MRC Institute for Environment and Health

Airborne particles: Exposure in the home and health effects

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This report is dedicated to the memory of Dr Graham Patrick of the MRC Toxicology Unit, Leicester.

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Executive summary

Background

A number of epidemiological studies have demonstrated apparent associations between ambient pollution by airborne particles (generally measured at fixed-site monitors) and various measures of mortality or morbidity. However, since people spend the majority of their time indoors, there are concerns that outdoor exposure data may not reflect an individual's true level of exposure to airborne particles. In addition, the inter-relationships between outdoor, indoor and personal exposures to particles and the factors affecting these relationships are currently poorly understood. This could lead to an inadequate assessment of the dose–response relationship between particle exposure and health effects, possibly with important consequences for the assessment of the public health significance of pollution by airborne particles.

Objectives of the report

This report summarises current understanding of the likely health effects of airborne particles and explores possible mechanisms by which such particles might impact on health, in order to assess the validity of the reported epidemiological associations. Available data on outdoor, indoor and personal exposure to airborne particles and the inter-relationships between these are extensively tabulated and reviewed. The report focuses on indoor air quality in the home and, in particular, attempts to evaluate data on UK indoor sources, levels and exposures, in order to assess the likely significance for health of indoor exposure to particles in the UK. This report was commissioned by Department of the Environment, Transport and the Regions as part of a wider programme of work by the Institute for Environment and Health (IEH) on indoor air quality in the home.

The report deals with nonbiological particles, in particular those with an aerodynamic diameter of less than 10 μm (i.e. PM_{10}). Environmental tobacco smoke (ETS) and particles of biological origin are not addressed in detail in this report, although they are acknowledged to be important contributors to the indoor particulate load. These types of particle are the subject of separate reviews by IEH.

Review process

An extensive literature review was undertaken on exposure to airborne particles in ambient air and the home and on the potential health effects of such exposure. From this review, a background paper was developed which was used as a basis for discussions by international experts and representatives of relevant Government departments at a workshop held at IEH in January 1998. The primary purpose of the workshop was to ensure that the review was comprehensive, accurate and balanced. Expert opinion was also sought to identify key knowledge gaps and to assist in the development of recommendations for future research, although the conclusions and recommendations presented in this report do not necessarily represent a consensus opinion of the meeting delegates. This report is based on the background paper presented at the workshop, and incorporates the output from the meeting along with additional material subsequently provided and produced by workshop participants and IEH staff.

Exposure and health effects assessment

Potential indoor sources of particles include cooking, certain heating appliances, and human activity. Although outside the scope of the current review, a major contributor to indoor particles is ETS, and the role of allergenic (biological) particles must also be recognised. Indoor particle levels (measured as a mass concentration) are generally lower than, but correlated with, outdoor levels, except when a significant indoor source is present. However, personal exposure levels are generally higher than either indoor or outdoor levels.

There is considerable epidemiological evidence that airborne particles may adversely affect human health. Short-term elevations in ambient particle levels have been strongly associated with increases in mortality, morbidity, and/or hospital or emergency room admissions: acute cardiopulmonary impairment is the predominant effect, and the elderly or infirm are particularly at risk. Short-term changes in pulmonary function and respiratory symptoms have also been detected, particularly in people with asthma. Long-term exposure to particles may increase mortality and morbidity rates and levels of respiratory symptoms, and impair pulmonary function, although the evidence for adverse effects being associated with long-term exposure is less certain.

There is a degree of mechanistic explanation for the observed toxicity of particles. Attention is increasingly being focused on the role of particles in the initiation or promotion of pulmonary inflammation. Several mechanisms by which pulmonary inflammation could lead to systemic effects have been proposed: inflammatory mediators released from the lungs into the systemic circulation could promote the release of blood coagulation factors and white blood cells from their sites of production and thereby increase the risk of blood clotting; cardiotoxic chemicals could be released during the inflammatory response; the systemic oxidant–antioxidant balance could be changed; or the central nervous system could be affected through stimulation of neural receptors in the lung. The validity and/or relative importance in humans of these hypothetical mechanisms at normal exposure levels is, as yet, uncertain.

Personal exposure is of considerable importance as it is the key determinant of the particle dose received by an individual and thus directly influences any impact on health. As indoor sources have been shown to raise personal exposure levels substantially, and the population subgroups most at risk from particle exposure are likely to spend the majority of their time indoors, it is considered possible that indoor sources of particles could play an important role in any health effects attributable to particle exposure, although information on the relative contribution of these sources is currently limited. Control of indoor sources could be a valuable component of possible remedial strategies to reduce total personal exposure to particles.

Conclusions

There is evidence to suggest that exposure to small airborne particles may have an adverse impact on human health, with those suffering from chronic obstructive pulmonary disease or other cardiopulmonary conditions and patients with asthma being at greatest risk. However, the mechanisms underlying the observed effects are at present far from certain. The relative importance of indoor sources of particles is not known but, as these have the potential to elevate personal exposures, it is important to advance understanding about their role and contribution to adverse human health impacts.

Principal research recommendations

Exposure assessment

- Improved monitoring devices to measure outdoor, indoor and personal particle composition should be developed.
- The size, number and composition of particles in the indoor air and the personal cloud should be better characterised, and particle movement into and through representative homes studied.
- Modelling of exposure should be undertaken.

- Biomarkers should be identified that permit identification of exposure to different types of particle.
- Effectiveness of possible strategies to reduce particle exposure indoors should be assessed.

Epidemiology and human volunteer studies

- The strength of the relationship between health endpoints and particle size, number and composition should be established, using epidemiological studies focusing on identified 'at risk' groups.
- The influence of indoor/outdoor activity and behaviour patterns and the role of indoor combustion sources should be systematically investigated.
- Research approaches should be developed and implemented that focus on chronic rather than shorter-term health endpoints.

Mechanistic studies

- Techniques capable of collecting environmentally-relevant samples of particles should be developed to provide sufficient quantities of material for use in *in vivo* studies.
- Mechanistic studies should be extended to size ranges, compositions and concentrations of particles relevant to normal human exposures.
- Bioavailability of chemicals (e.g. polycyclic aromatic hydrocarbons and metals) present on or in particles should be investigated.
- Animal models of normal and susceptible human populations should be further developed.

1 Introduction

1.1 Background

A number of epidemiological studies have suggested an association between particulate air pollution and increased mortality (e.g. Dockery *et al.,* 1993; Schwartz, 1994b; Pope *et al.,* 1995c). In these studies the data on exposure to airborne particles were derived from monitoring of outdoor particle levels. However, there is concern that monitoring ambient levels may not adequately represent personal exposures, particularly since it has been estimated that most people spend the majority (approximately 90%) of their time indoors, either at home or at work (e.g. Daisy & Lee, 1996; Valberg & Watson, 1996b; Wallace, 1996). Indeed the elderly, the diseased and the infirm, who may be at greatest risk from particulate air pollution, are likely to spend substantially more time indoors than the general population. Little is known about the relationship between indoor and outdoor particle levels in the UK and their relative influence on personal exposure, although some research on this is now underway.

1.2 Aims and scope

This review is part of a wider programme of work on indoor air quality in the home sponsored by the Department of the Environment, Transport and the Regions; previous Institute for Environment and Health (IEH) assessments on indoor air quality in the home have been published on nitrogen dioxide, formaldehyde, volatile organic compounds, house dust mites, fungi and bacteria (IEH, 1996) and on carbon monoxide (IEH, 1998). This report explores the evidence for the potential effect on health of exposure to airborne particles and the potential mechanisms by which such particles could cause toxicity, and assesses available data on outdoor, indoor and personal exposure to particles, with particular emphasis on exposure in the home. The main focus is on nonbiological particles with an aerodynamic diameter[a] of less than 10 µm (i.e. PM_{10}), although data relating to other sizes and types of particles are also considered, where appropriate. Although a significant contribution to indoor particle levels arises from environmental tobacco smoke (ETS) and allergenic (biological) particles, health effects specific to exposure to biological particles and ETS are not considered in detail here as these are the subject of separate IEH reports (IEH, 1996; IEH, in preparation[b]). However, measurement of these pollutants as a component of indoor particles is referred to in the exposure section.

[a] Aerodynamic diameter is defined as the diameter of an equivalent spherical particle of density 10^3 kg/m^3 that has the same falling speed as the particle in question; this normalises particles of different shapes and densities.

[b] IEH (in preparation) *Environmental tobacco smoke and children: Exposure in the home and health effects*

A primary objective of this report is to review and interpret the existing data on indoor and outdoor airborne particle levels and personal exposure, so as to facilitate an understanding of how well measurements of indoor or outdoor particle concentrations can act as surrogates for personal exposure. Epidemiological and human experimental evidence for adverse effects on health associated with airborne particle exposure are also reviewed, along with possible mechanisms by which such particles may elicit toxicity.

On the basis of the reviewed evidence, the relevance to human health of indoor (nonworkplace) exposure in the home to suspended particulate matter is assessed, and gaps in current knowledge and recommendations for future research are made.

1.3 Review process and report structure

To ensure a balanced and scientifically robust assessment, a background document was produced with the guidance of a small expert steering group and then subject to thorough review and evaluation by a group of international experts and government scientists at a workshop hosted by IEH in January 1998. The experts also suggested additional source material for consideration. This report is based largely on published literature identified using structured searches of recognised sources including online databases such as MEDLINE® , TOXLINE® , EMBASE® and NTIS. While the majority of papers considered have been published in a peer reviewed journal, other documents, such as conference papers or unpublished reports, have also been used where they contain data considered to be useful.

The remainder of this section presents an overview of the types and sources of airborne particulate material, together with a brief description of the various types of equipment used for particle monitoring. In Section 2, data on outdoor, indoor and personal exposure levels and the inter-relationships between these compartments are assessed. Section 3 presents a detailed review of the epidemiological evidence and human experimental data on the health effects of airborne particles. Potential mechanisms of toxicity are also reviewed with reference to *in vitro* and *in vivo* experimental evidence. Section 4 draws together considerations on the exposure, health effects and the likely impact on the population of airborne particle exposure, highlights pertinent knowledge gaps and presents recommendations for the direction of future research activities in this field.

1.4 Definition and measurement of airborne particulate matter

Definitions

Airborne particulate matter encompasses a complex group of organic and inorganic substances and mixtures of substances, their principal common feature is their existence as small discrete particles. Such particles are emitted by all combustion and metallurgical processes and many other industrial operations (QUARG, 1996). They are also formed by processes which are not a result of human activity, such as the suspension of soil dust or sea salt, volcanic emissions, forest or bush fires, and the ingress of micrometeorites to the Earth's atmosphere. Biological particulates include fungal spores, house dust mite faeces, pollen grains, cat dander, bacteria and viruses. The major chemical constituents of nonbiological particulate matter are sulphates, nitrates, carbonaceous compounds, acids, ammonium ions, metal compounds, water and crustal materials.

Depending upon the area of interest, various conventions have been used to define particles. For sampling purposes, particles are generally defined in terms of their size distribution. The size of particulate matter may span several orders of magnitude, from molecular clusters with an aerodynamic diameter of the order of 0.005 µm to large particles with diameters of approximately 100 µm (QUARG, 1996). Also, some very small particles may cluster to form larger agglomerations. Conventionally, particles are described in three size ranges or four 'modes', as described below.

Nucleation mode — particles below 0.2 µm in diameter. These particles are formed by condensation of hot vapours (e.g. in gas flames or vehicle exhausts) or by conversion of gases to particles (e.g. oxidation of sulphur dioxide to sulphuric acid particles).

Accumulation mode — particles between 0.2 and 2 µm diameter. These are particles which have grown from the nucleation mode by coagulation or condensation of vapours. Accumulation particles may remain airborne for 7 to 30 days (EPAQS, 1995), longer than the other particle modes. This is because accumulation particles do not tend to coagulate and are not readily removed by rain.

'Fine' particle mode — represented by the combined nucleation and accumulation modes.

Coarse mode — particles greater than 2 µm diameter. These particles consist mainly of minerals derived from soil, sea spray or industrial processes and are formed by mechanical attrition (EPAQS, 1995). As these particles are relatively large, they remain airborne for only short periods of time.

Particles that are emitted directly from a source are termed 'primary' particles. 'Secondary' particles are those that are formed within the atmosphere as a result of the chemical reaction of gases.

Devices for particle measurement have been developed to capture the particles in various size fractions. The four most common measurements are defined below.

PM_{10} — particulate matter measured with a sampler which has a 50% collection efficiency (known as the 'cutpoint') for particles with an aerodynamic diameter of 10 µm. PM_{10} samplers collect particles in the size range which is virtually equivalent to the International Organization for Standardization (ISO) definition of the 'thoracic fraction'.

$PM_{2.5}$ — particulate matter measured with a sampler which has a cutpoint of 2.5 µm aerodynamic particle diameter. This is equivalent to the ISO 'high-risk respirable fraction'.

RSP (respirable suspended particles) — particulate matter measured with a sampler which has a cut point of 3.5 µm. Most commonly used in US studies, and similar to the ISO 'respirable fraction'.

TSP (total suspended particles) — particulate matter measured with a sampler which has a cut point of between 25 and 40 µm aerodynamic diameter.

When considering the biological activity of particles the site of deposition in the human respiratory tract is the

main criterion used to define a particle. Thus, while the size, shape and density of particles determine their ability to remain suspended in the air, these properties also determine where particles are deposited in the human respiratory tract. ISO defines four main fractions of airborne dusts (see Figure 1.1). These are described by QUARG (1996) as summarised below.

The **inhalable fraction** is the mass fraction of total airborne particles that is inhaled through the nose and/or mouth. For ambient atmospheres it is calculated using the equation:

$$E_1 = 0.5\,[1 + \exp(-0.06D)] + 10^{-5}\,U^{2.75}\exp(0.05D)$$

where E_1 is the inhalable fraction, D is the aerodynamic diameter of the particle, and U is the wind speed (up to 10 m/s).

The **thoracic fraction** is the mass fraction of inhaled particles that penetrates the respiratory system beyond the larynx. As a function of total airborne particulate matter, the thoracic fraction is represented by a lognormal curve with a median aerodynamic diameter of 10 µm and a geometric standard deviation of 1.5.

The **respirable fraction** is the mass fraction of inhaled particles that penetrates to the unciliated airways, or alveolar region, of the lung, where gas exchange occurs. It is represented by a cumulative lognormal curve with a median aerodynamic diameter of 4 µm and a geometric standard deviation of 1.5.

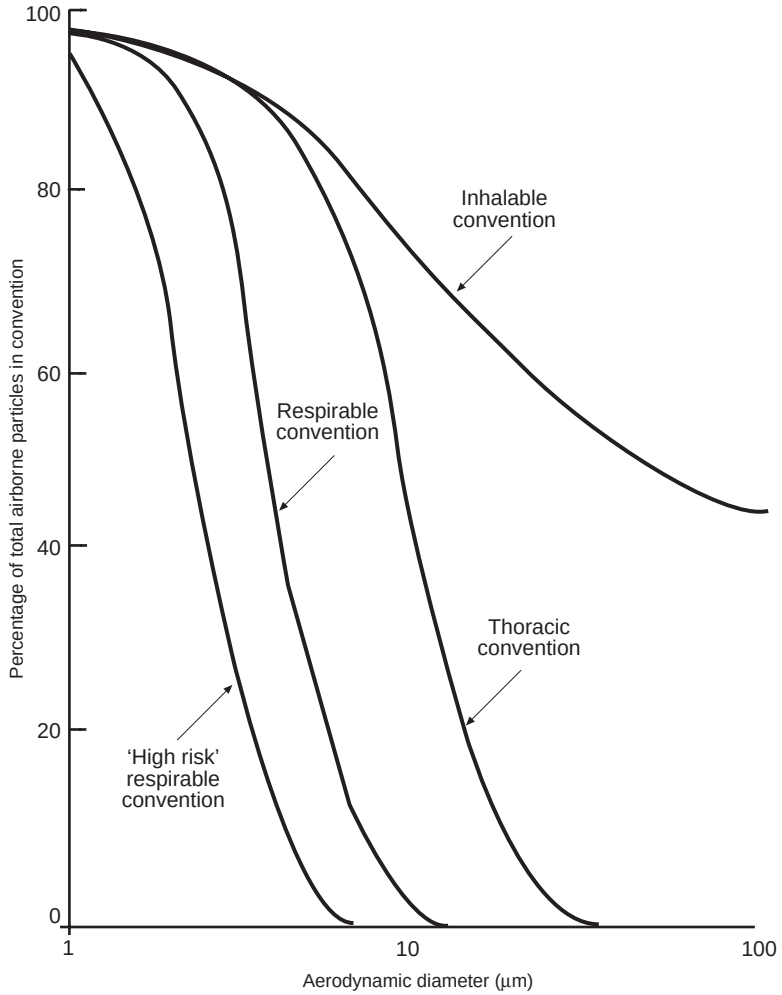
The **'high risk' respirable fraction** is a definition of the respirable fraction for the sick and the infirm, or children. As a function of total airborne particulate matter it is represented by a cumulative lognormal curve with a median aerodynamic diameter of 2.5 µm and a geometric standard deviation of 1.5.

Methods of measuring particles

Methods for the measurement of particles have been extensively reviewed by QUARG (1996), as summarised below.

Particles were originally measured in the UK by the 'black smoke' method, in which air is drawn through a funnel onto filter paper and the blackness of the stain on the paper measured; data derived by this method are usually quoted in terms of µg/m^3 British black smoke (BBS) or black smoke (BS). The method is still used and gives a good indication of the concentration of particles that have a high elemental carbon content, such as particles produced by coal burning and diesel engines. However, it is less sensitive for particles with low carbon content, and is insensitive to secondary particles, such as ammonium sulphate and ammonium nitrate, and primary particles of sodium chloride.

Figure 1.1 ISO health-related particle sampling conventions IS 7708 (1994)



From QUARG (1996)

The black smoke method tends to collect particles below 4 µm diameter with high efficiency, and therefore approximates to the 'respirable' particle fraction as defined by ISO. However, the majority of particle sampling which currently takes place targets the PM_{10} or $PM_{2.5}$ size fractions. Calibrated sampling heads split the total particle mass to select the required fraction. The sample may then be analysed using gravimetric samplers or direct-reading (real time) devices.

