjects who may be very susceptible to a small pollution insult. Thus, the population at risk of dying as a result of an episode of relatively low air pollution concentrations, may be larger than it was before.

As the time-series studies focus on relationships between short-term changes in air pollution exposure and mortality, their results cannot easily be used to infer whether deaths attributed to air pollution exposure were occurring days, weeks, months or even years before they would

have otherwise occurred. Other study designs are needed to answer this question more fully, and studies following such designs are the subject of the next subsection.

C. Mortality: effects from chronic exposure as suggested by cross-sectional and cohort studies

Data on chronic effects of airborne particulate matter on mortality come from cross-sectional studies, comparing air pollution exposure and mortality rates between locations, and from cohort studies documenting the mortality experience of differentially exposed subjects over time.

An example of a cross-sectional analysis of the association between mortality rates and airborne particulate matter is a study by Özkaynak and Thurston (113). They compared US 1980 mortality rates with various measures of exposure to airborne particulate matter. In this analysis, sulfates, fine particles, inhalable particles and total suspended particulates were found to be associated, in decreasing order, with total mortality, after adjustment for a number of socioeconomic predictors of mortality. An example from Europe is a study reported by Bobak and Leon from the Czech Republic (114). These authors correlated infant mortality with particulate matter air pollution over the years 1986–1988. Annual geometric mean particle concentrations were $68.5 \mu\text{g}/\text{m}^3$ overall. Concentrations were subdivided into quintiles, the highest quintile relating to areas with annual mean particle concentrations above $84.7 \mu\text{g}/\text{m}^3$. Postneonatal mortality was found to increase almost monotonically with particle concentrations, the highest quintile having a relative risk of 1.42. The estimated risk ratios were higher for postneonatal respiratory mortality. Particle concentrations were reported as PM₁₀, and the analysis was made with adjustment for a number of socioeconomic indicators, proportion of total births outside marriage and abortion rate, as well as annual mean sulfur dioxide and nitrogen dioxide concentrations.

The general criticism of such studies is that they are “ecological” in comparing aggregate data on mortality with aggregate data on pollution, with no possibility of taking individual confounders into account.

Recently, however, the suggestive evidence coming from cross-sectional studies has been supplemented with data from two cohort studies. Dockery et al. (26) followed a cohort of more than 8000 adults living in six US cities with varying levels of air pollution exposure for periods of 14–16 years, between 1974 and 1991. After adjustment for age, sex, smoking, education, occupational exposure and body mass index, a significant relationship was found between exposure to fine particles and survival. The closest association was found for PM_{2.5} and sulfate, with less clear relationships with total suspended particulates, aerosol acidity (only measured for one year in each city) and sulfur dioxide, and virtually no relationship with ozone. The estimated effect was a mortality-rate ratio of 1.26, comparing the most polluted city (Steubenville, OH) with the least polluted city (Portage, WI). The mean fine particle concentrations ranged from 11.0 to $29.6 \mu\text{g}/\text{m}^3$ with little change over the study period (fine particle measurements were reported for the 1980–1988 period). Compared to, for example, the mortality-rate-ratio associated with active smoking in this cohort (1.59), this represents a sizeable effect of particulate air pollution on survival. Pope et al. (115) analysed data from a large cohort study conducted by the American Cancer Society since 1980. Pollution data from 151 US metropolitan areas were linked to 8 years of follow-up data from about 500 000 subjects. After adjustment for age, sex, race, active and passive smoking, occupational exposure, education, body mass index and alcohol intake, a significant association between fine particulate air pollution exposure and survival emerged. Comparing the highest polluted area

with the lowest polluted area, an adjusted mortality-rate ratio of 1.17 was found for PM_{2.5}.

In view of the estimated large magnitude of the effect of relatively low particle concentrations on survival, the results of these two studies require further scrutiny and replication. No comparable data from Europe or elsewhere are currently available.

To illustrate the potential impact of long-term particulate matter exposure on mortality, the results of the cohort studies can be used to estimate the reduction of life expectancy associated with a certain difference in long-term exposure. Combining the effect estimates from both studies for fine particles results in an estimated relative risk of 1.10 per 10 µg/m³ difference in long-term exposure to fine particles (i.e. a difference well within the range that was actually observed in the two studies). In Table 3, this relative risk estimate has been applied to the 1992 life table for Dutch men. The estimated effect on life expectancy is 1.1 years. The calculation has been restricted to ages 25–90 years, as the cohort studies have not gone beyond the age of 90 (Dockery et al. investigated a random sample of subjects aged 25–75 years, who were followed for approximately 15 years). It is well known that at very high age, competing risks reduce the risk ratios for even strong determinants of mortality such as smoking (116) so that it is not appropriate to estimate the effects of particulate matter on subjects in age ranges not actually studied.