In gravimetric devices, particles pass through the sampling head and are deposited on a filter. Samples are collected over a period of around 24 hours, after which the filter is removed and weighed to determine the mass of particles collected (usually PM_{10} or $PM_{2.5}$). These types of monitor sample at flow rates ranging from 16.7 to 1130 l/min. They include the PM_{10} Hi-Vol samplers, which have been widely used in the USA (QUARG, 1996). High flow rate samplers permit sufficient sample to be collected over the 24-hour sampling period to allow both gravimetric and chemical analysis. A number of low flow rate PM_{10} samplers are available in the UK. These all use a validated PM_{10} inlet and, like the Hi-Vol samplers, have an omnidirectional entry and a single-stage impactor that allows the PM_{10} fraction to penetrate to a filter. A version of one low flow rate sampler incorporates a virtual impactor with a 50% penetration at 2.5 µm, after the PM_{10} inlet. This enables the 10 µm to 2.5 µm ($PM_{10–2.5}$) and $PM_{2.5}$ fractions to be separated and collected on Teflon filters.

In direct-reading devices, sampling and analysis are performed within the monitor, and particle concentration can be determined almost immediately (QUARG, 1996). There are three main types of direct-reading particle samplers — optical, resonance oscillation, and beta-particle attenuation devices.

Optical devices use light scattering by airborne particles to detect the concentration or number of particles present. The response given will depend on the size distribution, shape and refractive index of the particles. Calibration of the samplers is required, and inaccuracies can occur if the nature of the particles is variable.

Resonance oscillation samplers operate on the theory that the frequency of oscillation of a tapered glass tube is directly proportional to the mass of that tube (QUARG, 1996). Deposition of particles onto the tube produces a change in resonant frequency. The Rupprecht and Patashnick Tapered Element Oscillating Microbalance (TEOM) is perhaps the most commonly used of these devices, and is utilised in the Department of the Environment, Transport and the Regions' Automated Urban Network (AUN). The TEOM has a standard PM_{10} inlet and operates at a flow rate of 16.7 l/min. Particles collect on a filter at the end of the glass tube, and the tube's frequency of oscillation is directly proportional to the mass of particles on the filter. The inlet and sensing system are heated to a temperature of 50 °C, to remove water from hygroscopic salt droplets, which would otherwise block the filter. Every 13 seconds, a microprocessor determines the mass concentration of particles deposited. Average concentrations are recorded every 30 minutes to 1 hour.

Beta-particle attenuation devices measure the reduction in intensity of radioactive beta particles passing through a dust-laden filter or collection substrate. The rate of collection of particles on the filter is reflected by a change in attenuation of the beta particles. The mass of particles collected is calculated according to their mass absorption coefficient. This coefficient may vary by ± 20%, which can result in inaccuracies. Nevertheless, beta-particle attenuation devices are widely used, mainly because of their relatively low cost and the ability of some later models to provide data resolved to 1-hour intervals. They fall into two main types — one which utilises a filter tape to collect particles, and the other which uses a stack of conventional filters in a sequential loader (QUARG, 1996).

Accuracy and comparability of particle monitors

A wide range of monitors is available for the measurement of particulate matter. As described above, these monitors use a variety of different techniques for sampling and calculation of the mass or number of particles present. Differences in these techniques can result in inconsistencies in the results obtained by different monitors, so that different types of monitor used at the same time in the same location may produce quite different results. This variability has to be borne in mind whenever comparisons are made between studies employing different types of monitor.

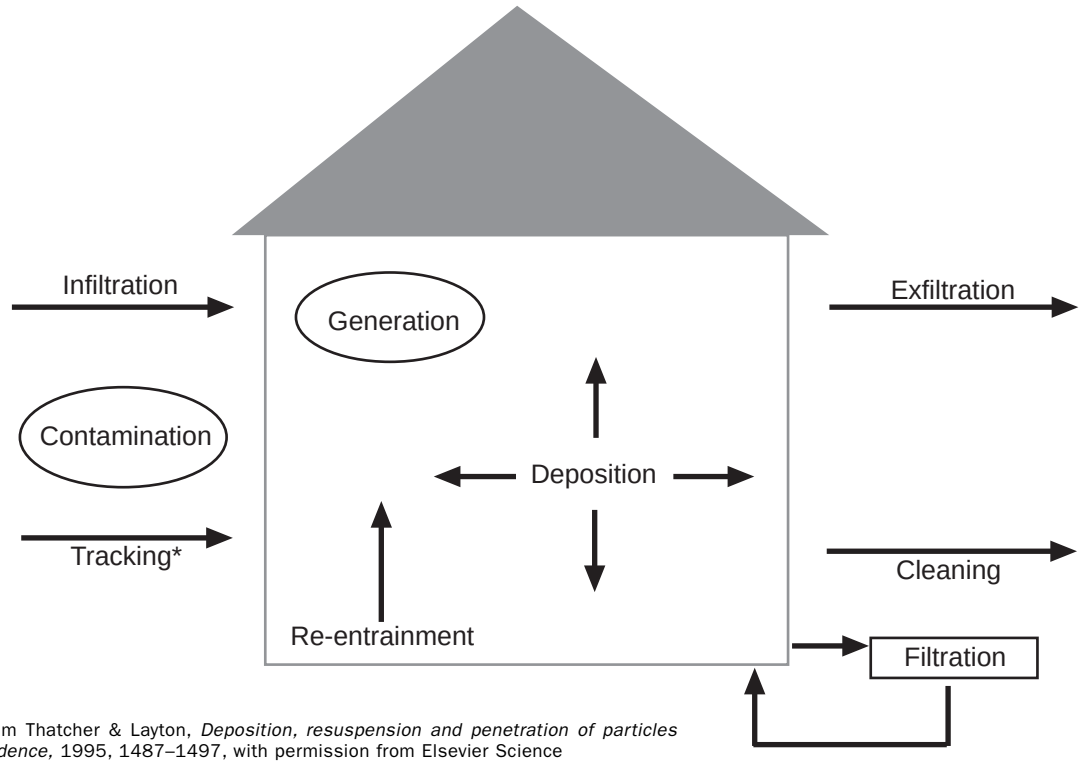
2 Particles in indoor air

2.1 Sources

In the indoor domestic environment, sources of airborne particles include the re-entrainment of existing particles through activities such as sweeping or dusting, indoor emissions from cooking or cigarette smoking, and transport from outdoors by leakage through the walls, windows, doors and ventilation systems (Kamens *et al.*, 1991). Particles of biological origin also occur indoors (see Section 1.4) but are not discussed in detail in this report; they cover a wide size range and can affect health through both allergic and toxic mechanisms.

Figure 2.1 illustrates the primary routes through which particles enter and leave the air in a home. Although there are sources of particles in the indoor environment, a major factor determining the level of particles indoors is the ingress of particles from the outdoor environment. Thatcher and Layton (1995) calculated that, for particles between 1 and 25 μm diameter, the building shell is not effective at removing infiltrating particles. Experimental data on indoor:outdoor particle concentration ratios in dwellings are presented in the following section.

Figure 2.1 Routes of movement of particles into and out of a building



Reprinted from Thatcher & Layton, *Deposition, resuspension and penetration of particles within a residence,* 1995, 1487–1497, with permission from Elsevier Science

* Particle transportation indoors as a result of entry of individuals into the building

2.2 Levels of particles in the home

There are currently no detailed published data on levels of particles in UK homes, although some studies are now underway.[a] A few studies conducted elsewhere in Europe and some studies in nonwestern countries are summarised at the end of this section. However the largest sources of data on levels of particles in homes come from studies in the USA. Studies on the relationship between levels of particles in indoor and outdoor air in US homes have been reviewed in some detail by Wallace (1996), who focused mainly on three large-scale studies — the Harvard Six Cities Study, the New York State Study and the US Environmental Protection Agency (EPA) Particle Total Exposure Assessment Methodology (PTEAM) Study. Numerous papers have been published from these studies, the most relevant of which are discussed below.

US studies: Harvard Six Cities, New York State and PTEAM

The air pollution measurements conducted in the Harvard Six Cities Study were performed in conjunction with epidemiological studies in the cities of Portage (Wisconsin), Topeka (Kansas), Kingston/Harriman (Tennessee), Watertown (Massachusetts), St. Louis (Missouri) and Steubenville (Ohio; Spengler *et al.,* 1981).[b] About ten homes in each city were monitored every sixth day for 24 hours over a period of 2 years. Monitors were sited in the lounge of each home and directly outside a nearby window. The monitors collected particles in the respirable fraction ($PM_{3.5}$), depositing them on a 37 mm filter. For the year ending April 1978, the annual mean mass of particles collected by the indoor samplers in the six cities ranged from around 20 to 50 µg/m^3. In all cities except Steubenville, the overall indoor annual mean levels were higher than the outdoor levels, which averaged approximately 10 to 45 µg/m^3. The difference between indoor and outdoor levels was found to be associated with cigarette smoke (Table 2.1). On average, and excluding one outlying result, one smoker in the home raised mean indoor respirable suspended particulate levels by around 20 µg/m^3, and the presence of two or more smokers resulted in a mean particulate level of 51.8 µg/m^3.

Later results from the Harriman/Kingston element of the Harvard Six Cities Study, which included measurements of personal exposure to respirable particles (see Section 2.3) in addition to indoor and outdoor levels, were reported by Spengler *et al.* (1985). A total of 101 volunteers from the two towns participated in the study for 38 days over a 46-day period beginning in February 1981. Indoor monitors were Harvard/EPRI samplers (gravimetric devices with a cutpoint of 3.5 µm), which were also used for personal sampling. The outdoor measurements were taken at monitoring stations, located centrally in each town, using a combination of dichotomous samplers, high volume samplers, the Harvard/EPRI samplers, and cyclone respirable-suspended particulate samplers. Cutpoints for the outdoor measurements ranged from 15 µm to 2.5 µm particle diameter. In both towns, the 24-hour averages of indoor respirable suspended particle (RSP) concentrations (taken to be equal to the 3.5 µm cutpoint measurements) were around 25 µg/m^3 higher than the outdoor RSP concentration, which averaged 18 µg/m^3. This again suggested that there was a significant indoor source of such particles. As with the earlier studies, the difference between indoor and outdoor levels was found to be significantly (but not solely) related to smoking in the home. In no-smoking homes, average RSP concentrations were only around 10 µg/m^3 higher than the outdoor environment, while for homes with smokers indoor levels averaged at least 30 µg/m^3 more than outdoor levels.

In the New York State Study, indoor and outdoor aerosols were sampled from homes in two counties, Suffolk and Onondaga (Leaderer *et al.*, 1994). A total of 594 week-long samples were taken in 394 homes using the

[a] Recent studies in the UK on particles in the home include those from the Institute of Public and Environmental Health, University of Birmingham, on the relationship between outdoor, indoor and personal particle exposure; the Centre for the Environmental Technology, Imperial College, on indoor particle exposure in the urban population; and the Department of Child Health, Southampton General Hospital, on the links between indoor air pollution and respiratory disease in asthmatic children and their mothers. Preliminary results from some of these studies can be found in the Proceedings of Indoor Air '99 Conference, Edinburgh, UK and IEH (2000) Joint Research Programmes on Outdoor and Indoor Air Pollution (A Review of Progress, 1999), Leicester, UK, MRC Institute for Environment and Health.

[b] Also reported as study communities: Boston (MA), Knoxville (TN), St Louis (MO), Steubenville (OH), Madison (WI), Topeka (KS) with sampling sites at: Watertown (MA), Harriman (TN, including Kingston), Carondelet (MO), Steubenville (OH), Portage (WI), Topeka (KS), respectively (e.g. Dockery *at al.,* 1993; Schwartz *et al.,* 1996)

Table 2.1 Mean respirable particulate ($PM_{3.5}$) concentrations for the Harvard Six Cities Study for the year ending April 1978

Location	No. of homes	No. of samples	Mean concentration (μg/m³)	Standard deviation of home means
Outdoor	55	1676	21.1	11.9
Indoor				
No smokers	35	1186	24.4	11.6
1 Smoker	15	494	36.5	14.5
2+ Smokers*	4	133 (approx)	51.8	12.3

From Spengler *et al.* (1981)

* Excluding one outlying home with an exceedingly high value

Harvard Impactor, which collected particles with aerodynamic diameters of less than 2.5 μm at a flow rate of 4 l/min. The homes were selected with different indoor sources of particles, such as cigarette smoking, kerosene heaters, wood burning and gas stoves. Homes with none of these sources were also sampled. The relative contribution of the sources to indoor particle levels was determined, using X-ray fluorescence to provide elemental analysis of the collected samples.

The geometric mean weekly concentration of $PM_{2.5}$ in the Suffolk homes ranged from 17.3 μg/m³, for homes with no indoor particle sources, to 61.4 μg/m³, for homes with both smokers and kerosene heaters. Outdoor concentrations averaged 19 μg/m³. In Onondaga the equivalent figures were 14.1 μg/m³ for homes with no sources, 35.3 μg/m³ for the homes with smokers or kerosene heating (again the highest average figure), and 15.8 μg/m³ outdoors. Smoking was found to be the most important of the indoor particle sources studied, whilst kerosene heaters and wood burning stoves also contributed to indoor particle concentrations. In contrast, gas stoves and humidifiers were found not to affect indoor particle mass and elemental composition. Indoor concentrations in homes with no kerosene heaters, smokers or wood burning sources were similar to outdoor concentrations.

In the PTEAM Study, levels of particles were measured inside and outside the homes of 178 residents of Riverside (California; Özkaynak *et al.*, 1996). Measurements of PM_{10} and $PM_{2.5}$ were performed using monitors similar to those used for personal exposure measurements, which were taken concurrently (see Section 2.3). Average PM_{10} levels over 12 hours were 95 μg/m³ for both outdoor and indoor measurements during the day, and 86 μg/m³ outdoors and 63 μg/m³ indoors at night. The outdoor concentration of particles was found to be the major factor affecting both PM_{10} and $PM_{2.5}$ particle mass indoors, contributing about three-quarters of the $PM_{2.5}$ and two-thirds of the PM_{10} in the average home. Other important factors were smoking and cooking. Smoking added around 27 to 38 μg/m³ to PM_{10} and $PM_{2.5}$ concentrations, respectively, whilst cooking added 12 to 16 μg/m³ to PM_{10} levels [cooking fuel not specified]. Activities such as vacuuming and dusting appeared to make smaller contributions to measured indoor particle levels. The volume of the house was found to be negatively correlated with particle concentrations, and air exchange rate was positively correlated, though with a relatively small effect. Table 2.2 shows the relative contribution of the main particle sources to indoor concentrations in a subset of the homes where either a smoker was present or cooking was underway.

Table 2.2 Sources of airborne particles in homes in Riverside, California

Particle source	Homes with smoker present (No. of homes = 31)		Homes with cooking* (No. of homes = 33)	
	PM_{10}	$PM_{2.5}$	PM_{10}	$PM_{2.5}$
Outdoor	56%	60%	56%	62%
Smoking	24%	30%	4%	5%
Cooking	3%	3%	25%	25%
Other indoor	17%	7%	15%	8%

Data from Özkaynak *et al.* (1996)

* Cooking activity during measurement period

The main findings of the three US studies, as interpreted by Wallace (1996), were that cigarette smoking was a major source of particles indoors, with concentrations of particles in the $PM_{3.5}$ and $PM_{2.5}$ ranges being raised by between 1.1 and 2.1 µg/m3 per cigarette smoked in the home over a 24-hour period. After environmental tobacco smoke (ETS), the second largest source of indoor $PM_{10,}$ and possibly $PM_{2.5}$, found in the PTEAM Study was cooking. (This was the only one of the three studies that investigated the influence of cooking.) Air exchange rates (measured in the New York State and PTEAM studies) were found to have a significant effect on indoor particle levels; in situations where indoor levels generally exceeded those outdoors, high air exchange rates reduced indoor levels. A small, but significant effect of house volume was also noted in the PTEAM Study, with particle levels being lower in larger properties.

In reviewing the various studies, Wallace (1996) queried how much protection is offered against the ingress of outdoor particles into a home. He concluded that three factors affected the fraction of outdoor particles found indoors; namely, the ability of particles to penetrate the building envelope (the penetration factor — P), the air exchange rate (a) and the deposition rate (k). These can be related by an equation derived from a mass-balance model developed by Koutrakis *et al.* (1992) as follows:

$$\frac{C_{in}}{C_{out}} = \frac{Pa}{a + k}$$

(where C = concentration of particles)

The penetration factor would be expected to be equal to 1 for gases, decreasing towards zero with increasing particle size (provided no doors or windows are open).

Other US studies

The three large scale US studies described above provide much valuable data on the levels and sources of particles in homes. However, smaller scale studies also provide useful information.

As part of a project known as the Total Human Environmental Exposure Study (THEES), Lioy *et al.* (1990) measured indoor and outdoor concentrations and personal exposure to PM_{10} during winter in homes in a small US city, Phillipsburg, New Jersey. The results of the personal exposure element of the study are summarised in Section 2.3. A major point source of pollution in the city was an iron pipe manufacturing plant, and one objective of the study was to investigate the influence of the plant on local concentrations of PM_{10}. Four outdoor and eight indoor monitoring sites were set up. All of the eight homes were within 2 km of the manufacturing plant and had a sampler located in the living room/dining room. Three of the outdoor measurements were taken on nearby rooftops using the high volume Wedding PM_{10} sampler, which operated at around 1100 l/min for 24 hours over the 14 days of the study. Two of the outdoor sites were within 0.5 km of the manufacturing plant, one on the east and the other on the west side; a third outdoor site was near a main road, 1.5 km from the plant. The fourth outdoor sampler was placed on the porch of a participating home. This sampler was the same type as that used for the indoor samples, which was a single stage impactor operating at 10 l/min for 24 hours a day and collecting the particle mass on 37 mm filters.

During the 14 days of the study, outdoor levels of PM_{10} ranged from 12 to 165 µg/m3, with a mean of 48 µg/m3. On two days levels exceeded 100 µg/m3 for all of the rooftop sites, and on one day levels were greater than 150 µg/m3. The mean indoor level was 42 µg/m3, and the relationship between indoor and outdoor levels was variable, even though there were no smokers in the homes. Outdoor concentrations around some homes were always higher than the indoor concentrations, whilst for other homes the outdoor concentrations were sometimes higher and sometimes lower than indoor concentrations. On two sampling days when outdoor concentrations exceeded 100 µg/m3, indoor concentrations were found to be strongly associated with outdoor PM_{10} levels.

Kamens *et al.* (1991) took measurements of particle levels in three North Carolina homes. The homes were situated in residential areas, adjacent to quiet streets or lanes, and the occupants did not smoke. A single sampling location between the kitchen and dining room was chosen for each home. Particle sampling was performed for at least two 8-hour daytime periods and

one 13-hour evening to early morning period. Two fixed $PM_{10}/PM_{2.5}$ ambient Sierra Andersen dichotomous samplers with 10 µm inlets were used. Prototype personal exposure monitors (PEMs), consisting of an impactor element covering a 2 µm pore Teflon filter and a 37 or 47 mm inlet, were mounted alongside the fixed monitors (i.e. not worn by the occupants). Of the three PEMs with 37 mm inlets used, two had a 10 µm particle cut size and the third had a 2.5 µm cut size. One PEM with a 47 mm open faced inlet was used to determine total particle mass. Three automated samplers (a TSI electrical aerosol mobility analyser, which measured particles in ten size intervals between 0.01 and 1.0 µm and two PMS laser optical light scattering instruments, which sized particles from 0.09 to 3.0 µm and 2.6 to 19.4 µm) were also used during the study.

In the three homes, particle concentrations ranged from 14 to 42 µg/m^3. On average, 37% of the particle mass was 2.5 µm or less in diameter, 26% was between 2.5 and 10 µm, and 37% was greater than 10 µm. There was reasonable agreement between the measurements taken using the dichotomous samplers and the prototype PEMs. Measurements from the automated samplers suggested that cooking was the most significant source of small particles in all of the homes. One house had a gas cooker; during use of the gas hob, particles with diameters less than 0.10 µm accounted for 30% of the particle volume sampled by the electrical aerosol mobility analyser. Overall, for all homes, it was estimated that cooking one meal contributed between 5 and 18% of the 8-hour average daytime particle mass measured at the sampling point.

Household dusting was found to generate large diameter particles, ranging in size from 13 to 100 µm. Particles including stove ash, insect parts and hair were identified by scanning electron microscopy (SEM) and energy dispersive X-ray (EDX) analysis. Grilling cheese sandwiches on an electric stove produced soot and salt particles. Particles collected at the exhaust of vacuum cleaners during use appeared to be mainly mineral in content. Around a third of particles in the size range 2 to 60 µm were of biological origin, including danders and insect parts. In all three homes there were large numbers of airborne mineral particles, including clay, quartz, magnetite, salt and chalk. Mineral particles accounted for around 30% of the particles analysed by EDX. In general, the three homes all contained the same kinds of particles. Table 2.3 illustrates the sizes of different types of particles found during the study, as analysed by SEM and EDX.

Colome *et al.* (1992) used a Marple 4 l/min sampler with twin impaction plates to monitor PM_{10} levels over 24 hours inside and outside ten homes (eight of which had occupants who were asthmatic) in southern California. Particles were collected on Teflon filters, and mass was determined gravimetrically. Personal exposure measurements were also made and are summarised in Section 2.3. Indoor concentrations were generally found to be lower than the corresponding outdoor concentrations, with the 24-hour mean mass indoors being 42.5 µg/m^3, compared with 60.8 µg/m^3 outdoors. Indoor concentrations were found to be moderately correlated with outdoor concentrations; outdoor concentrations accounted for between 34 and 56% of the variation of indoor concentrations, for all homes.

Table 2.3 Sizes of different indoor particles from homes in North Carolina by scanning electron microscopy/energy dispersive X-ray analysis

Particle type	Number of samples analysed	Geometric mean (µm)	Geometric standard deviation	Major elements
Mineral				
Silicate	19	4.21	2.39	Si, Al, Ca, K, Fe
Salt	2	4.98	NA	Na, Cl
Other	7	3.32	1.25	Ca, Fe, Ti, Cr
Soot	96	0.14	1.42	
Sulphate	153	0.15	1.36	S
Biological	32	5.41	3.97	

From Kamens *et al.* (1991)

NA, Not available

Indoor particle sources were not apparent in the homes with asthmatic residents. This was attributed to the fact that those with asthma tended to avoid potential triggers of asthma, such as pets, smoking and certain cleaning compounds. There were no smokers in the study, and wood stoves, fireplaces and unvented kerosene heaters were not used in the homes studied.

Bunding Lee *et al.* (1995) monitored levels of respirable particles in six residences in Racine (Wisconsin). An aerodynamic particle sizer, sampling at a rate of 5 l/min, was used for the real-time monitoring of particles between 0.5 and 15 µm diameter. The levels of particles in the homes were greatly affected by human activity. For example, levels in a kitchen briefly rose to around 200 µg/m^3 whilst the floor was being swept. Smoking in the same room as the particle monitor caused measured levels to increase by around 50 µg/m^3. Background levels in a home situated close to a busy street and in which the windows were left open were around 15 to 20 µg/m^3; these levels were double those found in a home which was not near a busy road.

European studies

In Europe, Janssen has published a series of papers on studies of personal exposure to PM_{10} and its correlation with indoor and outdoor particle concentrations. In one of these studies (Janssen *et al.*, 1998a), the personal exposure of 37 nonsmoking adults aged between 50 and 70 years living in a total of 36 homes in Amsterdam, the Netherlands was measured. The monitoring periods were from January to March and from October to December 1994. For each participant, monitoring was conducted over 24-hour periods on weekdays only, for between 5 and 8 days, with each day being separated by approximately a week. Participants also completed questionnaires on their activity during sampling periods, including details of cooking, cleaning and exposure to ETS.

Indoor measurements were taken in the living rooms of the participants' homes using Harvard Impactors with 37 mm diameter, 2 µm pore size Teflon filters and a flow rate of 10 l/min. Outdoors, measurements were taken continuously at a fixed monitoring site located in a park near the city centre. This site was about 150 m from the nearest busy road, away from local particle sources and a maximum of 4 km away from the homes of the participants. The monitor had an inlet similar to the Sierra Anderson dichotomous sampler, and a flow rate of 16.7 l/min was used (details of the personal sampler are described in the next section). When the personal sampler and the indoor and outdoor samplers were run alongside each other at the outdoor monitoring site, no significant difference was found in the concentrations recorded by the three monitors (Janssen *et al.,* 1998b).

The results of the personal exposure measurements from the Janssen *et al.* (1998a) study are reported in the next section. The median and mean of the indoor concentrations were 34.4 and 35.0 µg/m^3, respectively (concentrations measured ranged from 18.6 to 65.3 µg/m^3), and both the mean and median of outdoor concentrations were 41.5 µg/m^3 (range 31.9 to 50.2 µg/m^3). The median and mean of the difference between indoor and outdoor concentrations were -10.8 and -7.1 µg/m^3 (indoor - outdoor concentration), with a range from -20.3 to 15.2 µg/m^3. Regression analysis of the results for each individual's indoor and outdoor PM_{10} concentrations produced a median correlation coefficient (Pearson's R) of 0.73, with a range of -0.88 to 0.95, which again suggests that indoor particle levels tend to be lower than those found outdoors. The results of the multiple regression analysis of the relationship between indoor and outdoor PM_{10} concentrations and variables which may affect this relationship are presented in Table 2.4.

Variables which significantly contributed to indoor PM_{10} concentrations were smoking in the living room and cooking in a kitchen which was in open connection with the living room. Cleaning activities, such as dusting, vacuuming cleaning and sweeping, did not contribute significantly to indoor particle levels.

Table 2.4 Multiple regression analysis of the relationship between the difference between indoor and outdoor PM_{10} concentrations (μg/m3) and several other variables in homes (n = 241) in Amsterdam, the Netherlands

	Parameter estimate	SE	95% Confidence interval	Mean of the variable
Intercept	-12.48**	3.32	-19.23 to -5.74	
No. cigarettes smoked in the living room	2.33**	0.51	1.32 to 3.34	0.59[a]
Cooking: kitchen and living room openly connected	6.95*	3.94	-0.81 to 14.71	0.20
Cooking: kitchen and living room not openly connected	0.60	3.04	-5.40 to 6.59	0.62
Cleaning activities (yes/no)	2.97	2.31	-1.59 to 7.52	0.58
Living along a busy road (yes/no)	-2.12	3.48	-9.19 to 4.95	0.17
Living room window opened (yes/no)	2.19	2.46	-2.67 to 7.04	0.39

From Janssen *et al.* (1998a)

* $p<0.05$; ** $p<0.01$

[a] Smoking in the living room was reported 23 times

SE, Standard error of the mean

Other studies

All of the studies described above were performed in developed countries. In developing countries, levels of particles indoors may be far higher. For example, Brauer *et al.* (1996) measured particle levels in kitchens in rural Mexico. In these homes biomass, such as dried corn stalks and husks, is often used as a fuel for cooking. Measurements taken by inertial impactors sampling at 4 l/min for 24 hours in the kitchens revealed that mean levels of $PM_{2.5}$ and PM_{10} in eight biomass-cooking homes were 554.7 and 767.9 μg/m3 respectively, with the indoor to outdoor concentration ratio being between 10 and 12. Similarly in China, levels of $PM_{3.7}$, measured over 24 hours using constant flow samplers with nylon cyclone heads sampling at 2 l/min, in kitchens where coal stoves were in use, were as high as 665 μg/m3 (Qin *et al.*, 1991). Such extreme values are highly unlikely to be found in UK homes, which are very different in construction and use to dwellings in developing countries.

Synopsis

Table 2.5 presents a summary of the results from the major studies of indoor/outdoor particle levels in the USA and Europe. There are no detailed published data on particle levels in UK homes. In general, indoor levels of particles tend to be less than or equivalent to outdoor levels, unless there is an indoor particle source. The most substantial indoor source is ETS.

The main findings from these US and European studies may be applicable to UK homes, but differences in house construction, use and climate mean that this is far from certain. In addition, there is likely to be considerable heterogeneity in the indoor environment of homes in any one country, further complicating the prediction of 'typical' relationships between indoor and outdoor particle levels.

Table 2.5 Studies of levels of particles inside and outside homes

Study site	Particle size	No. in study	Averaging time (hours)	Indoor (μg/m³) Average	Indoor (μg/m³) Range	Outdoor (μg/m³) Average	Outdoor (μg/m³) Range	Comments	Reference
US studies									
Harvard Six Cities, New York State, PTEAM									
Kingston/Harriman, TN	$PM_{3.5}$	101 people	24	43		18		Significant effect of smoking	Spengler *et al.* (1985)
New York State	$PM_{2.5}$	394 homes	168		14.1–61.4		15.8–19	Significant effect of smoking and kerosene heating	Leaderer *et al.* (1994)
Riverside, Ca	PM_{10}	178 people	12	95 day 63 night		95 day 86 night		Significant effect of smoking and cooking	Özkaynak *et al.* (1996)
Other US studies									
Phillipsburg, NJ	PM_{10}	8 homes	24	42		48			Lioy *et al.* (1990)
S. California	PM_{10}	10 homes	24	42.5		60.8		No indoor sources found	Colome *et al.* (1992)
European study									
Amsterdam, the Netherlands	PM_{10}	37 people	24	35.0 mean 34.4 median	18.6–65.3	41.5 mean 41.5 median	31.9–50.2	Significant effect of smoking and cooking	Janssen *et al.* (1998a)

2.3 Personal exposure and the relationship to outdoor and indoor levels

Measurements of indoor and outdoor levels of particles are useful but may not relate well to the concentration, number or composition of particles to which individuals are actually exposed. Thus, measures of personal exposure are a crucial tool in assessing the potential health impact of exposure to particles.

As with the indoor and outdoor measurements of particles, the majority of the relevant data on personal exposure to particles have been collected in the USA. Very few studies on personal exposure to particles have been conducted in the UK or elsewhere in Europe.

US studies: Harvard Six Cities and PTEAM

During the Harvard Six Cities Study, in addition to indoor and outdoor measurements (described in Section 2.2), personal exposure levels were monitored for individuals in the rural towns of Kingston and Harriman (Tennessee; Spengler *et al.*, 1985). Personal exposures were measured for 97 nonsmoking volunteers and four field personnel on 38 days over a 46-day period beginning mid February 1981. The PEM used was the Harvard/EPRI sampler, which is designed to collect RSP and which sampled 50% of particles 3.5 µm in diameter and none 10 µm in diameter.

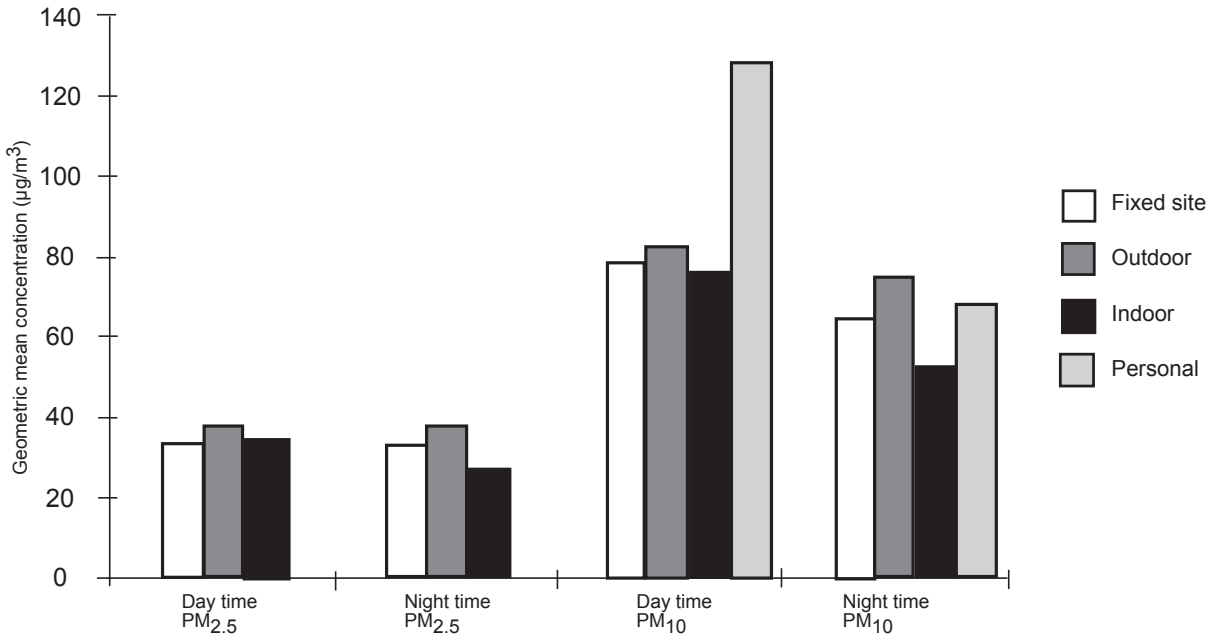
The 24-hour mean personal exposure to RSP for all subjects in the study was 44 µg/m^3. Exposures were higher for those living in smoking households than for those in homes with no smokers (mean concentrations 64 and 36 µg/m^3 respectively). Personal exposures were always higher than indoor exposures in households where there was no smoking (mean concentrations 36 and 28 µg/m^3 respectively), but for nonemployed subjects living in homes with smokers personal exposure was lower than the indoor particle concentration (mean concentrations 66 versus 86 µg/m^3). There was a strong correlation between personal exposure and indoor particle concentration, with 50% of the variance in personal exposures being explained by the indoor concentrations. By contrast, correlation between outdoor levels, measured at ambient monitoring sites centrally located in each town, and personal exposure was low, and explained less than 1% of the variance in personal exposures. Overall, 24-hour personal exposures were 25 µg/m^3 higher than outdoor RSP concentrations. For homes with no smokers, this excess was reduced to an average of 10 µg/m^3.

As part of the PTEAM Study (see Section 2.2), Özkaynak *et al.* (1996) monitored personal exposure to PM_{10} for 178 nonsmoking residents of Riverside (California) during the autumn of 1990. The PEMs operated at a constant flow rate of 4 l/min and had an inlet which selected PM_{10}, depositing the collected particles onto a 37 mm Teflon filter. Concurrent measurements of particle levels inside and outside homes were performed using samplers which were almost identical to the PEMs. $PM_{2.5}$ was measured as well as PM_{10} in the indoor and outdoor environments. All filters were analysed by X-ray fluorescence to determine the concentration of selected elements in the collected particles.

Each participant wore the PEM for two consecutive 12-hour periods and kept a note of activities, such as cooking or smoking nearby, that might have raised exposure to particles during this time. Population-weighted daytime personal PM_{10} exposures averaged around 150 µg/m^3, whilst concurrent indoor and outdoor concentrations were both about 95 µg/m^3. Personal exposures overnight were lower, at around 77 µg/m^3, and closer to the indoor (63 µg/m^3) and outdoor (86 µg/m^3) means. Figure 2.2 shows the relative levels of PM_{10} and $PM_{2.5}$ as measured by the indoor, outdoor, fixed site and personal monitors during the day and night, according to the PTEAM data presented by Clayton *et al.* (1993).

Analysis of the results revealed that outdoor PM_{10} concentrations could explain around 25 to 30% of the variance observed in indoor concentrations, but only 16% of the variance in personal exposure levels. Indoor PM_{10} concentrations could explain around 50% of the variance in personal exposures. Using time-weighted averages of indoor and outdoor concentrations, about two-thirds of the personal exposure variance could be accounted for. An unexpected result was that daytime

Figure 2.2 Comparison of particulate levels from Riverside, California



Data from Clayton *et al.* (1993)

PM_{10} personal exposures were around 27 µg/m^3 lower for those who went to work. The remaining variance in personal exposure was assumed to arise from either personal activities, resulting in a 'personal cloud' of particles, or exposure in microenvironments where particle levels were not well represented by the indoor or outdoor static measurements.

Based on the X-ray fluorescence data for personal and indoor samples, 14 out of 15 elements were uniformly higher, by 50 to 100%, in the personal samples than in the indoor samples; the results are presented in Table 2.6 (Clayton *et al.,* 1993). The uniformity of composition suggested that the 'personal cloud' had the same general composition as the indoor air, and could be formed by the re-entrainment of household dust during indoor activity. Only one of the elements measured, sulphur, was not present at higher concentrations in the personal samples than in the indoor samples. The fact that sulphur was associated with the smallest particles (<1 µm diameter), which are not readily resuspended indoors (Thatcher & Layton, 1995), lends support to the suggestion that the personal cloud arose from re-entrainment of household dust. It appears that the personal cloud may include coarse particles which are more than 5 µm diameter and some particles between 1 and 5 µm, but not those below 1 µm. Özkaynak *et al.* (1996) concluded that, given that these data suggested that there was no indoor or personal source of exposure to sulphur, outdoor measures of particle sulphur concentrations may be a better predictor of personal exposure levels than those for any other element. Thus, if the most biologically active portion of the outdoor particles was in the size fraction below 1 µm, outdoor particle sulphur concentration might be an acceptable surrogate of personal exposure to particles. Clearly there is a need to investigate this hypothesis further.