Table 3. Estimated effect of PM exposure on life expectancy of Dutch men

Age	Survivors	Observed no. of deaths in 15 years	Clean air, expected no. of deaths in 15 years	Clean air, expected no. of survivors
27.5	98 177	1 674	1 522	98 177
32.5	97 752	2 417	2 197	97 752
37.5	97 232	3 818	3 471	97 232
42.5	96,503	6 272	5 711	96 655
47.5	95 ,335	10 368	9 447	95 555
52.5	93 414	16 869	15 392	93 761
57.5	90 231	26 153	23 963	90 944
62.5	84 967	37 268	34 352	86 108
67.5	76 545	46 696	43 462	78 369
72.5	64 078	50 012	47 525	66 981
77.5	47 681			51 756
82.5	29 849			34 907
87.5	14 066			19 456
	Total no. of years lived: 4 929 150	Life expectancy between 25 and 90: 4 929 150/98 177 = 50.21	Life expectancy between 25 and 90: 5 038 265/98 177 = 51.32	Total no. of years lived: 5 038 265

The estimation of the long-term effect of air pollution on mortality in Dutch men proceeded as follows:

1. The study published by Dockery et al. (26) investigated a random cohort of subjects aged 25–75 years who were followed for about 15 years. It was assumed that for a calculation of effects of particulate matter on life expectancy, a restriction to this age groups, and to the expected mortality experience of this age group over a 15-year period was needed.
2. Mortality experience was estimated using the Netherlands Central Bureau of Statistics 1992 life table for men in the Netherlands. To simplify the calculations somewhat, only the data from the mid-points of the ten successive 5-year categories that make up the 25–75 year age range (27.5 years, 32.5 years, 72.5 years) were used. The expected number of deaths for each of the ten age categories was calculated over a 15-year period by subtraction of the number alive at age $n + 15$ from the number alive at age n .
3. It was assumed that if the air contained a significantly lower concentration of particulate matter, the mortality would be decreased by a factor of 1.1. The expected number of deaths for each age category over a period of 15 years therefore decreased by a factor of 1.1. This affected the number of survivors in the “clean air” category, and for simplification, it was assumed that the effect of particulate matter only started to become manifest after 15 years in subjects who were 27.5 initially, so that the number of survivors increased starting at age 42.5. This latter point was taken into account when estimating the expected number of deaths in the “clean air” category.
4. To calculate average life expectancy between age 25 and 90, the total number of years lived between ages 25 and 90 was calculated by multiplying the number of survivors at each of the 5-year interval cut-off points (27.5 87.5 years) by 5. The result was the total number of years lived between ages 25 and 90 for men in the Netherlands. Life expectancy at age 27.5 is defined as the total number of years lived, divided by the total number of subjects alive at age 27.5 (for men, 98 177 out of each 100 000 born).
5. By performing this calculation for Dutch men on the basis of the 1992 life table, and for the hypothetical Dutch population exposed to a lower concentration of fine particulates, it has been estimated what the effect of these particulates on life expectancy would be.
6. As shown in Table 3, the expected number of deaths in 15 years was been estimated by assuming that the mortality will be decreased by a factor of 1.1 compared to the number of deaths occurring according to the 1992 life table.

D. Hospital admissions

Schwartz et al. studied hospital emergency room visits for asthma in Seattle, Washington, over a 13-month period from September 1989 to September 1990 (117). The 24-hour average PM₁₀ concentrations ranged from 6 to 103 $\mu\text{g}/\text{m}^3$. Asthma visits by subjects under 65 were significantly associated with the PM₁₀ concentration measured on the previous day, after adjustment for weather variables and a number of other potential confounders. A graphical and tabular analysis suggested that an increase in asthma visits could be observed at levels below 24 $\mu\text{g}/\text{m}^3$. Sulfur dioxide and ozone were not found to be related to asthma visits. Sulfur dioxide concentrations never exceeded 81 $\mu\text{g}/\text{m}^3$, and ozone data were only available for a 4-month period within the period of observation. The estimated relative risk was 1.12 for a 30 $\mu\text{g}/\text{m}^3$ increase in the 4-day average PM₁₀ concentration and 1.11 for a similar increase in the 24-hour average concentration.

Using hospital data from Birmingham, AL for the years 1986–1989, Schwartz (118) reported a significant relationship between PM10 concentrations and hospital admissions for pneumonia and chronic obstructive pulmonary disease in the elderly. The mean PM10 concentration was $45 \mu\text{g}/\text{m}^3$ with a 90-percentile of $77 \mu\text{g}/\text{m}^3$. For each $100 \mu\text{g}/\text{m}^3$ increase in 24-hour average PM10, admissions for pneumonia increased by 19% and for chronic obstructive pulmonary disease by 27%. Excluding all days with PM10 levels above $150 \mu\text{g}/\text{m}^3$ did not change the effect estimates.

Schwartz (119) examined associations between daily PM10 and hospital admissions for respiratory disease in Minneapolis-St Paul, MN. Data on hospital admissions in persons aged 65 years and older were obtained for the years 1986–1989 by admission date for pneumonia and chronic obstructive pulmonary disease. Classification was by discharge diagnosis. Poisson regression was used to control for time trends, seasonal fluctuations and weather. PM10 was a risk factor for pneumonia admissions (relative risk (RR) = 1.17, 95% confidence interval (CI) = 1.02–1.33) and chronic obstructive pulmonary disease admissions (RR = 1.57, 95% CI = 1.20–2.06). Ozone was also associated with pneumonia admissions. The PM10 relative risk is for an increase of $100 \mu\text{g}/\text{m}^3$ in daily PM10.

Thurston et al. (120) examined air pollution and daily hospital admissions for respiratory causes in Toronto, Ontario. PM2.5 samples were collected daily at a central city site during July and August of 1986, 1987 and 1988 and were subsequently extracted and analysed for daily particulate phase aerosol strong acidity (hydrogen ion) and sulfates. Daily counts of respiratory admissions to 22 acute care hospitals and daily meteorological and environmental data on ozone, total suspended particulates and PM10 were also obtained. After controlling for temperature, ozone, hydrogen ion and sulfates were significantly associated with respiratory and asthma admissions. Comparing various particle parameters, the authors found that associations decreased in strength from hydrogen ion to sulfates to PM2.5 to PM10 to total suspended particulates, indicating that particle size and composition are important in defining the adverse human health effects of particulate matter. On average, summer-time haze was associated with 24% of all respiratory admissions (21% with ozone, 3% with hydrogen ion). On peak pollution days, however, hydrogen ion had the highest relative risk estimate (1.5 at $391 \text{ nmol}/\text{m}^3$ hydrogen ion) and summer-time haze was associated with roughly half of all respiratory admissions.

Burnett et al. (121) related the number of urgent daily respiratory admissions to 168 acute care hospitals in Ontario with ozone and sulfates for the years 1983–1988. Positive and statistically significant associations were found between hospital admissions and ozone and sulfates recorded on the day of admission and up to 3 days prior to the date of admission. These associations were observed for asthma, chronic obstructive pulmonary disease and infections in all age groups, the greatest impact being found in infants and the least effect in the elderly. Air pollution was not related to a class of non-respiratory admissions, which served as a negative control, nor was it related to admissions in the winter months December–March, when ozone and sulfate levels are low and when people spend a considerable amount of time indoors.

Thurston et al. (122) examined associations between air pollution (hydrogen ion and sulfates) and respiratory hospital admissions in Buffalo, Albany and New York. The summer months were selected for analysis because ozone and hydrogen ion concentrations are highest in the summer season. Summer admissions and environmental data were first corrected to eliminate long-wave autocorrelations, and day-of-week effects were removed via regression. Total

respiratory and asthma admissions were strongly associated with hydrogen ion, sulfates and ozone, especially in the summer of 1988 when pollution levels were more extreme. Ozone consistently had the highest mean effect estimates. Relative risk calculations indicated that the risk of admission for asthma was increased by a factor of 1.19–1.43 in these cities on maximum 1988 summer-time pollution days, with hydrogen ion having the highest estimates. The results are consistent with the hypothesis that ambient acid aerosol peaks (hydrogen ion $> 100 \text{ nmol/m}^3$) can potentiate the effects of ozone on respiratory hospital admissions.

Another recent series of studies by Schwartz (123–126) has provided further support for the hypothesis that the fluctuation in daily hospital admissions for respiratory disease among the elderly is associated with the daily fluctuation in PM₁₀. A recent study from Paris (127), conducted in the framework of the APHEA project, points in a similar direction. However, other studies in the APHEA project that have looked for effects of other measures of particulate matter pollution (notably black smoke) on hospital admissions have shown less consistent results (128,129).

Stimulated by the finding that in the mortality time-series studies, deaths from cardiovascular disease have been associated with air pollution exposure, studies have also been conducted on the association between air pollution and hospital admissions for cardiovascular disease. Two recent reports (130,131) showed that cardiovascular hospital admissions are also associated with PM₁₀ (130) and sulfates as indicators of fine particulate matter air pollution (131).

Hefflin et al. (132) studied the effect of a dust storm on emergency room visits in south-east Washington State. During the storm, 24-hour PM₁₀ levels exceeded $1000 \mu\text{g/m}^3$ for two days. There was a slight increase in emergency room visits for bronchitis, estimated at 3.5% per $100 \mu\text{g/m}^3$ increase in PM₁₀. Comparison of this estimate with the previous two suggests that the effect of naturally occurring PM₁₀ is much smaller than that of urban PM₁₀.

Several other hospital admission studies have been reported from the USA, Canada and Europe that have utilized total suspended particulate or black smoke data. Effect estimates derived from these studies are in the same range as those obtained from the two studies in which PM₁₀ was measured directly, after using the conversion factors discussed before (18,79,81).

The results of recent time-series studies of respiratory hospital admissions in which PM₁₀ (or a close surrogate) was actually measured are summarized in Table 4. Again, the effects have been scaled to a $10 \mu\text{g/m}^3$ increase in PM₁₀ by back-calculation of logistic regression coefficients, when appropriate, as explained in the section on time-series studies on mortality. The joint estimate points to a 0.80% increase of respiratory hospital admissions for every $10 \mu\text{g/m}^3$ increase in PM₁₀. There was also evidence of heterogeneity in the study results as in the mortality time-series studies, possibly reflecting variation in admission practices in the different study areas, which were located in three different countries.

E. Acute effects on lung function, respiratory symptoms, medication use and school absenteeism

Pope et al. studied daily changes in lung function and acute respiratory symptoms in a panel of subjects living in Utah Valley, UT, where a large steel mill causes increased concentrations of PM₁₀ but not of other measured pollutants (133). Subjects included a sample of wheezing school children and a sample of asthma patients aged 8–72 years. The observation period included the winter months of 1989–1990; 24-hour PM₁₀ concentrations ranged from 11 to 195

$\mu\text{g}/\text{m}^3$, and on only two days, a concentration of $150 \mu\text{g}/\text{m}^3$ was exceeded. The peak expiratory flow rate (PEF) was found to be related to PM₁₀ concentrations in the preceding days. Respiratory symptoms and asthma medication use increased with increasing PM₁₀ concentrations in the school-based sample of children. In the asthma patients, only the use of extra asthma medications was found to be associated with PM₁₀. After excluding the two days with PM₁₀ concentrations above $150 \mu\text{g}/\text{m}^3$, the highest PM₁₀ concentration was $114 \mu\text{g}/\text{m}^3$. The relationship between PEF and PM₁₀ remained unchanged after this exclusion.