Information on the activities of the participants during the PTEAM Study was used to evaluate the contribution to indoor levels of particles of activities such as housework (i.e. vacuuming, dusting, carpet cleaning, indoor cooking and using a clothes drier) and spraying (i.e. spraying of paints, cleaners, disinfectants, etc.), and of exposures such as exhaust fumes from vehicle engines running in an attached garage and ETS (Clayton *et al.,* 1993). Similar analyses were performed on the data for personal exposure and included going to work as an additional factor. Table 2.7 shows the effect of each of these activities or exposures on indoor PM_{10} levels and personal exposures measured over 12-hour periods during the day and night. ETS was associated with a significant increase in the indoor levels of PM_{10} during the day but not the night time. Surprisingly, this

Table 2.6 Estimated population percentiles (50%)* of elemental concentrations (ng/m^3) for indoor, outdoor and personal samples of $PM_{2.5}$ and PM_{10} fractions from Riverside, California

Element	PM_{10}						$PM_{2.5}$			
	Daytime			Night time			Daytime		Night time	
	Outdoors	Indoors	Personal	Outdoors	Indoors	Personal	Outdoors	Indoors	Outdoors	Indoors
Al	2500	1900	3400	1700	990	1000				
Br	10	11	18	12	10	12	7.8	7.9	8.9	7.1
Cl	160	280	700	360	230	370	53	77	84	60
Cu	14	16	34	14	12	15			6.7	6.3
Fe	2100	1400	2600	1430	840	960	340	270	230	170
K	1000	880	1500	720	540	680	180	200	120	140
Mn	46	30	49	30	20	20	11	8.2	8.6	6.3
Pb	27	23	32	25	22	19	18	15	18	15
S	1600	1600	1600	1700	1300	1300	1400	1200	1400	1100
Si	6800	4900	9200	4600	2700	3300	560	540	340	320
Sr	17	13	22	13	9.4	10				
Ti	180	150	260	120	83	110				
Zn	63	68	120	46	50	61	36	3	29	26
Total	14517	11271	19535	10770	6806.4	7857	2605.8	2321.1	2245.2	1850.7

From Clayton *et al.* (1993)

* Estimate of 50th percentile [median] value using value weighting to adjust for probability of subject being selected for sampling; calculated using SUDAAN (Survey Data Analysis) software

Table 2.7 Effect of activity on indoor and personal exposure to PM_{10} in Riverside, California

	Mean PM_{10} concentration ($\mu g/m^3$)							
	Indoors				Personal			
	Daytime		Night time		Daytime		Night time	
Activity	Yes	No	Yes	No	Yes	No	Yes	No
Housework	91.3	57.1	52.2	53.7	142.2	104.4*	65.9	69.4
Spraying	76.6	79.2	54.7	52.3	138.5	121.6	69.7	67.1
Smoking	114.0	72.0*	83.6	47.1	131.4	127.3	96.6	63.3
Exhaust	50.0	87.3*	NR	52.9	85.5	144.8*	NR	68.2
Work	NR	NR	NR	NR	107.6	141.6*	NR	NR

From Clayton *et al.* (1993)

* Population geometric means for homes or persons with and without the activity are significantly different, $p<0.05$;
Yes, Homes with activity or persons exposed to activity; No, Homes without activity or persons not exposed to activity;
NR, Not reported

was not reflected in the findings from the personal exposure monitoring, where levels were slightly (although not statistically significantly) higher for individuals in smoking households at night, in comparison with levels for individuals in homes with no smokers, but were similar for the daytime period. The reason for this apparent anomaly is unclear, although the authors note that the sample sizes for such comparisons were small, the length of exposure to ETS was not clearly defined, and the measurements would be susceptible to confounding effects from other particle generating activities [which would presumably be more likely to occur during the daytime than the night time period]. Daytime indoor levels and personal exposures were higher in homes in which no vehicles were run in attached garages; this unexpected result was suggested to be due to other factors correlated with the participants having a garage and indicated the need for additional analysis to address multiple variables. Personal exposure to particles was found to be higher for those performing housework during the day, and lower for those going to work.

Other US studies

In the THEES Study (see Section 2.2), personal exposure monitoring of 14 individuals was performed using single stage impactors, which collected PM_{10} samples on a 25 mm filter (Lioy *et al.*, 1990). The filters were changed every 24 hours during the 14 days of the study. At 66 $\mu g/m^3$, mean personal exposure levels were higher than either the indoor or outdoor measurements. The ratio of personal exposure to outdoor PM_{10} concentrations varied widely from day to day for each participant, and between participants. In general, there was no association between outdoor and personal exposure levels. However, when outdoor levels were higher than 100 $\mu g/m^3$, the personal exposure: outdoor PM_{10} ratio was below 1 for the majority of the samples. This suggested that outdoor air and the penetration of outdoor air to the indoor environment could have been the dominant source of PM_{10} exposure on these days.

In the study by Colome *et al.* (1992; see Section 2.2) in southern California, personal exposure measurements were made, in addition to sampling indoor and outdoor particle levels. Cyclone samplers, which excluded particles larger than 7 µm in diameter and had a 50% cut-off at 5 µm, were used. The samplers were worn by eight people with asthma for a period of 24 hours. The levels measured by personal exposure monitoring were consistently more closely related to the concurrent indoor samples than they were to the outdoor samples. However, indoor levels were driven by ambient concentrations, as there were no significant indoor particle sources.

UK studies

The first substantive study of personal exposure to particles in the UK has been undertaken by Mark *et al.* (1997).[a] A prototype personal sampler was used to measure exposure of 15 volunteers who lived or worked close to each of the two of the Department of the Environment, Transport and the Regions' Automated Urban Network (AUN) monitoring sites in the city of Birmingham (30 individuals in total). The personal sampler consisted of a sampling head with an internal cassette, which had an inhalable aerosol entry, and a cylindrical plug of porous polyester foam, which selected the thoracic fraction of the inhaled particles (PM_{10}). The particles were collected on 37 mm diameter glass-fibre filters. A specially-designed pump sucked air through the sampler at a rate of 2 l/min for a period of between 16 and 33 hours. The mean outdoor PM_{10} mass concentrations were calculated from 15-min averages of the continuous measurements from the TEOM monitors at the AUN sites. Regression analysis was performed to investigate the relationship between the personal exposure measurements and the AUN data, for the periods during which each personal sampler was in operation.

Three sampling surveys were performed (August to September 1995, October to December 1995 and February to March 1996), each with five exposure periods per person. The volunteers completed questionnaires about activities during the sampling period that may have raised exposure to particles. The results showed significant differences between the two sites, and between seasons. For the Birmingham Centre site, levels of personal exposure were around twice as high (median approximately 100 to 130 µg/m^3) for those living and working in the area or living in the area and working away as they were for those working in the area but living elsewhere (median approximately 60 µg/m^3). For the other site, Birmingham East, those living in the area but working elsewhere had the highest levels of exposure (median approximately 100 µg/m^3). Smokers were exposed to almost twice the mass of thoracic particles that nonsmokers were exposed to (medians approximately 150 versus 75 µg/m^3).

The regression analysis to investigate the relationship between the ambient levels and personal exposure to particles revealed a positive association for both sites, but this was only significant for the Birmingham East site. However, there was a wide spread of results, and the regression only explained 14% of the variability. The authors concluded that there was no simple relationship between the PM_{10} levels obtained by ambient monitoring at the two AUN sites and the thoracic particle exposure of the volunteers in the study. Subsequently, these data have been reanalysed by regression of the personal exposure data for individuals (rather than the pooled data for all subjects) against the AUN data.[b] The reanalysis has revealed that, for an individual whose activity patterns are similar from day to day, outdoor particle levels do have a significant effect on the variability in personal exposure levels.

Much of the work on personal exposure to particles that has been undertaken in the UK has been aimed at assessing exposure to ETS, rather than particulate matter *per se*. For example, Phillips *et al.* (1994) monitored ETS exposure among 255 nonsmokers in Leeds and Harrogate, using personal monitors for a period of 24 hours. The monitors sampled at a rate of 1.4 l/min and collected particles from all sources in the size range, from total suspended particles (approximately PM_{25}) to RSP ($PM_{3.5}$). Median particle levels were 142 µg/m^3, with ETS contributing only a small amount (median 2.5%) to the total particle exposure.

Other European studies

In the study by Janssen *et al.* (1998a) discussed in Section 2.2, in which monitoring was performed over 24-hour periods in Amsterdam, the Netherlands for five to 8 days, from January to March and from October to December 1994, personal PM_{10} exposures were measured for 37 nonsmoking adults, aged between 50

[a] The full results of the study are also presented in an unpublished report to the DETR (Mark D, Upton SL, Lyons CP, Appleby R, Dyment EJ, Griffiths WD & Fox AA (1997) *Personal exposure to atmospheric particles*. AEA Technical Report No. AEA-TPD-402. AEA unpublished report to DETR).

[b] see Mark D, Upton SL, Lyons CP, Appleby R, Dyment EJ, Griffiths WD & Fox A (1997) *Personal exposure to atmospheric particles.* AEA Technology Report No. AEA-TPD-402. AEA unpublished report to DETR

and 70 years, using a personal impactor with 25 mm diameter, 3 µm pore size Teflon filters. As previously mentioned, associated indoor measurements were taken in the living rooms of the participants' homes and outdoor measurements were taken at a fixed site in a city centre park.

The median and mean of the personal concentration measurements were 56.4 and 61.7 µg/m^3 PM_{10}, respectively (concentrations measured ranged from 38.0 to 112.8 µg/m^3). The median and mean of the difference between personal and outdoor concentrations were 15.9 and 20.4 µg/m^3 (personal - outdoor range -6.4 to 68.8 µg/m^3), while median and mean values for the difference between personal and indoor concentrations were 22.4 and 26.9 µg/m^3 respectively (personal - indoor range -1.0 to 99.9 µg/m^3). Regression analysis gave median Pearson's R values of 0.50 (personal - outdoor) and 0.72 (personal - indoor). Given the established comparability of the measurement devices used, the higher PM_{10} level recorded for personal exposures compared with either indoor or outdoor concentrations indicates that there must have been additional factors contributing to the personal exposure. The results of multiple regression analysis of the relationship between personal and outdoor levels and other variables (Table 2.8) suggest that exposure to ETS (at home or elsewhere), proximity of the home to a busy road and time spent in vehicles can all contribute to the difference between personal and ambient exposure. It is noteworthy that 21 of the 37 subjects reported exposure to ETS on at least 1 day of the measurement period, but of these only seven were actually exposed in their own home. The effects of cleaning, cooking, time spent outdoors, gender and ventilation did not attain statistical significance.

Phillips *et al.* (1996), who studied ETS exposure in UK nonsmokers (see above), also assessed exposure to RSP ($PM_{3.5}$) among 190 nonsmokers living in Stockholm, Sweden. Samples were collected using a cyclone-type personal monitor sampling at 1.72 l/min for 24 hours. The median level of particle exposure for all those in no-smoking homes was 16 µg/m^3, compared with 27 µg/m^3 for those in smoking homes. The median exposure to ETS was 0.12 µg/m^3 for those in no-smoking homes, compared with 1.2 µg/m^3 in smoking homes. The difference between particle and ETS exposure levels in smoking and no-smoking homes was more marked for those who did not go out to work (39 versus 18 µg/m^3 RSP and 17 versus 0.12 µg/m^3 ETS, respectively).

Table 2.8 Multiple regression analysis of the relationship between the difference between personal and outdoor PM_{10} concentrations (µg/m^3) and several other variables in Amsterdam, the Netherlands (n = 256)

	Parameter estimate	SE	95% Confidence interval	Mean of the variable
Intercept	4.35	5.96	-7.76 to 16.46	
No. cigarettes smoked in the living room	2.33**	0.70	0.94 to 3.72	0.56[a]
No. hours in presence of smokers	5.70**	1.38	2.98 to 8.43	0.57[b]
Time in vehicle (hours)	5.42*	2.73	0.05 to 10.80	0.29
Time outdoors (hours)	-1.19	1.33	-3.81 to 1.43	1.29
Gender	3.80	4.37	-5.08 to 12.67	0.50
Cooking (yes/no)	4.82	3.89	-2.86 to 12.50	0.81
Cleaning activities (yes/no)	2.16	3.06	-3.87 to 8.19	0.58
Living along a busy road (yes/no)	22.73**	5.36	11.84 to 33.62	0.20
Living room window opened (yes/no)	-1.60	3.61	-8.71 to 5.51	0.38
Slept with bedroom window open (yes/no)	1.40	3.76	-6.01 to 8.80	0.61

From Janssen *et al.* (1998a)

* $p<0.05$; ** $p<0.01$

[a] Smoking in the living room was reported 26 times

[b] Exposure to ETS elsewhere reported 64 times

SE, Standard error of the mean

Synopsis

A summary of the main personal exposure studies mentioned above is provided in Table 2.9. The general conclusions to be derived from these studies are that personal exposure levels are higher than indoor or outdoor exposure levels, and that where there are significant indoor sources, personal exposures are more closely correlated with indoor than outdoor exposure. Conversely, where significant indoor sources are absent, outdoor levels more closely correlate with personal exposure. The reason for personal exposure levels being higher than either indoor or outdoor levels is the local re-entrainment of settled particles resulting from human activity. This is known as the 'personal cloud' effect. As with the studies of indoor versus outdoor concentrations, smoking was found to be the most significant indoor source of particles, and had a large effect on personal exposure. Other indoor sources of particles, such as cooking fumes, can also markedly affect personal exposure levels. Activities such as dusting and vacuuming also raise personal exposure.

2.4 Evaluation of the literature on levels of particles in the home and personal exposure to particles

Most of the data on indoor levels of particles in homes and on personal exposure to particles come from studies from the USA. The three major studies, the Harvard Six Cities Study, the New York State Study and the PTEAM Study, are large and so provide good indications of the sources and levels of particles in homes. However, a number of smaller studies, which have investigated individual homes more thoroughly and measured different factors, provide valuable additional information. The evidence from the different studies is not always in agreement, but in general the following conclusions may be drawn.

- Major indoor sources of particles are ETS and biological particles. Cooking and heating, particularly using kerosene heaters, coal or wood, can also contribute to indoor levels of particles.
- Indoor levels of particles are lower than, but correlated with, outdoor levels, unless there is a significant indoor source.
- Where there is no major indoor source of particles, outdoor levels may be a reasonable surrogate of personal particle exposure, although they will not allow accurate estimation of the actual exposure levels.
- Personal exposures to particles are higher than indoor or outdoor levels, due to the 'personal cloud' effect.
- The 'personal cloud' is created by human activity, and is the result of re-entrainment of settled particles; indoor sources raise personal exposure levels substantially.

These conclusions probably hold true for most indoor environments in temperate climates. However, the majority of the data on which these conclusions are based come from the USA. Differences in house construction, ventilation and meteorological factors mean that it is essential to gather data in the UK to determine whether the patterns in particle levels and exposure in the home found in other countries also apply in the UK.

Table 2.9 Studies of personal exposure to particles

Site	Measurement method[a]	Size range	No. in study	Averaging time	Mean level (μg/m³)		Comments	Reference
					Personal	Indoor		
US studies								
Harvard Six Cities, PTEAM								
Kingston/ Harriman, TN	Harvard/EPRI, gravimetric	$PM_{3.5}$	101	24 hours	44	43	Significant effect of smoking Correlation with outdoor levels low	Spengler *et al.* (1985)
Riverside, CA	PEM, gravimetric	PM_{10}	178	12 hours	105 day 77 night	95 day 63 night	Higher correlation with indoor than outdoor levels	Özkaynak *et al.* (1996)
Other US study								
Phillipsburg, NJ	Single stage impactor & Hi-vol. samplers, gravimetric	PM_{10}	8	24 hours	66	42		Lioy *et al.* (1990)
European study								
Amsterdam, the Netherlands	Personal impactor/ gravimetric (personal only)	PM_{10}	37	24 hours	61.7	35.0	Significant effect of exposure to ETS, proximity of the home to busy road & time spent in vehicles Lower correlation with outdoor than indoor levels	Janssen *et al.* (1998a)
UK study								
Birmingham centre	Inhalable aerosol entry, porous foam particle size selector	PM_{10}	15	16–33 hours	100–130[b,c] 60[b,d]	NA NA	For individuals with similar daily activity patterns outdoor particle levels affect variability in personal exposure	Mark *et al.* (1997)[f]
Birmingham east	Inhalable aerosol entry, porous foam particle size selector	PM_{10}	15	16–33 hours	100[b,e]	NA	For individuals with similar daily activity patterns outdoor particle levels affect variability in personal exposure	

[a] Similar measurement method for personal and indoor exposures unless otherwise stated
[b] Median level
[c] For people living in area
[d] For people working in area, living elsewhere
[e] For people living in area, working elsewhere
[f] Additional results in Mark D, Upton SL, Lyons CP, Appleby R, Dyment EJ, Griffiths WD & Fox A (1997) *Personal exposure to atmospheric particles.* AEA Technology Report No AEA-TPD-402. AEA unpublished report to DETR

NA, Not applicable

3 Health effects of particles

3.1 Introduction

Current concern about the potential public health impact of airborne particles is largely based on epidemiological studies of the relationship between outdoor particle levels and death, disease or hospital admission rates. In these studies, air quality has generally been assessed using outdoor fixed-site monitors which have recorded particle levels in terms of aerodynamic diameter (PMs), black smoke (frequently measured as British black smoke, BBS), total suspended particles (TSP), or sulphate or nitrate particles (SO_4^{2-} and NO_3^-, respectively; abbreviated herein as SO_4 and NO_3). This variety in species measured, together with national differences in the composition of air pollutants and in categorising health outcomes, limits comparison between studies. Nonetheless, a remarkable degree of concordance is seen in the association between ambient particle level and certain health endpoints (see Section 3.2). Schwartz *et al.* (1996), for example, noted the association between particle exposure and daily mortality was robust, appeared independent of temperature, and occurred at locations where co-exposure to sulphur dioxide or ozone was essentially absent. Nonetheless, it must be appreciated that other pollutants in ambient air (e.g. sulphur dioxide, nitrogen oxides, carbon monoxide and ozone) also show associations with the same health endpoints, and the relative contribution of the various pollutants and the degree to which interactions and confounding occur is as yet unclear and an area of current research. In addition, to date, very few studies have investigated the association between indoor particle levels and health and, therefore, any assessment of the health significance of indoor particle exposure is only possible by extrapolation from studies using measurements of particle exposure outdoors.