Table 4. Summary of studies relating daily fluctuations in respiratory hospital admissions to daily fluctuations in PM₁₀, relative risks per $10 \mu\text{g}/\text{m}^3$

Reference	Relative risk	95% Confidence limits
(123)	1.016	1.007–1.026
(124)	1.012	1.000–1.025
	1.019	1.006–1.032
(127)	1.004	1.000–1.008
(126)	1.011	1.001–1.022
(120)	1.047	1.005–1.088
Joint estimate	1.0080	1.0048–1.0112
Test of heterogeneity (Q)	13.66	
P value of Q	$0.01 < P < 0.025$	

Pope and Dockery studied panels of symptomatic and asymptomatic children in Utah Valley in the winter of 1990-1991 (134). 24-hour PM₁₀ concentrations ranged from 7 to $251 \mu\text{g}/\text{m}^3$. On 14 days during the study period, a level of $150 \mu\text{g}/\text{m}^3$ was exceeded. PEF was decreased, and the reporting of respiratory symptoms was increased in both panels when PM₁₀ concentrations increased. All observations from days with or immediately following days with PM₁₀ concentrations above $150 \mu\text{g}/\text{m}^3$ were excluded from some of the analyses. The results remained essentially unchanged. A tabular analysis further suggested that PEF was decreased, and respiratory symptoms were increased at PM₁₀ concentrations exceeding $39 \mu\text{g}/\text{m}^3$.

In another study from the Utah Valley, Ransom and Pope investigated elementary school absences in relation to PM₁₀ pollution over a period of six years, 1985–1990 (135). The highest PM₁₀ concentration observed in this period was $365 \mu\text{g}/\text{m}^3$, and exceeded $150 \mu\text{g}/\text{m}^3$ on approximately 10 days each year. School absenteeism was found to be related to 4-week moving average PM₁₀ concentrations, after adjustment for weather variables and a number of other potential confounders. The relationships generally remained after excluding observations obtained on days when PM₁₀ had exceeded $150 \mu\text{g}/\text{m}^3$ within the previous four weeks.

Roemer et al. studied a panel of children with chronic respiratory symptoms in the Netherlands in the winter of 1990-1991 (136); 24-hour average PM₁₀ concentrations exceeded $150 \mu\text{g}/\text{m}^3$ on one day only in the observation period, reaching $171 \mu\text{g}/\text{m}^3$. Sulfur dioxide levels were never higher than $105 \mu\text{g}/\text{m}^3$, and black smoke concentrations (24-hour averages) ranged from 2 to $120 \mu\text{g}/\text{m}^3$. Daily changes in PEF, asthma attacks, wheeze and bronchodilator use were found to

be associated with PM₁₀, black smoke and sulfur dioxide. A tabular analysis suggested that effects on wheeze and bronchodilator use were observable from concentrations exceeding 40 µg/m³ (the baseline category in this analysis included all concentrations of less than 40 µg/m³). Sulfur dioxide, black smoke and PM₁₀ were fairly highly correlated in this data set, so that the effects of particles and sulfur dioxide on lung function could not be separated. However, later analyses of these data have shown that effects of PM₁₀ on symptoms and medication use remained after adjustment for sulfur dioxide, whereas there was no independent effect of sulfur dioxide (137).

A group of normal, randomly selected schoolchildren not participating in the above study was investigated in this period with repeated spirometry (138,139). FVC and FEV₁ were associated with PM₁₀ and sulfur dioxide as well as black smoke. There was no relationship between air pollution and acute respiratory symptoms in this panel.

Hoek and Brunekreef (140) studied panels of schoolchildren in the winters of 1988–1990 in the Netherlands. All children were tested repeatedly with spirometry over periods of about 10–15 weeks. In the observation period, 24-hour PM₁₀ concentrations ranged from 14 to 126 µg/m³, sulfur dioxide from 0 to 94 µg/m³ and nitrogen dioxide from 2 to 70 µg/m³. PEF and maximum mid-expiratory flow rate (MMEF) were found to be negatively associated with PM₁₀ and nitrogen dioxide concentrations measured either on the same day or the day before the lung function tests, after adjustment for ambient temperature.

Pope and Kanner (141) utilized lung function data obtained from smokers with mild to moderate chronic obstructive pulmonary disease, living in Salt Lake City; 251 subjects had two lung function measurements, and the difference between the two was found to be related to PM₁₀ concentration differences between the measurement days. PM₁₀ never exceeded 162 µg/m³ during the study. The estimated effect was in the order of a 2% decline in FEV₁ for each 100 µg/m³ increase in 24-hour average PM₁₀.

Additional studies from the USA (143–146) and Europe (147,148) have added to the weight of evidence that particulate matter air pollution is associated with increases in acute respiratory symptoms and medication use, and with small reductions in lung function.

Table 5. Summary of studies relating daily fluctuations in the prevalence of bronchodilator use to daily fluctuations in PM₁₀, relative risks estimated per 10 µg/m³

Reference	Relative risk	95% Confidence limits
(146)	1.034	1.018–1.051
(133)	1.112 (wheezing schoolchildren)	1.024–1.207
	1.120 (patient panel)	1.047–1.197
(136)	1.022	1.008–1.036
Joint estimate	1.0305	1.0201–1.0410
Test of heterogeneity (Q)	10.71	
P value of Q	0.01 < P < 0.025	

Table 5 shows the estimated relative risks of bronchodilator use associated with a 10 µg/m³ increase in PM₁₀, from studies in which PM₁₀ was actually measured. The estimates from the

Utah Valley studies (suggesting a 11–12% increase) were different from the estimates of the two Dutch studies (implying a 2–3% increase over the same PM₁₀ range). These differences suggest that day-to-day changes in the prevalence of bronchodilator use are related to differences in the composition of panels, and/or differences in the management of asthma in different countries.

Table 6 shows the estimated effects of PM₁₀ on the day-to-day variation in cough reporting. Again the US studies tend to show higher effect estimates than the Dutch studies, and the overall effect estimate was a 3.6% increase in cough reporting per 10 µg/m³ PM₁₀, with no significant heterogeneity between studies.

Table 6. Summary of studies relating daily fluctuations in the prevalence of cough to daily fluctuations in PM₁₀, relative risks estimated per 10 µg/m³

Reference	Relative risk	95% Confidence limits
(142)	1.086	1.022–1.155
(146)	1.027	0.997–1.058
(134)	1.052 (symptomatic schoolchildren)	1.023–1.082
	1.034 (asymptomatic schoolchildren)	0.999–1.070
(136)	1.000	0.961–1.039
Joint estimate	1.0356	1.0197–1.0518
Test of heterogeneity (Q)	6.85	
P value of Q	0.10 < P < 0.25	

Table 7 shows the estimated effects of PM₁₀ on the day-to-day variation in reporting of lower respiratory symptoms (either separately or in combination). The overall effect estimate was a 3.2% increase in reporting of symptoms per 10 µg/m³ of PM₁₀, without significant heterogeneity between studies.

Table 7. Summary of studies relating daily fluctuations in acute, lower respiratory symptoms (LRS) to daily fluctuations in PM₁₀, relative risks estimated per 10 µg/m³

Reference	Relative risk	95% Confidence limits
(146)	1.039 (shortness of breath)	1.010–1.068
	1.041 (wheeze)	0.994–1.090
(133)	1.051 (LRS, wheezing schoolchildren)	1.010–1.093
	1.002 (LRS, patient panel)	0.958–1.048
(136)	1.029 (wheeze)	1.009–1.047
Joint estimate	1.0324	1.0185–1.0464
Test of heterogeneity (Q)	2.90	
P value of Q	0.50 < P < 0.75	

Table 8 shows the estimated reductions in PEF associated with PM₁₀ from studies with daily recording of both PM₁₀ and PEF. The overall estimate is a 0.13% reduction per 10 µg/m³, without significant heterogeneity between studies.

Table 8. Summary of studies relating daily fluctuations in peak expiratory flow (PEF) to daily fluctuations in PM₁₀, relative decrease in PEF relative to mean PEF estimated per 10 µg/m³

Reference	Relative lung function decreases	95% Confidence limits
(147)	0.9960	0.9880–1.0040
(146)	0.9978	0.9966–0.9990
(134)	0.9988 (symptomatic schoolchildren)	0.9980–0.9996
	0.9992 (asymptomatic schoolchildren)	0.9986–0.9998
(133)	0.9975 (wheezing schoolchildren)	0.9966–0.9990
	0.9985 (patient panel)	0.9966–1.0004
(136)	0.9986	0.9975–0.9996
Joint estimate	0.9987	0.9983–0.9991
Test of heterogeneity (Q)	7.84	
P value of Q	0.25 < P < 0.50	

Meanwhile, some epidemiological information on the effects of ultrafine particles has become available (148). In a panel study in Erfurt (Germany), ambient particles in the range 0.01–2.5 µm were determined with a differential mobility analyser and an optical particle counter. The correlation in time between numbers of ultrafine particles (< 0.1 µm) and particle mass in the size range 0.1–0.5 µm was moderate at 0.51, which made a separate evaluation of the effects of particle numbers and particle mass possible. Both fractions were found to be associated with a decrease in PEF, and an increase in acute respiratory symptoms including cough. Effects of particle numbers were also independent of effects of PM₁₀. Consequently, the suggestion coming from this study is that the number of ultrafine particles in ambient air may predict acute health effects independent of PM₁₀.

F. Effects of long-term exposure on lung function and respiratory symptoms

As with mortality, it is important to consider not only the short-term, but also the long-term effects of particles on respiratory health. Three recent reports indicate associations between aggregate data on lung function and chronic respiratory disease on the one hand and airborne particles on the other hand. Chestnut et al. (149) used lung function data collected among 6900 adults living in 49 different locations in the USA during the first National Health and Nutrition Examination Survey (NHANES I) between 1971 and 1975. FVC was found to decrease with increasing annual average total suspended particulate levels with an apparent threshold at about 60 µg/m³. Schwartz (150) used chronic respiratory disease data from the same source. After adjustment for smoking, occupational exposure and a number of other risk factors, the risk of chronic bronchitis increased with increasing particulate concentrations, with no apparent threshold. A Swiss cross-sectional study also found an effect of PM₁₀ on FVC and FEV₁ (151).