Studies in human volunteers have investigated physiological differences between population subgroups and have suggested that some particles can elicit effects in humans, while experimental models have suggested a number of possible, though unproven, mechanisms of toxicity. These findings are outlined in Sections 3.3 and 3.4, respectively (based largely on published reviews).

3.2 Epidemiological studies

For many years there has been concern about the effects of air pollution on rates of death and disease. For example in the London smog episode* of 1952, marked increases in daily death rate were observed, mainly in infants and the mid- to older-age groups (Table 3.1). During a 4-day period in December, 1952 daily ambient TSP levels varied between 0.03 mg/m^3 in outer London and 4.46 mg/m^3 in central London. At this time the use of coal fires was still widespread, which would not only have facilitated the ingress of the ambient air into houses but also, under conditions of low wind speed, might have resulted in a back-flow of chimney gases into houses (Biersteker & de Graaf, 1967).

The possible role of ambient particle exposure has been further highlighted by many studies conducted in North America, while adverse responses to air pollution have also been noted in Europe. In central London in 1991, small increases in mortality (10%) and hospital respiratory admission rates (4%), especially among those over 65 years of age with cardiovascular or ischaemic heart conditions, were explained on the basis of increased particle levels (measured as black smoke; daily maximum of 148 µg/m^3, i.e. 3.4 times monthly average value). However, during this episode nitrogen dioxide levels were also high (maximum 1-hour average of 795 µg/m^3 (423 ppb), i.e. 4.7 times monthly average value) and the possible role of this co-pollutant as the sole, additive or interactive factor remains unclear (Anderson *et al.*, 1995).

Many of the epidemiological studies on air pollutants have used so called 'ecological' designs, in which data are aggregated on the basis of geography or time units. Such studies are essentially descriptive and hypothesis generating rather than of use in establishing causation. The geographical (spatial) studies allow study of long-term differences in health by, for example, comparing health outcomes across different geographical areas. These designs benefit from the use of existing routinely collected data on health outcomes and from the relative ease with which exposure can be characterised in different areas, but control of confounding factors can be difficult. In temporal (time-series) studies on aggregated data, the relationship between exposure and outcome is measured over defined time periods. This design is suitable for the investigation of short-term effects and is less prone to confounding, since the same population is studied and confounding variables are restricted to those that vary with the units of time used. Individuals can also be studied for effects; designs include cross-sectional surveys, and panel, cohort and case–control studies. Within the context of an ecological comparison using geographically-defined units, there is a role for conducting cross-sectional surveys to provide data on the prevalence of a health outcome in a defined area and to improve identification of potential confounding variables. The panel study is a prospective design in which a cohort of individuals is followed for a relatively short period. As such it is used to investigate health effects through, for example, self reporting of symptoms, medication use and respiratory function. Cohort studies have many similarities to panel studies but address longer-term effects. Little use has been made of case–control studies in air pollution research. In these, individuals showing a particular disease are matched with one or more 'controls' who have not displayed the disease, with a view to identifying the causative agent(s) (Katsouyanni, 1995). Overall, the epidemiological evidence for the potential adverse health effects of ambient particle exposure is extensive and has been comprehensively addressed in published meta-analyses, reviews and assessments (e.g. Dochery & Pope, 1994; COMEAP, 1995a; NILU, 1996). Detailed analyses of the relevant studies are not presented here; the following text summarises key aspects. Some individual studies are presented either because they have been highlighted in previous assessments or they are considered appropriate to illustrate a particular point.

3.2.1 Daily mortality rates

Many time-series studies have investigated the association between short-term variations in the level of particles in ambient air and the daily variation in numbers dying (Table 3.2). In a review of studies performed in the USA between 1973 and 1986, Dockery and Pope (1994) noted that a 10 µg/m^3 increase in ambient PM_{10} level appeared to be associated with an

* smog defined as smoke plus fog; episode lasted for 4 days on 5–8th December 1952

Table 3.1 Number of deaths during the London fog of 1952

Period	Age range					
	<4 weeks	4 weeks–1 year	1–14 years	15–44 years	45–74 years	>75 years
Week before episode	16	12	10	61	491	355
Week of episode	28	26	13	99	1369	949
% Increase	75	117	30	62	179	167

Adapted from Ministry of Health (1954)

increase of approximately 1% in overall death rate (excluding accidental causes). Subsequent studies in the USA have tended to report smaller effects (Table 3.2). A value of 0.8% per 10 μg/m^3 increase in PM_{10} was noted by Schwartz *et al.* (1996) from the Harvard Six Cities Study; of particular interest was the finding of a stronger correlation with small particles (1.5% per 10 μg/m^3 $PM_{2.5}$).

Investigations in Europe have shown a similar picture. For example, the Air Pollution and Health: A European Approach (APHEA) project has investigated the relationship between changes in ambient particle level and daily mortality in a number of European cities, using a similar time-series study design at all locations. A quantitative combination of the results from the individual cities, to give an overall estimate of the effect level, identified a small but consistent effect of ambient particle exposure on death rate (approximately 0.5% per 10 μg/m^3 increase in PM_{10}) across the western European cities, despite widely differing climatic and environmental conditions (Katsouyanni *et al.*, 1997). Seasonal differences in response were apparent (0.86% versus 0.2% per 10 μg/m^3 PM_{10} for warm versus cold seasons) and the effect was less well defined in eastern Europe. The APHEA Study also found an independent, positive association between mortality and sulphur dioxide exposure. Similar associations have also been found for nitrogen dioxide and ozone using data from 10 European cities (including six within the APHEA project; Touloumi *et al.*, 1997); analyses suggested that nitrogen dioxide, but not ozone, may act as a proxy for particles or other vehicle-derived pollutants. Katsouyanni *et al.* (1997) have speculated that the lower percentage effect per increase in particle level in Europe compared with the USA may be attributable to differences in the complexity of the pollutant mix, in the size and toxicity of particles, or in the size of susceptible populations. The aetiology of the less consistent association between particles and death rates in eastern European cities may be explained by comparable factors (Katsouyanni *et al.,* 1997), although Bobak and Roberts (1997) have suggested that the results may be influenced by residual confounding effects from differences in temperature and climate. Again, as in US studies, there are limited data suggesting that smaller particles could be exerting a greater effect than coarse particles. For example, based on studies in Amsterdam, the Netherlands (Verhoeff *et al.,* 1996) and in other western European cities in the APHEA project (Katsouyanni *et al.,* 1997) mortality correlated more strongly with exposure to black smoke (a measure of fine particles) than PM_{10}.

One aspect to consider in such studies is the apparent absence of a threshold effect level over the range of atmospheric concentrations investigated (Schwartz, 1991, 1992, 1994a). Through the use of covariate adjusted quantile plots on data derived from a series of studies in US cities, Schwartz identified a 0.6% increase in mortality for each 10 μg/m^3 increase in daily TSP with no evidence for a threshold even at concentrations below 40 μg/m^3. A meta-analysis of data derived from a number of US and European studies on various types of particle also found total mortality increased linearly with particle concentration at a rate of 0.6% per 10 μg/m^3 of PM_{10} up to 200 μg/m^3 (24-hour average; NILU, 1996). Occurring as this does over environmentally-relevant concentrations, there are potentially serious implications for public health. However, time-series studies are not well suited to defining a 'no effect' level, a process which involves extrapolation of findings outside the exposure ranges measured in the studies. As discussed in COMEAP (1998), it is likely that each individual will have a level of particle exposure below which no significant effect on health is likely; however, this will probably differ widely across the population. Indeed, there is good evidence that the elderly or chronically ill are major 'at risk' groups (Utell & Frampton, 1995; COMEAP, 1995a;

Table 3.2 Summary of studies investigating the relationship between ambient particle level and daily mortality (any cause)

Study area/period	Particles measured	Mean (range) (μg/m³)	% increase in mortality per 10μg/m³ increase (95%CI)[a]	Reference (Primary source)
US studies				
Meta-analysis 8 US cities (below)			1.0	Dockery & Pope (1994)
St. Louis, MO 1985–1986	PM_{10} (previous day)	28	1.5 (0.1, 2.9)	(Dockery *et al.,* 1992)
Kingston, TN 1985–1986	PM_{10} (previous day)	30	1.6 (-1.3, 4.6)	(Dockery *et al.,* 1992)
Santa Clara, CA 1980–1982, 1984–1986	Coefficient of haze	35	0.8 (0.2, 1.5)	(Fairley, 1990)
Philadelphia, PA 1973–1980	TSP (2-day mean)	40	1.2 (0.7, 1.7)	(Schwartz & Dockery, 1992b)
Utah Valley, UT 1985–1989	PM_{10} (5-day mean)	47	1.5 (0.9, 2.1)	(Pope *et al.,* 1992)
Birmingham, AL 1985–1988	PM_{10} (3-day mean)	48	1.0 (0.2, 1.9)	(Schwartz, 1993)
Detroit, MI 1973–1982	TSP	48	1.0 (0.5, 1.6)	(Schwartz, 1991)
Steubenville, OH 1974–1984	TSP (previous day)	61	0.7 (0.4, 1.0)	(Schwartz & Dockery, 1992a)
Los Angeles, CA 1985–1990	PM_{10} (daily mean)	58 (15–177)	0.5 (0.0, 1.1)	Kinney *et al.* (1995)
Philadelphia, PA 1973–1988	TSP (previous day)	67.0 Spring 74.0 Summer 64.9 Autumn 66.3 Winter	0.16 (-0.07, 0.39) Overall	Moolgavkar *et al.* (1995)
San Bernadino & Riverside, CA 1980–1986	$PM_{2.5}$ (visibility based)	32.5 (9.3–190.1)	0.11 (-0.28, 0.56)	Ostro (1995)
Harvard Six Cities Study 1979–1988	(2-day mean)		All nonaccidental deaths	Schwartz *et al.* (1996)
	PM_{10}[b]	25.0	0.8 (0.5, 1.1)	
	$PM_{10-2.5}$[b]	9.0	0.4 (-0.1, 1.0)	
	$PM_{2.5}$	14.7	1.5 (1.1, 1.9)	
			Over 65 years	
	$PM_{2.5}$	14.7	1.7 (1.2, 2.2)	

Table 3.2 continued

Study area/period	Particles measured	Mean (range) (μg/m³)	% increase in mortality per 10μg/m³ increase (95%CI)[a]	Reference (Primary source)
UK studies				
Greater London winters 1963–1972	 BBS Acid aerosol	 100.3 (SE 2.8) 6.5 (SE 0.2)	Bivariate Pearson correlation with same-day exposure 0.14 0.20	Thurston *et al.* (1989)
Greater London 1-week pollution episode, 1991	BBS	148 (3.4 times monthly average)	Increased risk during pollution episode All ages 10% (2, 19) 0–64 years 21% (-1, 29) >64 years 8% (-1, 18)	Anderson *et al.* (1995)
Greater London 1987–1992	BBS (24-hour average; 1-day lag)	14.6 ± 7.0	All year 1.13 (0.55, 1.72) Cool season 0.92 (0.26, 1.57) Warm season 2.04 (0.73, 3.38)	Anderson *et al.* (1996)
Birmingham 1992–1994	PM_{10} (24-hour mean; 1-day lag)	 25.6 (2.8–130.9)	 1.1 (0.1, 2.1)	Wordley *et al.* (1997)
Other European studies				
Greater Athens, Greece 1975–1982	BBS	Range of mean daily values 35.0–109.4	No significant correlation with daily death rate	Hatzakis *et al.* (1986)
Erfurt, former East Germany 1980–1989	TSP (daily mean)	106 (10–650) All year 120 (21–650) Winter 98 (10–600) Summer	0.41	Spix *et al.* (1993)
Amsterdam, the Netherlands 1986–1992	BBS PM_{10} (24-hour average; current day)	12 38	1.87 (0.2, 3.8) 0.62 (-0.14, 1.44)	Verhoeff *et al.* (1996)
Zurich, Basle, Switzerland 1984–1989	TSP (3-day lag)	 46.2 ± 27.5 Zurich 45.2 ± 28.9 Basle	For PM_{10} derived from TSP level 0.7 Zurich 2.6 Basle	Wietlisbach *et al.* (1996)

Table 3.2 continued

Study area/period	Particles measured	Mean (range) (μg/m³)	% increase in mortality per 10μg/m³ increase (95%CI)[a]			Reference (Primary source)
APHEA Study				PM_{10}	BS	Katsouyanni *et al.* (1997)
Athens, Greece	BS	73	All cities	0.44	0.26	
Barcelona, Spain	PM_{10}	85		(0.26, 0.62)	(0.02, 0.34)	
Bratislava, Slovakia	PM_{10}	39	Western European	0.42	0.58	
Cracow, Poland	BBS	73	cities	(0.24, 0.60)	(0.42, 0.74)	
Cologne, Germany	PM_{10}	34	Central eastern	0.86	0.01	
Lodz, Poland	BBS	57	cities	(0.06, 1.70)	(0.00, 0.22)	
London, UK	BBS	13				
Lyons, France	PM_{10}	33				
Milan, Italy	PM_{10}	66				
Paris, France	PM_{10}	47				
Pozna, Poland	BBS	34				
Wroclaw, Poland	BBS	54				
Various periods, 1975–1992	(1-day mean)					

[a] Values reported in original paper recalculated, where possible, to give standard presentation of effect per 10 μg/m³ increase
[b] Upper limit of particle size measured was 15 μm up to 1984

BBS, British black smoke; BS, Black smoke; CI, Confidence interval; SE, Standard error of the mean; TSP, Total suspended particles

NILU, 1996) and, although not detected in all studies, a particularly strong association appears to exist between particle exposure and respiratory or cardiovascular causes of mortality (Tables 3.3 and 3.4). Thus, it cannot be expected that it will be possible to identify thresholds for effects in a large population whose exposure is defined using fixed-site monitors. Even when levels recorded by fixed-site monitors are low, some individuals may have personal exposures to concentrations that may cause them (even if not others) adverse effects.

As noted above, the influence of particles on death rates does not appear uniform for all causes of death. Although estimates of the strength of association are quite variable (Tables 3.3 and 3.4), respiratory and, to a lesser extent, cardiovascular causes generally predominate. However, Utell and Frampton (1995) have noted that the recording of cause of death as cardiovascular may represent a misclassification and/or complication of the condition of subjects primarily suffering from chronic respiratory disease.

The aetiology of the association between changes in death rate and outdoor particle levels is perplexing, particularly since infirm individuals would be expected to spend much of their time indoors, protected to some extent from exposure to outdoor air pollution. Given that the associations appear to operate over relatively short time frames (a few days at most), the promotion of infection is an unlikely cause (Utell & Frampton, 1995). Wichmann and Heinrich (1995), in a review of East German studies since 1968, noted that the rise in deaths in association with smog was followed by a fall to below usual numbers 1–2 weeks later, suggesting that the death of critically ill individuals might have been hastened by a transitory increase in environmental stress (the so called harvesting effect). However, the evidence for such a process remains equivocal (Utell & Frampton, 1995). Clearly, additional information on the relationship between indoor, outdoor and personal levels for different sizes and types of particle, and the development of understanding of potential toxic mechanisms will be required before these aspects can be satisfactorily resolved.

Table 3.3 Summary of studies investigating the relationship between ambient particle level and daily mortality (respiratory causes)

Study area/period	Particles measured	Mean (range) (μg/m³)	% increase in mortality per 10μg/m³ increase (95%CI)[a]	Reference (Primary source)
US studies				
Meta-analysis 4 US cities			3.4	Dockery & Pope (1994)
Santa Clara, CA 1980–1982; 1984–1986	Coefficient of haze	35	3.5 (1.5, 5.6)	(Fairley, 1990)
Philadelphia, PA 1973–1980	TSP (2-day mean)	40	3.3 (0.1, 6.6)	(Schwartz & Dockery, 1992b)
Utah Valley, UT 1985—1989	PM_{10} (5-day mean)	47	3.7 (0.7, 6.7)	(Pope *et al.*, 1992)
Birmingham, AL 1985–1988	PM_{10} (3-day mean)	48	1.5 (-5.8, 9.4)	
San Bernadino & Riverside, CA 1980–1986	$PM_{2.5}$ (visibility based)	32.5 (9.3–190.1)	0.83 (-0.28, 1.67)	Ostro (1995)
Harvard Six Cities Study 1979–1988	PM_{10}[b] $PM_{10-2.5}$[b] $PM_{2.5}$ (2-day mean)	25.0 9.0 14.7	$PM_{2.5}$ only **COPD** 3.3 (1.0, 5.7) **Pneumonia** 4.0 (1.8, 6.2)	Schwartz *et al.* (1996)
UK studies				
Greater London 1-week pollution episode 1991	BBS	148 (3.4 times monthly average)	Increased risk during pollution episode All ages / >64 years **All respiratory causes** 22% (-2, 51) / 19% (-5, 49) **Respiratory infections** 23% (-11, 60) / 24% (-11, 73) **COPD** 23% (-10, 68) / 19% (-14, 65)	Anderson *et al.* (1995)
Greater London 1987–1992	BBS (24-hour average; 1-day lag)	14.6 ± 7.0	All year 0.44 (-1.08, 1.99) Cool season 0.45 (-1.21, 2.14) Warm season 0.53 (-3.17, 4.41)	Anderson *et al.* (1996)
Birmingham 1992–1994	PM_{10} (24-hour mean; 1-day lag)	25.6 (2.8–130.9)	**COPD** 5.0 (0.5, 8.6)	Wordley *et al.* (1997)

Table 3.3 continued

Study area/period	Particles measured	Mean (range) (μg/m³)	% increase in mortality per 10μg/m³ increase (95%CI)[a]	Reference (Primary source)
Other European studies				
Paris, France 1987–1992			**All respiratory causes**	Dab *et al.* (1996)
	PM_{13} (24-hour mean)	54.4 Winter 47.5 Summer 50.8 Annual	1.68 (0.41, 3.1)	
	BS (24-hour mean)	39.9 Winter 24.6 Summer 31.9 Annual	0.71 (-0.25, 1.77)	
Zurich, Basle, Switzerland 1984–1989	TSP (3-day lag)	46.2 ± 27.5 Zurich 45.2 ± 28.9 Basle	For PM_{10} derived from TSP levels 2.5 Zurich 1.8 Basle	Wietlisbach *et al.* (1996)

[a] Values reported in original paper recalculated, where possible, to give standard presentation of effect per 10 μg/m³ increase
[b] Upper limit of particle size measured was 15 μm up to 1984

BBS, British black smoke; BS, Black smoke; CI, Confidence interval; TSP, Total suspended particles

Table 3.4 Summary of studies investigating the relationship between ambient particle level and daily mortality (cardiovascular causes)