A cohort study is being conducted among (mostly) nonsmoking Seventh-Day Adventists living

in various areas in California (152). Recently reported results suggest that the risk of developing definite symptoms of airway obstructive disease between 1977 and 1987 was related to exposure to total suspended particulates, with a relative risk of 1.36 per 1000 hours per year in which a concentration of 200 $\mu\text{g}/\text{m}^3$ was exceeded. No increased risk was observed at levels below the pre-1987 US federal standard of 75 $\mu\text{g}/\text{m}^3$.

In contrast to the studies on short-term health effects, there are few studies documenting morbidity effects of long-term exposure to PM₁₀ and other measures of fine particulate matter. Data from the Harvard Six Cities Study indicate increased respiratory illness rates among children exposed to increasing concentrations of total suspended particulates, sulfates and hydrogen ion as indicators of exposure to fine particulate matter (153). Relative risk estimates suggested an increase of 11% in cough and bronchitis rates for each 10 $\mu\text{g}/\text{m}^3$ increase in annual average total suspended particulate concentration. There was no clear relationship between airborne particulate matter exposure and lung function in this population. In a survey of respiratory symptoms among children in 24 communities in the USA and Canada, the incidence of bronchitis was found to increase by 29% for each 10 $\mu\text{g}/\text{m}^3$ increase in annual average PM₁₀ concentration though the relation with other measures of particulate matter was better pronounced (154).

Measurements of particulate acidity in terms of hydrogen ion concentration have been incorporated in some epidemiological studies in North America. In the 24-cities study mentioned earlier, with mean hydrogen ion levels ranging from 0 to 51.9 nmol/ m^3 (20) an association was found with bronchitis, but not with asthmatic symptoms (154). From the same 24-cities study, significant associations between FVC and FEV₁ and particle strong acidity, sulfate particles, PM_{2.5} and PM₁₀ have been reported (155). The estimated effect, comparing lowest to highest exposed communities, was in the order of 3.5% for FVC.

Evaluation of human health risks

Evaluation of current exposure levels via air

Data on exposure levels to airborne inhalable particles are still limited for Europe. Data have mostly been obtained from studies not directly aimed at providing long-term distributions of exposure data for large segments of the population. Nevertheless, it seems that in northern Europe, PM₁₀ levels are low, with winter averages even in urban areas not exceeding 20–30 $\mu\text{g}/\text{m}^3$. In western Europe, levels seem to be higher at 40–50 $\mu\text{g}/\text{m}^3$ with only small differences between urban and non-urban areas. Levels in some central and eastern European locations from which data are available suggest that nowadays, these are only somewhat higher than those measured in cities such as Amsterdam and Berlin. As a result of the normal day-to-day variation in PM₁₀ concentrations, 24-hour averages of 100 $\mu\text{g}/\text{m}^3$ are regularly exceeded in many areas in Europe, especially during winter inversions.

Health Risk Evaluation

General remarks

A variety of methods exist to measure particulate matter in air. For the present evaluation, studies have been highlighted in which particulate matter exposure was expressed as the thoracic fraction (~ PM₁₀) or size fractions or constituents thereof. Practically speaking, at least some data are also available on fine particles (PM_{2.5}), sulfates and strong aerosol acidity. Health effect studies conducted with (various forms of) total suspended particulates or black

smoke as exposure indicators have provided valuable additional information in recent years, but they are less suitable for the derivation of exposure–response relationships for particulate matter because total suspended particulates include particles that are too large to be inhaled or because the health significance of particle opacity as measured by the black smoke method is uncertain.

Recent studies suggest that short-term variations in particulate matter exposure are associated with health effects even at low levels of exposure (below $100 \mu\text{g}/\text{m}^3$). The current database does not allow the derivation of a threshold below which no effects occur. This does not imply that no threshold exists; epidemiological studies are unable to define such a threshold, if it exists, precisely.

Although at low levels of (short-term) exposure (defined as $0\text{--}100 \mu\text{g}/\text{m}^3$ for PM₁₀), the exposure response curve fits a straight line reasonably well, there are indications from studies conducted in the former German Democratic Republic and in China that at higher levels of exposure (several hundreds of $\mu\text{g}/\text{m}^3$ PM₁₀), the curve is shallower for at least effects on mortality than at low levels of exposure. In the London mortality studies, there was also evidence of a curvilinear relationship between black smoke and daily mortality, the slope becoming shallower at higher levels of exposure. Estimates of the magnitude of effect occurring at low levels of exposure should therefore not be used to extrapolate to higher levels outside the range of exposures that existed in most of the recent acute health effect studies.

Although there are now many studies which show acute effect estimates of PM₁₀ that are quantitatively reasonably consistent, this does not imply that particle composition or size distribution within the PM₁₀ fraction is unimportant. Limited evidence from studies on dust storms indicates that such PM₁₀ particles are much less toxic than those associated with combustion sources. Recent studies in which PM₁₀ size fractions and/or constituents have been measured suggest that the observed effects of PM₁₀ are in fact largely associated with fine particles, strong aerosol acidity or sulfates (which may serve as a proxy for the other two), and not with the coarse (PM₁₀ minus PM_{2.5}) fraction.

Traditionally, particulate matter air pollution has been thought of as a primarily urban phenomenon. It is now clear that in many areas of Europe, urban–rural differences in PM₁₀ are small or even absent, indicating that particulate matter exposure is widespread. Indeed, several of the health effect studies reviewed in this chapter were conducted in (semi-)rural rather than urban areas. This is not to imply that exposure to primary, combustion-related particulate matter may not be higher in urban areas. At present, however, data are lacking on the specific health risks of such exposures.