Study area/period	Particles measured	Mean (range) (μg/m³)	% Increase in mortality per 10μg/m³ increase (95%CI)[a]	Reference (Primary source)
US studies				
Meta-analysis 4 US cities			1.4	Dockery & Pope (1994)
Santa Clara, CA 1980–1982, 1984–1986	Coefficient of haze	35	0.8 (0.1, 1.6)	(Fairley, 1990)
Philadelphia, PA 1973–1980	TSP (2-day mean)	40	1.7 (1.0, 2.4)	(Schwartz & Dockery, 1992b)
Utah Valley, UT 1985–1989	PM_{10} (5-day mean)	47	1.8 (0.4, 3.3)	(Pope *et al.*, 1992)
Birmingham, AL 1985—1988	PM_{10} (3-day mean)	48	1.6 (-0.5, 3.7)	(Schwartz, 1993)
San Bernadino & Riverside, CA 1980–1986	$PM_{2.5}$ (visibility based)	32.5 (9.3–190.1)	0.28 (-0.28, 0.56)	Ostro (1995)
Harvard Six Cities Study 1979–1988	PM_{10}[b]	25.0	$PM_{2.5}$ only	Schwartz *et al.* (1996)
	$PM_{10-2.5}$[b]	9.0	**Ischaemic heart disease**	
	$PM_{2.5}$ (2-day mean)	14.7	2.1 (1.4, 2.8)	
UK studies				
Greater London 1-week pollution episode 1991	BBS	148 (3.4 times monthly average)	Increased risk during pollution episode **Cardiovascular** All ages 14% (1, 28) 0–64 years 4% (-28, 51) >64 years 15% (2, 31) **Ischaemic heart disease** All ages 18% (0, 39) 0-64 years -1% (-36, 54) >64 years 22% (3, 45)	Anderson *et al.* (1995)
Greater London 1987–1992	BBS (24-hour average; 1-day lag)	14.6 ± 7.0	All year 0.39 (-0.45, 1.23) Cool season 0.08 (-0.86, 1.02) Warm season 1.56 (-0.23, 3.44)	Anderson *et al.* (1996)
Birmingham 1992–1994	PM_{10} (24-hour mean; 1-day lag)	25.6 (2.8–130.9)	**Circulatory** 1.7 (0.2, 3.2)	Wordley *et al.* (1997)
European study				
Zurich, Basle, Switzerland 1984–1989	TSP (3-day lag)	46.2 ± 27.5 Zurich 45.2 ± 28.9 Basle	For PM_{10} derived from TSP levels 0.5 Zurich 3.1 Basle	Wietlisbach *et al.* (1996)

[a] Values reported in original paper recalculated, where possible, to give standard presentation of effect per 10 μg/m³ increase
[b] Upper limit of particle size measured was 15 μm up to 1984

BBS, British black smoke; BS, Black smoke; CI, Confidence interval; TSP, Total suspended particles

3.2.2 Hospital admissions and related indicators

Despite using various measurement techniques, several epidemiology studies in the USA and Europe have demonstrated associations between ambient particle level and daily hospital admission rate (summarised in Table 3.5; detailed in Tables 3.6–3.8). Caution is necessary when attempting to compare the data for different countries because of the differences that exist in their health-care systems and recording practices. Nonetheless, it is clear that, particularly in the elderly, the effects of particles on sufferers from cardiopulmonary conditions (such as chronic obstructive pulmonary disease, COPD) may be substantial. The apparent differences in strength of response between the USA (e.g. Dockery & Pope, 1994) and Europe (e.g. Anderson *et al.,* 1997) are of interest although the basis for the differences is as yet uncertain.

In the USA, another available measure of response is the level of emergency room (ER) visits, and the available data suggest that there is a similar trend to that for hospital admissions (Table 3.9). An increase in ER admission rates for COPD has also been reported in Barcelona, Spain by Sunyer *et al.* (1993). In a 5-year study, a 0.97% change was noted per 25 μg/m^3 of black smoke during winter periods, while in summer, the effect was smaller at 0.32%. In the UK, the nearest equivalent to ER visits is attendance at an Accident and Emergency facility and, although currently unavailable, analyses of such data would be of interest.

Table 3.5 Summary of range of effects on hospital admissions quoted in literature

Location	Condition	Range (% change per 10 μg/m^3)*
USA	**Respiratory causes**	0.8 to 3.4
	COPD	2.0 to 5.7
	Asthma	1.9 to 2.5
	Various cardiovascular	0.56 to 2.5
Europe	**Respiratory causes**	-1.23 to 2.8
	COPD	0.2 to 1.0
	Asthma	-0.3 to 4.0
	Various cardiovascular	-0.21 to 2.02

* For any type of particle

The increase in hospital attendance for asthma is also an important finding, especially since children appear at risk (Dockery & Pope, 1994; COMEAP, 1995a; Pope *et al.*, 1995a). It must be acknowledged that 'asthma attack' is a poorly defined health endpoint, given that the criteria for what constitutes an asthma attack have not been consistently adopted (COMEAP, 1998). However, measures of effect such as increased use of medication and increases in respiratory symptoms also support the existence of an effect of outdoor particle levels on people with asthma (see Section 3.2.4). Bronchodilator use has been evaluated as a measure of the degree of exacerbation of asthma (Table 3.10). The number and scale of such studies is small and hence the results may be unrepresentative of the general population. Nonetheless, positive associations have been found for both adults and children although the dose–response relationships are variable.

Further support for an adverse effect on children comes from changes in school absence rates. For example, Ransom and Pope (1992) reported an increase of approximately 0.2% in absences from school, in Utah Valley, UT, USA, during 1985–1991, for each 10 μg/m^3 rise in ambient PM_{10} level.

As is the case for daily death rates (see Section 3.2.1), all these associations appear to operate even at relatively low exposure levels (Brunekreef *et al.*, 1995) that are within the ranges commonly encountered in developed countries.

As for many of the identified health endpoints, there is a dearth of studies investigating possible links between hospital admission rates and indoor or personal exposure to particles such that, at present, these aspects cannot be confidently assessed. However, Robin *et al.* (1996) have reported an increased risk of hospitalisation from acute lower respiratory illness in Navajo children (USA) exposed to wood-burning cooking and heating stoves (OR 7.0, CI 0.9–56.9 for living in homes with PM_{10} levels above 65 μg/m^3).

Table 3.6 Summary of studies investigating the relationship between ambient particle level and hospital attendance (respiratory disease)

Study area/period	Particles measured	Mean (range) (μg/m³)	% Increase in attendance per 10 μg/m³ increase (95%CI)*	Reference (Primary source)
North American studies				
Meta-analysis 4 North American cities			0.8	Dockery & Pope (1994)
New York City, NY 1988–1989	SO_4 particles (daily mean)		1.0 (0.2, 1.8)	(Thurston *et al.*, 1992)
Buffalo, NY 1988–1989	SO_4 particles (daily mean)		2.2 (0.6, 3.8)	(Thurston *et al.*, 1992)
Toronto, Canada 1986–1988	$PM_{2.5}$ (daily mean)		3.4 (0.4, 6.4)	(Thurston *et al.*, 1993)
Southern Ontario, Canada 1983–1988	SO_4 particles (daily mean)		0.8 (0.4, 1.1)	(Burnett *et al.*, 1994)
Detroit, MI 1986-89	PM_{10}	48	For >64 years **Pneumonia** 1.2 (0.4, 1.9) **COPD** 2.0 (0.4, 3.2)	Schwartz (1994b)
Minneapolis–St. Paul, MN 1986–1989	PM_{10} (same or 1-day lag)	36	For > 64 years **Pneumonia** (same day) 1.7 (0.3, 3.3) **COPD** (weighted average of current and previous day) 5.7 (2.0, 10.6)	Schwartz (1994c)
Ontario, Canada 1983–1988	SO_4 particles (1-day lag)	4.37	**All respiratory causes** 2.7 (1.8, 3.6) **COPD** 3.7 (1.6, 6.6) **Infection** 2.9 (1.3, 3.8)	Burnett *et al.* (1995)
UK studies				
Greater London 1-week pollution episode, 1991	BBS	148 (3.4 times monthly average)	Increased risk during pollution episode **All respiratory** **COPD** All ages 4% (-4, 13) 27% (3, 55) 0–14 years 1% (-11, 14) 15–64 years -5% (-20, 14) -1% (-39, 60) >64 years 19% (4, 37) 36% (8, 71)	Anderson *et al.* (1995)
Greater London 1987–1992	BBS (1-day lag)	14.6 ± 7.7	All ages -0.17 (-0.95, 0.61) 0–14 years -1.23 (-2.39, -0.05) 15–64 years 1.11 (-0.27, 2.52) >64 years 0.76 (-0.45, 1.99)	Ponce de Leon *et al.* (1996)
Birmingham 1992–1994	PM_{10} (24-hour mean)	25.6 (2.8–130.9)	**All respiratory** **Bronchitis** **Pneumonia** For same day 2.4 (1.1, 3.7) 5.8 (1.7, 11.9) For 3-day mean 2.8 (1.2, 4.4) 6.3 (2.5, 9.7)	Wordley *et al.* (1997)

Table 3.6 continued

Study area/period	Particles measured	Mean (range) (μg/m³)	% Increase in attendance per 10 μg/m³ increase (95%CI)*		Reference (Primary source)
Other European studies					
Paris, France 1987–1992			**All respiratory** (no lag)	**COPD** (2-day lag)	Dab *et al.* (1996)
	PM_{13} (24-hour mean)	54.4 Winter 47.5 Summer 50.8 Annual	0.5 (0.0, 0.9)	-0.5 (-1.3, 0.4)	
	BS (24-hour mean)	39.9 Winter 24.6 Summer 31.9 Annual	0.4 (0.1, 0.8)	-0.5 (-1.0, 0.3)	
APHEA Study Amsterdam, the Netherlands; Barcelona, Spain; London, UK; Milan, Italy; Paris, France; Rotterdam, the Netherlands Various periods between 1977–1992		Yearly range of mean values			Anderson *et al.* (1997)
	BS (not Milan; 1-day lag)	6–41		**COPD** (All ages)	
			All year	0.7 (0.2, 1.2)	
			Cool season	0.6 (0.0, 1.2)	
			Warm season	1.0 (-0.4, 2.4)	
	TSP (not London or Paris)	41–155	All year	0.44 (-0.04, 0.94)	
			Cool season	0.8 (-0.2, 1.8)	
			Warm season	0.2 (-0.4, 1.0)	
				COPD (>64 years) TSP only	
			London	0.78	
			Paris	0.64	
			Combined	0.68	
APHEA Study Amsterdam, the Netherlands; London, UK; Milan, Italy; Paris, France; Rotterdam, the Netherlands Various years between 1987–1992		Range of means			Spix *et al.* (1998)
	BS (not Milan)	6–26	**All respiratory causes**		
				15–64 years	>64 years
			All year	0.56 (0.12, 1.02)	0.4 (-0.08, 0.92)
			Cool season	0.8 (0.4, 1.4)	0.0 (-1.0, 0.8)
			Warm season	-0.2 (-2.0, 1.8)	1.4 (0.0, 3.0)
	TSP (not London or Paris)	41–120		15–64 years	>64 years
			All year	0.2 (-0.22, 0.62)	0.32 (-0.12, 0.78)
			Cool season	-0.6 (-1.4, 0.4)	0.4 (0.00, 1.00)
			Warm season	0.6 (0.00, 1.2)	0.2 (-0.4, 0.8)

* Values reported in original paper recalculated, where possible, to give standard presentation of hospital attendance per 10 μg/m³ increase

BBS, British black smoke; BS, Black smoke; CI, Confidence interval; TSP, Total suspended particles

Table 3.7 Summary of studies investigating the relationship between ambient particle level and hospital attendance (asthma)

Study area/period	Particles measured	Mean (range) (μg/m³)	% Increase in attendance per 10 μg/m³ increase (95%CI)*	Reference (Primary source)
North American studies				
Meta-analysis 3 North American cities			1.9	Dockery & Pope (1994)
New York City, NY 1988–1989	SO_4 particles (daily mean)		1.9 (0.4, 3.4)	(Thurston *et al.*, 1992)
Buffalo, NY 1988–1989	SO_4 particles (daily mean)		2.1 (-0.6, 5.0)	(Thurston *et al.*, 1992)
Toronto, Canada 1986–1988	$PM_{2.5}$ (daily mean)		2.1 (-0.8, 5.1)	(Thurston *et al.*, 1993)
Ontario, Canada 1983–1988	SO_4 particles (1-day lag)	4.37	2.5 (1.1, 4.3)	Burnett *et al.* (1995)
UK studies				
Greater London 1-week pollution episode 1991	BBS	148 (3.4 times monthly average)	Increased risk during pollution episode All ages 8% (-9, 28) 0–14 years 5% (-17, 33) 15–64 years -2% (-25, 30) >64 years 97% (10, 253)	Anderson *et al.* (1995)
Birmingham, UK 1992–1994	PM_{10} (3-day mean)	25.6 (7.3–104.7)	4.0 (0.8, 7.6)	Wordley *et al.* (1997)
Other European studies				
Paris, France 1987–1992	PM_{13} (24-hour mean; 2-day lag)	54.4 Winter 47.5 Summer 50.8 Annual	-0.3 (-1.0, 0.5)	Dab *et al.* (1996)
	BS (24-hour mean; no lag)	39.9 Winter 24.6 Summer 31.9 Annual	0.4 (-0.3, 1.2)	
APHEA Study Barcelona, Spain; Paris, France; London, UK Various periods between 1986–1992	BS	Range of means 13–40 (min 3, max 258)	<14 years London (no lag) 0.62 Paris (2-day lag) 0.6 Combined 0.6 (-0.42, 1.68) 15–64 years Barcelona (3-day lag) 0.72 London (no lag) 0.70 Paris (no lag) 0.24 Combined 0.42 (-0.0, 1.18)	Sunyer *et al.* (1997)

* Values reported in original paper recalculated, where possible, to give standard presentation of hospital attendance per 10 μg/m³ increase

BBS, British black smoke; BS, Black smoke; CI, Confidence interval

Table 3.8 Summary of studies investigating the relationship between ambient particle level and hospital attendance (cardiovascular disease)

Study area/period	Particles measured	Mean (range) (μg/m³)	% Increase in attendance per 10 μg/m³ increase (95%CI)*		Reference
North American studies					
Ontario, Canada 1983–1988	SO_4 particles (1-day lag)	4.37	**Any cardiac condition** **Coronary artery** **Cardiac dysrhythmia** **Heart failure**	2.5 (1.3, 3.7) 1.8 (0.5, 2.9) 1.0 (-1.5, 3.5) 2.3 (0.5, 4.1)	Burnett *et al.* (1995)
Detroit, Michigan 1986–1989	PM_{10} (same day)	48.0	>64 years **Ischaemic heart disease** **Congestive heart failure**	 0.56 (0.16, 1.00) 1.00 (0.38, 1.63)	Schwartz & Morris (1995)
UK studies					
Greater London 1-week pollution episode 1991	BBS	148 (3.4 times monthly average)	Increased risk during pollution episode **Ischaemic heart disease** All ages 15–64 >64 years	 4% (-10, 21) 3% (-20, 33) 4% (-23, 26)	Anderson *et al.* (1995)
London 1987–1994	BBS (1-day lag)	Median 12 (1–62)	**Acute myocardial infarction** **Angina pectoris** **Cardiac arrhythmia** **Heart failure** **Other circulatory disease** **Cardiovascular disease**	2.02 (0.61, 3.52) 2.02 (0.20, 3.95) 1.69 (-0.28, 3.80) 1.53 (-1.03, 2.06) 1.05 (0.39, 2.57) -0.21 (-1.52, 1.17)	Poloniecki *et al.* (1997)
Birmingham 1992–1994	PM_{10} (24-hour mean)	25.6 (2.8–130.9)	**Cerebrovascular**	2.1 (0.03, 4.1) (for same day)	Wordley *et al.* (1997)

* Values reported in original paper recalculated, where possible, to give standard presentation of hospital attendance per 10 μg/m³ increase

BBS, British black smoke; CI, Confidence interval

Table 3.9 Summary of studies investigating the relationship between ambient particle level and emergency room visits in USA

Study area	Particles measured	% Increase in ER visits per 10 μg/m³ increase (95%CI)*	Reference (Primary source)
Steubenville, OH 1974–1977	TSP (daily mean)	**Respiratory disease** 0.5 (0.0, 1.0)	Dockery & Pope (1994) (Samet *et al.,* 1981)
Seattle, WA 1989–1990	PM_{10} (daily mean)	**Asthma** 3.4 (0.9, 6.0) (<65 years of age)	Dockery & Pope (1994) (Schwartz *et al.,* 1993)

* Values reported in original paper recalculated where possible, to give standard presentation of ER visits per 10 μg/m³ increase

CI, Confidence interval; TSP, total suspended particulate

3.2.3 Short-term changes in lung function

A number of studies in the USA and Europe have investigated the effect of short-term changes in particulate air pollution on various measures of pulmonary function (Table 3.11). It appears that variations in ambient particle concentration within environmentally-relevant ranges may result in small, but measurable, reductions in lung function. Although most studies reviewed relate to symptomatic or asymptomatic children, effects have also been reported for adults (Dusseldorp *et al.*, 1995 & Peters *et al.*, 1997).

A small study in the USA (Hosein & Corey, 1986) showed significant negative correlations between indoor (home) PM_{10} levels and lung function, among nonsmoking, but not among smoking, housewives. Of interest in this study was the finding that, among nonsmokers, lung function was impaired in those using gas cookers relative to those using electric cookers. The authors attributed this to elevated nitrogen dioxide levels in homes using gas, although it should be noted that gas cookers also produce significant numbers of small particles (Kamens *et al.*, 1991).

The mechanisms that could underlie a change in lung function are as yet unclear, although Scarlett *et al.* (1996) suggest that effects may be due to lung restriction (possibly as a result of inflammation of lung parenchyma causing stiffening of the lung) rather than airway narrowing. Asthma sufferers appear to be affected to a greater degree than asymptomatics (i.e. those with no history of wheeze). Timonen and Pekkanen (1997) suggested that this could be due to pre-existing airway narrowing causing greater bronchial hyper-responsiveness, and mechanisms to explain such an effect have been suggested. The increased bronchial tone of people with asthma may potentiate an irritant response or the altered deposition pathway among asthma sufferers may favour more central deposition in a region where receptors are most numerous. Generally, the reported magnitude of effects on lung function is small and unlikely to cause lower respiratory symptoms in healthy individuals or even those with asthma. However, it is possible that a small shift in the distribution of pulmonary function across a population could have a disproportionate effect at the extreme, that is among symptomatic individuals with lung disease (Scarlett *et al.*, 1996). Thus, small changes in the lung function of individuals in a borderline state of health might be sufficient to elicit a clinically important response. Owing to the numbers of individuals potentially in such a state and the potential public health implications, these apparently small changes in lung function remain a cause for concern.