Evidence is emerging also that long-term exposure to low concentrations of particulate matter in air is associated with mortality and other chronic effects such as increased rates of bronchitis and reduced lung function. Two cohort studies conducted in the USA suggest that life expectancy may be shortened by more than a year in communities in communities exposed to high concentrations compared to those exposed to low concentrations. This is consistent with earlier results from cross-sectional studies comparing age-adjusted mortality rates across a range of long-term average concentrations. Again, such effects have been suggested to be associated with long-term average exposures that are low, i.e., starting at a concentration of fine particulate matter of about $10 \mu\text{g}/\text{m}^3$. Whereas such observations require further corroboration, preferably also from other areas in the world, these new studies suggest that the public health implications of particulate matter exposure may be large.

Evaluation of effects of short-term exposure on morbidity and mortality

Table 9 shows the summary estimates (from Tables 1 and 4–8) of relative increase in daily mortality, respiratory hospital admissions, reporting of bronchodilator use, cough and lower respiratory symptoms, and changes in peak expiratory flow associated with a $10 \mu\text{g}/\text{m}^3$ increase in PM₁₀ or PM_{2.5}, as reported in studies in which PM₁₀ and/or PM_{2.5} concentrations have actually been measured (as opposed to being inferred from other measures such as coefficient of haze, black smoke or total suspended particulates). The database for parameters other than PM₁₀ is still limited, but for the reasons noted above, it is very important to state that even though the evaluation of (especially the short-term) health effects is largely expressed in terms of PM₁₀, future regulations and monitoring activities should put the emphasis on (appropriate representations of) the respiratory fraction in addition to, or even preferred to PM₁₀ (157).

Table 9. Summary of relative risk estimates for bronchodilator use, cough and lower respiratory symptom (LRS) reporting, PEF changes, respiratory hospital admissions and daily mortality, associated with a $10 \mu\text{g}/\text{m}^3$ increase in the concentration of PM₁₀ or PM_{2.5}

Endpoint	Relative risk for PM _{2.5} (95% confidence interval)	Relative risk for PM ₁₀ (95% confidence interval)
Bronchodilator use		1.0305 (1.0201–1.0410)
Cough		1.0356 (1.0197–1.0518)
LRS		1.0324 (1.0185–1.0464)
PEF change (relative to mean)		– 0.13% (– 0.17% to – 0.09%)
Respiratory hospital admissions		1.0080 (1.0048–1.0112)
Mortality	1.015 (1.011–1.019)	1.0074 (1.0062–1.0086)

It is important to realize that at present, it is not known what reduction in life expectancy is associated with daily mortality increases related to particulate matter exposure. If effects are restricted to subjects in poor health, effects on age at death may be small.

The effect estimates in Table 9 can be used, with considerable reservation, to estimate for a population of a given size and mortality and morbidity experience how many subjects would be affected over a short period of time with increased particulate matter levels. The reservation stems from the finding that for some of the estimated effects, there was no evidence of heterogeneity between studies in the magnitude of the effect estimate. An investigation of the reasons for heterogeneity is beyond the scope of this chapter. As a consequence, the pooled effect estimates may not be applicable in all possible circumstances.

For illustrative purposes, Table 10 contains an estimate of the effect of a 3-day episode with daily PM₁₀ concentrations averaging 50 and $100 \mu\text{g}/\text{m}^3$ on a population of 1 million people, having a 3-day average mortality of 100, a 3-day average number of respiratory hospital admissions of 75, and having 10 000 asthmatics using bronchodilators and/or experiencing asthma symptoms on any given day. Table 10 makes clear that in a population of that size, the number of subjects dying, or having to be admitted to hospital as a result of particulate matter exposure is small relative to the additional number of “person-days” with increased medication use and/or increased respiratory symptoms due to particulate matter exposure.

Table 10. Estimated number of subjects (in a population of 1 million) experiencing health effects over a period of 3 days characterized by a mean PM₁₀ concentration of 50 or 100 µg/m³

Health effect indicator	No. of subjects affected by a three-day episode of PM ₁₀ at:	
	50 mg/m ³	100 mg/m ³
Mortality	4	8
Respiratory hospital admissions	3	6
Person-days of bronchodilator use	4863	10 514
Person-days of symptom exacerbations	5185	11 267

Whereas these calculations should be modified according to the size, mortality and morbidity experience of populations of interest and, where possible, for factors contributing to the heterogeneity in the effect estimates, they do provide some insight into the public health consequences of certain particulate matter exposures.

Evaluation of effects of long-term exposure on mortality and morbidity

The most convincing information on long-term effects of particulate matter exposure on mortality is provided by two recent cohort studies (26,115). Relative risk estimates for total mortality from the first study (26), expressed per 10 µg/m³, were 1.10 for inhalable particles (measured as either PM₁₅ or PM₁₀), 1.14 for fine particles (PM_{2.5}) and 1.33 for sulfates. Relative risk estimates for total mortality from the second study (115), expressed per 10 µg/m³, were 1.07 for fine particles (PM_{2.5}) and 1.08 for sulfates. Sulfate levels used in the second study (which ranged from 3.6 to 23.6 µg/m³) may have been inflated owing to sulfate formation on filter material used in earlier studies. The first study included one of the high sulfate communities (Steubenville) and yet, the range of sulfate levels in this study was much lower (4.8–12.8 µg/m³), possibly owing to more adequate methods of measurement for sulfates employed in this study.