The lack of correlation between number concentration (NC) and mass concentration (MC) of particles in the 0.01–2.5 μm range, in the eastern German study by Peters *et al.* (1997) warrants special mention, as it permitted the relative influence of NC and MC to be addressed. The NC in the range 0.01–2.5 μm was dominated by particles less than 0.1 μm, whereas most of the MC was due to particles ranging from 0.1–0.5 μm. The correlation with peak expiratory flow (PEF) was stronger for number of ultrafine particles ($NC_{0.01–0.1}$) than for mass measures (MC or PM_{10}). However, this was too small a study to enable definitive interpretation. Indeed, caution is generally necessary when considering lung function data from epidemiological studies because the potential for bias or confounding is high when

Table 3.10 Summary of studies investigating the relationship between ambient particle level and bronchodilator use

Study area/period	Particles measured	Mean (range) (μg/m³)	Subjects	% Increase in bronchodilator use per 10 μg/m³ increase (95%CI)*	Reference (Primary source)
US studies					
Utah valley, UT Winter 1989–1990	PM_{10} (daily mean)	46	34 Children 21 Adults	11.2 (2.4, 20.7) 12.0 (4.7, 19.7)	Dockery & Pope (1994) (Pope *et al.*, 1991)
European studies					
Wageningen & Bennekom, the Netherlands 1990–1991			73 Children with chronic respiratory symptoms	Regression coefficient for concentration on day	Roemer *et al.* (1993)
	PM_{10} BS (daily mean)			0.023 0.021	
Wijk aan zee, the Netherlands 1993	PM_{10} (daily mean)	53.7 (4.4–137.1)	32 Adults (26–79 years)	2.0 (0.0, 4.3) (No lag)	Dusseldorp *et al.* (1995)

* Values reported in original paper recalculated where possible, to give standard presentation of bronchodilator use per 10 μg/m³ increase

BS, Black smoke; CI, Confidence interval

Table 3.11 Summary of studies investigating the relationship between short-term changes in ambient particle level and lung function measurements

Study location/ period	Particles measured	Mean (range) (μg/m³)	Subjects	Result	Reference
US studies					
Steubenville, OH 1978–1980	TSP (24-hour period)	Max. 422	335 Children	Lung function assessed at intervals before and after a series of short-term pollution episodes; data combined using regression analysis Median FVC -0.81ml per 10 μg/m³ Median $FEV_{0.75}$ -0.18ml per 10 μg/m³	Dockery *et al.* (1982)
Lebanon, CO Winnsboro, SC	PM_{10}	Range of means 21.8–75.4	Women (25–44 years) 11 nonsmokers, 15 smokers	Correlations between indoor particle levels and lung function changes Nonsmokers / Smokers $MMEF_{25\%}$ -0.41 / -0.09 $MMEF_{50\%}$ -0.41 / -0.19 FEV_1 -0.31 / -0.11 Gas cooker / Electric cooker $MMEF_{25\%}$ -32.5 ± 25.0 / -1.3 ± 15.9 $MMEF_{50\%}$ -32.0 ± 26.0 / -2.7 ± 13.7 FEV_1 -25.3 ± 26.2 / -2.2 ± 14.9	Hosein & Corey (1986)
Utah Valley, UT 1990–1991	PM_{10} (24-hour)	Range of means 7–251	Children (10–12 years) 39 symptomatic and 40 asymptomatic	Δ PEFR (l/min per 10 μg/m³) Symptomatic / Asymptomatic Current day -0.175 (SE 0.094) / -0.110 (SE 0.82) 5-day av. -0.359 (SE 0.117) / -0.254 (SE 0.095)	Pope & Dockery (1992)
Seattle, WA Winter periods 1988–1990	$PM_{2.5}$ (by light scattering)		Children 24 symptomatic and 322 asymptomatic	Analysis based on 12-hour night time exposure data Symptomatic / Asymptomatic FEV_1 -0.017 per 10 μg/m³ / -0.0015 per 10 μg/m³ FVC -0.018 per 10 μg/m³ / 0.0034 per 10 μg/m³	Koenig *et al.* (1993a)
Uniontown, PA Summer 1990	Particle strong acidity (12-hour average)	64.7 nmol/m³ (night) 139.4 nmol/m³ (day)	Children 71 symptomatic and 27 asymptomatic	Adjusted for time outdoors in previous 12 hours Δ PEFR (l/min per 125 nmol/m³) -2.5 (CI -4.2, -0.8) all children	Neas *et al.* (1995)
Los Angeles, CA 4-day period, 1995	PM_{10} (24-hour average)	Fixed site 55.1 (25.1–141.8) Outdoor 53.3 (4.5–149.0) Indoor 37.0 (14.3–85.8) Personal 42.3 (16.8–104.6)	COPD sufferers (61–82 years)	Preliminary study; only association with fixed site PM_{10} levels assessed: significant decrease ($p<0.05$) in peak flow associated with increased PM_{10}; no effect on FVC or FEV_1	Linn *et al.* (1996)
	$PM_{2.5}$ (24-hour average)	Fixed site 55.4 (23.8–174.8) Outdoor 33.6 (5.9–96.3) Indoor 26.4 (8.8–97.3) Personal 28.2 (8.2–70.0)			

Table 3.11 continued

Study location/ period	Particles measured	Mean (range) (μg/m³)	Subjects	Result	Reference
UK study					
Surrey Summer, 1994	PM_{10} (24-hour mean)	71.0 (20–150)	Children (7–11 years) 63 boys and 91 girls; 14 reporting pre-existing wheeze	$FEV_{0.75}$ -0.67 ml per 10 μg/m³ (CI -1.6, 0.22) FVC -0.17 ml per 10 μg/m³ (CI -2.7, -0.53)	Scarlett *et al.* (1996)
Other European studies					
Wageningen & Bennekom, the Netherlands 1990–1991	(Daily mean) PM_{10} BS		73 Children with chronic respiratory symptoms	Δ PEF (l/min per μg/m³) Same day Morning Evening -0.041 -0.028 -0.038 0.005	Roemer *et al.* (1993)
Deurne, Enkhuizen, Venlo, Nijmegen, the Netherlands Various winter periods 1987–1990	(24-hour average) PM_{10} Fine SO_4 particle Fine NO_3 particle	 44.9 (14.1–126.1) 6.7 (0.0–29.7) 7.3 (0.9–36.8)	871 Children (7–11 years)	ΔFVC (ml/μg/m³) ΔFEV$_1$ (ml/μg/m³) ΔPEF (ml/sec/μg/m³) ΔMMEF (ml/sec/μg/m³) 0.07 (SE 0.07) -0.06 (SE 0.08) -0.93 (SE 0.34) -0.43 (SE 0.21) -0.65 (SE 0.33) -0.84 (SE 0.34) -4.04 (SE 1.54) -1.50 (SE 0.87) -0.32 (SE 0.36) -0.58 (SE 0.34) -1.45 (SE 1.49) -1.33 (SE 0.85)	Hoek & Brunekreef (1994)
Wijk aan zee, the Netherlands 1993	PM_{10} (24-hour average)	53.7 (4.4–137.1)	32 Adults with obstructive airway disease (26–79 years)	PEF Evening -0.54 per 10 μg/m³ Morning -0.92 per 10 μg/m³	Dusseldorp *et al.* (1995)
Kuopio, Finland 1994	PM_{10} (24-hour average)	Urban 18 (max 60) Suburban 13 (max 37)	197 Symptomatic children (7–12 years)	Morning PEF Urban, Regression coefficient -17.55 Suburban -26.48 (for 4-day lagged average PM_{10})	Pekkanen *et al.* (1995)
The Netherlands 1995	BS (24-hour average)	8 ± 3.9 (3–23)	61 Children (7–13 years; 77% asthmatics)	PEF reduced at 41 μg/m³ BS	Gielen *et al.* (1997)
Erfurt, eastern Germany 1991–1992	(5-day mean) PM_{10} $NC_{0.01–2.5}$ $NC_{0.01–0.1}$ $NC_{0.1–0.5}$ $NC_{0.5–2.5}$ $MC_{0.01–2.5}$ $MC_{0.01–0.1}$ $MC_{0.1–0.5}$ $MC_{0.5–2.5}$	 60 17 130 12 920 4140 37 53.1 0.7 44.5 7.7	27 Adult asthmatics	Association with evening PEF -2.31 (CI -4.54, -0.08) per 50 μg/m³ -3.58 (CI -5.28, -1.89) per 10 580cm³ -4.04 (CI -6.06, -2.01) per 9200 cm³ -2.24 (CI -3.93, -0.55) per 3000 cm³ -1.35 (CI -3.10, 0.41) per 44 cm³ -2.18 (CI -3.80, -0.57) per 50 μg/m³ -3.90 (CI -5.60, -2.21) per 0.5 μg/m³ -2.13 (CI -3.67, -0.59) per 39.7 μg/m³ -2.02 (CI -3.89, -0.14) per 9.9 μg/m³	Peters *et al.* (1997)

Table 3.11 continued

Study location/ period	Particles measured	Mean (range) (μg/m³)	Subjects	Result				Reference
Kuopio, Finland 1994			Children (7–12 years)	Δ PEF regression coefficient				Timonen & Pekkanen (1997)
			Urban: 39 asthmatics, 46 cough only	Urban		Suburban		
				Asthmatic	Cough	Asthmatic	Cough	
	PM_{10}	Urban 18 Suburban 13	Suburban: 35 asthmatics, 49 cough only	-0.911 (SE 0.386)	0.345 (SE 0.295)	-1.05 (SE 0.596)	-0.487 (SE 0.424)	
	BS	Urban 13 Suburban 8		-0.868 (SE 0.413)	-0.016 (SE 0.383)	-0.780 (SE 0.461)	-0.354 (SE 0.361)	
	(2-day lag)			Statistical significance attained only for children with asthma				

BS, Black smoke; CI, Confidence interval; FEV_1 or $_{0.75,}$ Forced expiratory volume in 1 or 0.75 seconds; FVC, Forced vital capacity; MC, Mass concentration; MMEF, Maximal midexpiratory flow; NC, Number concentration; Δ PEFR, Deviation in peak expiratory flow rate; SE, Standard error of the mean

pulmonary function changes are only a few percent (Rodan *et al.*, 1995). Careful standardisation is essential, particularly since variability may arise from many sources including, for example, technical variability (accuracy of equipment/measurement technique), within-subject variability (blow-to-blow coefficient of variation in forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) may be up to 3%, but over longer durations of study variations of up to 6% may be noted) and between-subject variability (variations of greater than 10% are possible; modifying factors include age, gender, race, height, weight, occupation). The endpoints measured may also be affected by co-pollutants, temperature and different seasonal conditions which may impact on behaviour/exposure patterns, and potentially introduce bias.

Based on the available studies, Ostro *et al.* (1996) considered that there is strong evidence for an adverse effect of particles on lung function in asthmatics. COMEAP (1995b) also have reported studies showing that airborne particles alter lung function, especially in asthmatic children, although they suggest ozone levels may be more important; Brunekreef *et al.* (1995) likewise concluded that existing data are sufficient to establish such an association.

3.2.4 Short-term effects on respiratory symptoms

The relationship between short-term changes in outdoor particle level and the occurrence of respiratory symptoms has been widely investigated (see Tables 3.12–3.14); much attention has focused on children. The designs of the epidemiological studies conducted vary but have generally involved the completion of a daily diary of symptoms by participants or, in the case of children, by the parents. Symptoms have frequently been grouped into three categories:

- upper respiratory symptoms, such as hoarseness, sore throat and fever;
- lower respiratory symptoms, principally based upon presence of wheeze, but also including symptoms such as cough, chest pain and phlegm; or
- cough, as a single marker of effect.

Some studies have failed to show a clear relationship between particle level and symptoms. For example, in a study of urban and suburban children in Kuopio, Finland, Timonen and Pekkanen (1997) found no association with either PM_{10} or black smoke levels although sulphur dioxide levels were associated with upper respiratory symptoms in the urban group. The potential complexity of the situation is shown by a study of Dutch children aged 6 to 12 years, in which symptoms were associated with levels of ETS and dampness in the home; regrettably no assessment of non-ETS particle levels was made in this study (Dijkstra *et al.*, 1990). However, the majority of studies have shown associations between ambient particle level and symptoms, with upper and lower respiratory symptoms apparently aggravated by increased particle exposure. The evidence also suggests that effects may be exaggerated in people with asthma.

A potential measure that has been suggested as a tool for monitoring adverse health effects is the number of 'restricted activity days'. However, no UK studies have investigated restricted activity days and COMEAP (1998) has expressed concern regarding the variability in the use of this measure in different countries and its imprecise definition; it is therefore not considered in this report.

Table 3.12 Summary of studies investigating the relationship between short-term changes in ambient particle level and upper respiratory tract symptoms

Study location/period	Particles measured	Mean (range) (μg/m³)	Subjects	Results	Reference
US studies					
Utah Valley, UT 1990–1991	PM_{10} (24-hour)	Range of means 7–251	Children (10–12 years) 39 symptomatic and 40 asymptomatic	Logistic regression coefficient (x100) for symptoms Symptomatics / Asymptomatics Current day 0.364 (SE 0.153) / -0.022 (SE 0.244) 5-day av 0.519 (SE 0.203) / 0.072 (SE 0.325)	Pope & Dockery (1992)
Harvard Six Cities Study April–August of one year during 1984–1987	(24-hour average) PM_{10} $PM_{2.5}$ $PM_{2.5}$ sulphur	 30.0 18.0 2.5	1844 Elementary school children	Analysis allowed for temperature, day of week & location Odds ratio for exposure two days before symptoms 1.22 (CI 0.98, 1.52) per 30 μg/m³ 1.22 (CI 1.00, 1.49) per 20 μg/m³ Not given	Schwartz *et al.* (1994)
European studies					
Wageningen & Bennekom, the Netherlands 1990–1991	(daily mean) PM_{10} BS		73 Children with chronic respiratory symptoms	**Runny nose** Regression coefficient for concentration on day 0.035 0.053	Roemer *et al.* (1993)
Deurne, Enkhuizen, Venlo, Nijmegen, the Netherlands Various winter periods 1987–1990	(24-hour) PM_{10} Fine SO_4 particles Fine NO_3 particles	 44.9 (14.1–126.1) 6.7 (0.0–29.7) 7.3 (0.9–36.8)	695 Children (7–11 years)	Odds ratio for 1-day lag 1.01 (CI 0.68, 1.49) for 100 μg/m³ change 0.97 (CI 0.69, 1.38) for 20 μg/m³ change 0.97 (CI 0.68, 1.36) for 20 μg/m³ change	Hoek & Brunekreef (1994)
Deurne, Enkhuizen, the Netherlands Spring/summer 1989	PM_{10} (24-hour average)	Deurne 48 (13–124) Enkhuizen 36 (11–136)	300 Children (7–11 years)	No association for symptomatic or asymptomatic children	Hoek & Brunekreef (1995)

BS, Black smoke; CI, Confidence interval; SE Standard error of the mean

Table 3.13 Summary of studies investigating the relationship between short-term changes in ambient particle level and lower respiratory tract symptoms

Study location/ period	Particles measured	Mean (range) (μg/m³)	Subjects	Results	Reference
US studies					
Utah Valley, UT 1990–1991	PM_{10} (24-hour)	Range of means 7–251	Children (10–12 years) 39 symptomatic and 40 asymptomatic	Logistic regression coefficient (x100) for symptoms Symptomatic / Asymptomatic Current day 0.472 (SE 0.166) / 0.237 (SE 0.215) 5-day av 0.658 (SE 0.205) / 0.379 (SE 0.279)	Pope & Dockery (1992)
Harvard Six Cities Study April–August of one year during 1984–1987	(24-hour average) PM_{10} $PM_{2.5}$ $PM_{2.5}$ sulphur	 30.0 18.0 2.5	1844 Elementary school children	Analysis allowed for temperature, day of week and location Odds ratio for previous 24-hour exposure 1.53 (CI 1.20, 1.95) per 30 μg/m³ 1.44 (CI 1.15, 1.82) per 20 μg/m³ 1.82 (CI 1.28, 2.59) per 5 μg/m³	Schwartz *et al.* (1994)
Los Angeles, CA 1992	PM_{10} (24-hour average)	55.87 (19.63–101.42)	41 Afro-American asthmatic children (7–12 years)	No association between wheeze and exposure Odds ratio for shortness of breath 2.42 (CI 1.76, 4.68) (assessed for mean exposure level)	Ostro *et al.* (1995)
European studies					
Wageningen & Bennekom, the Netherlands 1990–1991	(daily mean) PM_{10} BS		73 Children with chronic respiratory symptoms	**Wheeze** Regression coefficient for concentration on day 0.027 0.030	Roemer *et al.* (1993)
Deurne, Enkhuizen, Venlo, Nijmegen, the Netherlands Various winter periods 1987–1990	(24-hour average) PM_{10} Fine SO_4 particles Fine NO_3 particles	 44.9 (14.1, 126.1) 6.7 (0.0, 29.7) 7.3 (0.9, 36.8)	695 Children (7–11 years)	Odds ratio for 1 day lag 0.99 (CI 0.47, 2.12) for 100 μg/m³ change 0.82 (CI 0.41, 1.62) for 20 μg/m³ change 1.07 (CI 0.57, 2.02) for 20 μg/m³ change	Hoek & Brunekreef (1994)
Wijk aan zee, the Netherlands 1993	PM_{10} (24-hour average)	53.7 (4.4–137.1)	32 Adults with obstructive airway disease (26–79 years)	**Wheeze** Odds ratio for 2-day lag 1.49 (0.94, 2.36)	Dusseldorp *et al.* (1995)
Deurine & Enkhuizen, the Netherlands Spring/summer 1989	PM_{10} (24-hour average)	Deurne 48 (13–124) Enkhuizen 36 (11–136)	300 Children (7–11 years)	No association for symptomatic or asymptomatic children	Hoek & Brunekreef (1995)