Long-term effects of particulate matter exposure on morbidity have been demonstrated in the Harvard 24 cities study among children (154,155). Expressed per 10 µg/m³, the relative risks for bronchitis were 1.34 for PM_{2.1}, 1.29 for PM₁₀, and 1.96 for sulfate particles. The corresponding changes in FEV₁ were -1.9% (PM_{2.1}), -1.2% (PM₁₀) and -3.1% (sulfate particles). Whereas such mean changes are clinically unimportant, the proportion of children having a clinically relevant reduced lung function (FVC or FEV₁ < 85% of predicted) was increased by a factor of 2–3 across the range of exposures (155). A recent study from Switzerland (151) has shown significant reductions in FEV₁ of -1.0% per 10 µg/m³ PM₁₀.

Table 11 provides a summary of the current knowledge of effects of long-term exposure to PM on morbidity and mortality endpoints.

Table 11. Summary of relative risk estimates for effects of long-term exposure to particulate matter on the morbidity and mortality associated with a 10 µg/m³ increase in the concentration of PM10 or PM2.5

Endpoint (reference)	Relative risk for PM2.5 (95% confidence interval)	Relative risk for PM10 (95% confidence interval.)
Mortality (26)	1.14 (1.04–1.24)	1.10 (1.03–1.18)
Mortality (115)	1.07 (1.04–1.11)	n.a.
Bronchitis (154)	1.34 (0.94, 1.99)	1.29 (0.96–1.83)
% change in FEV ₁ , children (155)	– 1.9% (– 3.1% to – 0.6%) ^a	– 1.2% (– 2.3% to – 0.1%)
% change in FEV ₁ , adults (151)		– 1.0% (n.a.)

^a These data are for PM2.1 rather than PM2.5.

Using the risk estimates presented in Table 11, Table 12 provides estimates of the number of subjects experiencing health effects associated with long-term exposure to particulate matter, using similar assumptions about population size and morbidity as in Table 10. Specifically, a population size of 1 000 000 has been assumed, 20% of which being children (200 000 subjects), with a baseline prevalence of 5% for bronchitis symptoms among children (i.e. 10 000 children are assumed to have bronchitis symptoms), and with a baseline prevalence of 3% of children having a lung function (FVC or FEV₁) lower than 85% of predicted (6000 children).

Table 12. Estimated number of children (out of 200 000 in a population of 1 million) experiencing health effects, per year, due to long-term exposure to a PM2.5 concentration of 10 or 20 µg/m³ above a background level of 10 µg/m³

Health effect indicator	No. of children affected per year at PM2.5 concentrations above background of:	
	10 µg/m ³	20 µg/m ³
No. of additional children with bronchitis symptoms	3350	6700
No. of additional children with lung function (FVC or FEV ₁) below 85% of predicted	4000	8000

In addition, the impact of long-term exposures to particulate matter on total mortality can be estimated. The number of persons surviving to a certain age will be smaller in a population exposed to higher concentrations, and the difference will depend on the age group. If the mortality structure of Dutch males is taken as a basis for calculation, and if the assumptions used in the construction of Table 2 are applied, in each birth cohort of 100 000 men the number of survivors exposed to pollution increased by 10 µg/m³ (PM10) will be reduced by 383 men before the age of 50, by 1250 men before the age of 60 and by 3148 men before the age of 70. An increase in the long-term exposure of 20 µg/m³ (PM10) corresponds an estimated reduction of the number of men surviving to a certain age in the cohorts by, respectively, 764, 2494 or 6250 men.

Guidelines

The weight of evidence from numerous epidemiological studies on short-term responses points clearly and consistently to associations between concentrations of particulate matter and adverse effects on human health at low levels of exposure commonly encountered in developed countries. The database does not, however, enable the derivation of specific guideline values at present. Most of the information that is currently available comes from studies in which particles in air have been measured as PM₁₀. There is now also a sizeable body of information on fine particulate matter (PM_{2.5}), and the latest studies are showing that this is generally a better predictor of health effects than PM₁₀. Evidence is also emerging that constituents of PM_{2.5} such as sulfates and particle strong acidity are sometimes even better predictors of health effects than PM_{2.5} *per se*.

The large body of information on studies relating day-to-day variations in particulate matter to day-to-day variations in health provides quantitative estimates of the effects of particulate matter that are generally consistent. The available information does not allow a judgement to be made of concentrations below which no effects would be expected. Effects on mortality, respiratory and cardiovascular hospital admissions as well as other health variables have been observed at levels well below 100 µg/m³, expressed as a daily average PM₁₀ concentration. For this reason, no guideline value for short-term average concentrations is recommended either. Risk managers are referred to the risk estimates provided in the tables for guidance in decision-making regarding standards to be set for particulate matter.

The body of information on long-term effects is still smaller. Some studies have suggested that long-term exposure to particulate matter is associated with reduced survival, and a reduction of life expectancy in the order of 1–2 years. Other recent studies have shown that the prevalence of bronchitis symptoms in children, and of reduced lung function in children and adults are associated with particulate matter exposure. These effects have been observed at annual average concentration levels below 20 µg/m³ (as PM_{2.5}) or 30 µg/m³ (as PM₁₀). For this reason, no guideline value for long-term average concentrations is recommended. Risk managers are referred to the risk estimates provided in the tables for guidance in decision-making regarding standards to be set for particulate matter.

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