Table 3.13 continued

Study location/ period	Particles measured	Mean (range) (μg/m^3)	Subjects	Results	Reference
Erfurt, eastern Germany	(5-day mean)		27 Adult asthmatics	Odds ratio for 'feeling ill during day' (taken to denote lower respiratory symptomology)	Peters *et al.* (1997)
1991–1992	PM_{10}	60		1.47 (CI 1.16, 1.86) per 50 μg/m^3	
	$NC_{0.01–2.5}$	17 130		1.39 (CI 1.15, 1.68) per 10580 cm^3	
	$NC_{0.01–0.1}$	12 920		1.44 (CI 1.15, 1.81) per 9200 cm^3	
	$NC_{0.1–0.5}$	4140		1.23 (CI 1.07, 1.42) per 3000 cm^3	
	$NC_{0.5–2.5}$	37		1.20 (CI 1.04, 1.39) per 44 cm^3	
	$MC_{0.01–2.5}$	53.1		1.21 (CI 1.06, 1.38) per 50 μg/m^3	
	$MC_{0.01–0.1}$	0.7		1.33 (CI 1.12, 1.58) per 0.5 μg/m^3	
	$MC_{0.1–0.5}$	44.5		1.19 (CI 1.05, 1.35) per 39.7 μg/m^3	
	$MC_{0.5–2.5}$	7.7		1.25 (CI 1.06, 1.46) per 9.9 μg/m^3	

BS, Black smoke; CI, Confidence interval; MC, Mass concentration; NC, Number concentration; SE, Standard error of the mean

Table 3.14 Summary of studies investigating the relationship between short-term changes in ambient particle level and cough

Study location/ period	Particles measured	Mean (μg/m³)	Subjects	Findings	Reference
US studies					
Utah Valley, UT 1990–1991	PM_{10} (24-hour)	Range of means 7–251	Children (10–12 years) 39 symptomatic and 40 asymptomatic	Logistic regression coefficient (x100) for symptoms Symptomatics Asymptomatics Current day 0.506 (SE 0.143) 0.334 (SE 0.173) 5-day av. 0.706 (SE 0.198) 0.605 (SE 0.243)	Pope & Dockery (1992)
Uniontown, PA 1990	Particle strong acidity (12-hour average)	64.7 nmol/m³ (night) 139.4 nmol/m³ (day)	Children 71 symptomatic and 27 asymptomatic	Adjusted for time outdoors in previous 12 hours Evening cough increase per 12-hour exposure to an increase of 125 nmol/m³ 1.6 (CI 1.1, 2.4) all children	Neas *et al.* (1995)
Los Angeles, CAL 1992	PM_{10} (24-hour average)	55.87 (19.63–101.42)	41 Afro-American asthmatic children (7–12 years)	No association between cough and exposure (assessed for mean exposure)	Ostro *et al.* (1995)
Harvard Six Cities Study April–August of one year during 1984–1987	(24-hour average) PM_{10} $PM_{2.5}$ $PM_{2.5}$ sulphur	 30.0 18.0 2.5	1844 Elementary school children	Analyses allowed for temperature, day of week and location Odds ratio for previous 72-hour exposure 1.28 (CI 1.07, 1.54) per 30 μg/m³ 1.19 (CI 1.01, 1.42) per 20 μg/m³ 1.23 (CI 0.95, 1.59) per 5 μg/m³	Schwartz *et al.* (1994)
European studies					
Wageningen & Bennekom, the Netherlands Winter 1990–1991	(daily mean) PM_{10} BS	 NR NR	73 Children with chronic respiratory symptoms	Regression coefficient for concentration on day 0.000 0.014	Roemer *et al.* (1993)
Dutch towns Deurne & Enkhuizen Venlo Nijmegen Various periods winter 1987–1990	 PM_{10} Fine SO_4 particles Fine NO_3 particles (24-hour average)	 44.9 (14.1–126.1) 6.7 (0.0–29.7) 7.3 (0.9–36.8)	695 Children (7–11 years)	Odds ratio for 1 day lag 0.94 (CI 0.57, 1.55) for 100 μg/m³ change 0.96 (CI 0.62, 1.51) for 20 μg/m³ change 0.54 (CI 0.30, 0.97) for 20 μg/m³ change	Hoek & Brunekreef (1994)
Wijk aan zee, the Netherlands 1993	PM_{10}	53.7 (4.4–137.1)	32 Adults with obstructive airway disease (26–79 years)	Odds ratio for no lag 1.31 (CI 0.94, 2.36) per 100 μg/m³	Dusseldorp *et al.* (1995)
Deurne & Enkhuizen, the Netherlands Spring/summer 1989	PM_{10} (24-hour average)	Deurne 48 (13–124) Enkhuizen 36 (11–136)	300 Children (7–11 years)	No association for symptomatic or asymptomatic children	Hoek & Brunekreef (1995)

Table 3.14 continued

Study location/ period	Particles measured	Mean (μg/m^3)	Subjects	Findings	Reference
Erfurt, eastern Germany 1991–1992	(5-day mean)		27 Adult asthmatics	Odds ratio of cough	Peters *et al.* (1997)
	PM_{10}	60		1.30 (CI 1.09, 1.55) per 50 μg/m^3	
	$NC_{0.01–2.5}$	17130		1.17 (CI 1.01, 1.37) per 10580 cm^3	
	$NC_{0.01–0.1}$	12920		1.26 (CI 1.06, 1.50) per 9200 cm^3	
	$NC_{0.1–0.5}$	4140		1.03 (CI 0.91, 1.16) per 3000 cm^3	
	$NC_{0.5–2.5}$	37		1.06 (CI 0.98, 1.20) per 44 cm^3	
	$MC_{0.01–2.5}$	53.1		1.02 (CI 0.91, 1.15) per 50 μg/m^3	
	$MC_{0.01–0.1}$	0.7		1.13 (CI 0.98, 1.30) per 0.5 μg/m^3	
	$MC_{0.1–0.5}$	44.5		1.02 (CI 0.91, 1.14) per 39.7 μg/m^3	
	$MC_{0.5–2.5}$	7.7		1.05 (CI 0.92, 1.21) per 9.9μg/m^3	

NR, not reported; CI, Confidence interval; SE, Standard error of the mean

3.2.5 Estimates of public health impact of short-term effects

Based on the available studies, several authors have estimated the impact on health of short-term exposures to airborne particulates, although specific causative agents (whether constituents of particles or co-pollutants) or mechanisms have not been identified.

NILU (1996) estimated an increased risk per 10 μg/m^3 (24-hour mean) rise in PM_{10}, under western European conditions, of 0.8% in cardiovascular mortality, which is considerable, although less than the 1.2% increased risk for respiratory disease, and 0.5% for hospital or ER admission for respiratory conditions. NILU (1996) also estimated a 0.1% reduction in lung function and a 5% exacerbation of asthma symptoms per 10 μg/m^3 increase in PM_{10}.

Ostro *et al.* (1996) estimated that urban particle levels in North America and Europe may be associated with increases of 2 to 5% in hospital admissions for asthma and 5 to 10% for ER visits.

Pope *et al*. (1995b), while noting that declines in lung function of up to 7% could occur at outdoor PM_{10} levels above 150 μg/m^3, concluded that over the short term a 10 μg/m^3 increase was associated with less than 1% reduction in lung function.

Brunekreef (1998) has estimated the effects on health for a population of 1 million of a 3-day period characterised by mean PM_{10} levels of 50 or 100 μg/m^3 (see Table 3.15).

COMEAP (1998) however, considers that, at present, it is prudent only to derive quantitative estimates of the magnitude of effects within the UK where these can be based on exposure–response relationships that can confidently be applied to the UK situation and where there are adequate data on the distribution of air pollutant levels across the country, suitable for combination with data on the population to provide estimates of the population exposure. Given these limitations COMEAP has proposed provisional estimates of the effect in the UK for two health endpoints, death from any cause and hospital admissions attributable to respiratory disease (see Table 3.15).

Table 3.15 Estimated effects of particle exposure on health

Health endpoint	Effect for stated level or change in level of particles		Reference
	No. of subjects per million affected by 3-day episode of PM_{10} at:		Brunekreef (1998)
	50 μg/m^3	100 μg/m^3	
Mortality	3.5	7	
Respiratory hospital admissions	3	6	
Person-days of bronchodilator use	5100	10 200	
Person-days of symptom exacerbation	6000	12 000	
	% Increase per 10 μg/m^3 increase in 24-hour mean PM_{10}		COMEAP (1998)
Deaths (all causes)	0.75		
Hospital admissions for respiratory causes	0.8		

3.2.6 Potential effects of long-term exposure to particles

Assessing the potential effects of long-term exposure to particles is problematic owing to the lack of adequate historical data, the potential for changes in atmospheric pollution levels and composition over time, the influence of weather, within area differences in exposure patterns and the effect of population migration into or out of an area over time. It is also feasible that exposure to specific high level pollution episodes could elicit long-term effects or that susceptibility to pollution may vary depending upon life stage. Confounding variables are also more difficult to address than for studies of acute effects. Factors such as lifetime experience of acute illnesses, which are often linked to socioeconomic circumstance, availability of medical services and smoking history may all influence the development of chronic disease and are frequently poorly documented. Parental occupation may also influence childhood exposure (i.e. para-occupational exposure, as noted by Sterling *et al.,* 1995). Few studies have addressed the potential impact of indoor particle sources other than ETS (e.g. use of different cooking or heating fuels). Overall, COMEAP (1995a) concluded that few of these aspects can be adequately addressed by current epidemiological studies and that, in general, the reliability of exposure estimates is poor. Despite such reservations, a number of epidemiological studies provide circumstantial evidence for an impact of long-term exposure to airborne particles on human health.

Mortality and morbidity

A number of extensive studies in the USA have addressed the potential impact of long-term differences in particle exposure (e.g., as might exist at different locations) on death and disease rates (Tables 3.16 and 3.17).

When nonneoplastic diseases are considered, both the Harvard Six Cities Study (Dockery *et al*., 1993) and a study of 151 metropolitan areas by Pope *et al*. (1995c) showed similar associations between fine particle ($PM_{2.5}$) levels, and/or sulphate particles and deaths from cardiopulmonary causes.

Abbey *et al*. (1996) reported particularly strong associations between $PM_{2.5}$ or sulphate particles and obstructive airway disease and, particularly in men, asthma; however, chronic bronchitis was better correlated with TSP or PM_{10} level. Fossil fuel combustion is the predominant source of $PM_{2.5}$, including the sulphate fraction, which is commonly generated from primary sulphur emissions during combustion (Pope *et al*., 1995c). More recently, associations between PM_{10} exposure and deaths from nonmalignant respiratory disease and from lung cancer (in men) have been reported for a cohort of 6338 Californian Seventh-Day Adventists (Abbey *et al.,* 1999), although it is of note that a stronger degree of association was noted for lung cancer deaths and ozone exposure.

Data from other studies are limited but, taken together, the available evidence suggests that increases in the incidence of nonneoplastic cardiopulmonary disease and asthma may be associated with long-term exposure to particles. This may not be surprising given the well-documented relationship between short-term particle levels and such diseases.

In an attempt to assess the impact on life expectancy in the Netherlands of ambient particle exposure, Brunekreef (1997) has applied a relative risk factor (1.10 per 10 μg/m^3 $PM_{2.5}$) derived from the US cohort studies to Dutch national mortality data for men aged 25 to 90 years, and calculated that a 10 μg/m^3 reduction in particle level would increase life expectancy by approximately 1.1 years. Although noting the general absence of European cohort or longitudinal studies, COMEAP (1998) refers to preliminary information suggesting that a similar magnitude of effect may occur in the UK, that is 1 year loss in life expectancy per lifelong exposure to 25 μg/m^3 PM_{10}.

In assessing the public health implications of long-term exposure to particles, Brunekreef (1998) has estimated that, for a population of 1 million, increases in long-term exposure to $PM_{2.5}$ of 10 and 20 μg/m^3, over a background of 10 μg/m^3, would be associated with 1200 and 2400 deaths per year, respectively.

Table 3.16 Summary of studies investigating the relationship between long-term ambient particle exposures and mortality rates

Study area/period	Particles measured	Mean (μg/m^3)	Results		Reference
US prospective cohort studies					
Harvard Six Cities Study 1974–1989			Adjusted for age, sex, smoking, education and body-mass index Mortality ratios for most vs least polluted city		Dockery *et al.* (1993)
	$PM_{2.5}$	For years 1979–1985 29.6 (Most polluted city) 11.0 (Least polluted city)	**All causes** **Lung cancer** **Cardiopulmonary** **Other**	1.26 (CI 1.08, 1.47) 1.37 (CI 0.81, 2.31) 1.37 (CI 1.11, 1.68) 1.01 (CI 0.79, 1.30)	
	Inhalable particles	For years 1979–1985 46.5 (Most polluted city) 18.2 (Least polluted city)	**All causes**	1.27 (CI 1.08, 1.48)	
	SO_4 particles	For years 1979–1984 12.8 (Most polluted city) 4.8 (Least polluted city)	**All causes**	1.26 (CI 1.08, 1.47)	
151 US metropolitan areas 1980–1989			Adjusted for age, sex, active or passive tobacco smoking, body-mass index, alcohol consumption, education and occupation Mortality ratios for most versus least polluted area		Pope *et al.* (1995c)
	$PM_{2.5}$	For years 1982–1989 33.5 (Most polluted) 9.0 (Least polluted)	**All causes** **Lung cancer** **Cardiopulmonary**	1.17 (CI 1.09, 1.26) 1.03 (CI 0.80, 1.33) 1.31 (CI 1.17, 1.46)	
	SO_4 particles	For years 1982–1989 23.5 (Most polluted) 3.6 (Least polluted)	**All causes** **Lung cancer** **Cardiopulmonary**	1.15 (CI 1.09, 1.22) 1.36 (CI 1.11, 1.66) 1.26 (CI 1.10, 1.37)	
California 1977–1992	PM_{10}		Adjusted relative risk for exposure to interquartile range difference of 43 days/year of PM_{10} exceeding 100 mg/m^3 **Nonmalignant respiratory disease** **Lung cancer** (males)	 1.18 (CI 1.02, 1.36) 2.38 (CI 1.42, 3.97)	Abbey et *al.* (1999)

Table 3.17 Summary of studies investigating the relationship between long-term ambient particle exposures and disease rates

Study area/period	Particles measured	Mean (μg/m³)	Results	Reference
US prospective cohort study			Relative risk for exposure to	Abbey *et al.* (1996)
California 1977–1982	TSP		200 μg/m³ for 42 days/year **AOD** 1.36 (CI 1.11, 1.66) **CB** 1.33 (CI 1.07, 1.65) **AS** 1.74 (CI 1.11, 2.71) **FC** 1.37 (CI 1.05, 1.80) **RC** 1.72 (CI 0.81, 3.65)	
	PM_{10}		100 μg/m³ for 42 days/year **AOD** 1.17 (CI 1.02, 1.33) **CB** 1.17 (CI 1.01, 1.35) **AS** 1.30 (CI 0.97, 1.73) **FC** 1.15 (CI 0.97, 1.38) **RC** 1.46 (CI 0.88, 2.40)	
	$PM_{2.5}$		Average annual increase of 45 μg/m³ **AOD** 1.46 (CI 0.48, 2.46) **CB** 1.81 (CI 0.98, 3.25) **AS** 1.41 (CI 0.47, 4.0) **FC** 2.01 (CI 1.05, 3.86)	
	SO_4 particles		Average annual increase of 7 μg/m³ **AOD** 1.43 (CI 0.88, 2.26) **CB** 0.96 (CI 0.58, 1.55) **AS** 2.85 (CI 1.03, 7.40)	
European cross-sectional study				
Romanian ferrous producing industrial area compared with control area	TSP	Range of annual means 54.2–83.9	Incidence of condition among children, aged 7—11 years (1084 exposed, 715 controls) Polluted : Control **Bronchitis/pneumonia** 52.1% : 42.3% **Chronic rhinitis** 21.4% : 10.2% **Acute rhinitis** 14.1% : 6.4%	Cucu *et al.* (1995)
Other cross-sectional study				
3 Areas (residential, suburban and industrial) of Beijing, China 1986	Total inhalable particles		Analysis adjusted for age, height, sex, education, income, number in home, occupation, passive smoking Odds ratio for condition among 1576 adults who never smoked	Xu & Wang (1993)
		Outdoor Residential (R) 230 ± 58, Suburban (S) 151 ± 57, Industrial (I) 256 ± 76	Area of high vs low outdoor particle levels — **Bronchitis** 1.9 (1.1, 3.2); **Asthma** 1.0 (0.4, 2.5)	
		Indoor, coal cooking R 90 ± 99, S 41 ± 57, I 152 ± 209	Use of coal cooking & heating — 2.4 (1.4, 4.1); 0.9 (0.4, 2.2)	
		Indoor, gas cooking R 60 ± 69, S 25 ± 27, I 99 ± 85 (Over 16–35 measurement occasions)		

AOD, Airway obstructive disease; AS, Asthma; CI, Confidence interval; CB, Chronic bronchitis; FC, Cancer in females; RC, Respiratory tract cancer

Lung function and respiratory symptoms

Although not shown by all studies, there is evidence that long-term differences in ambient particle levels may be associated with differences in measures of lung function (Table 3.18) and in the incidence of respiratory symptoms (Tables 3.19 to 3.21). Effects have been reported among both adults and children, for a range of particle measures, again including particles arising from fossil fuel combustion sources (e.g. Raizenne *et al.*, 1996). Studies of respiratory symptoms suggest that children, especially asthmatic children, may be particularly sensitive to long-term high ambient particle levels. Reductions in pulmonary function among children from communities where ambient particle levels are high are a cause for concern. If such effects were to be maintained throughout the period of lung growth, these children could be disadvantaged later in life (Raizenne *et al.,* 1996).

Studies from Beijing (Xu *et al.*, 1991; Xu & Wang, 1993), which include health effects associated with indoor exposures (such as increased severity of impairment of lung function and increased incidence of asthma or bronchitis), although relating to much higher levels of particle exposure than those encountered in more developed countries, demonstrate that the use of coal for cooking or heating can have a demonstrable health impact. Thus, as for short-term health effects, health effects are not simply related to outdoor concentrations; consideration of possible indoor sources is also required, as recognised by COMEAP (1995a).

A number of attempts have been made to assess the overall risk associated with long-term exposure to particles. An increase of 10 μg/m^3 PM_{10} has been estimated to cause increases of approximately 10–25% in bronchitis, 10–25% in chronic cough (Pope *et al.*, 1995a), 3% in lower respiratory tract symptoms and 1.2% in cough (COMEAP, 1995a). Brunekreef (1998) has estimated that, for a population of 1 million, an increase in level of $PM_{2.5}$ of 10 μg/m^3 above a background of 10 μg/m^3 would be associated with 3350 additional children per year with bronchitis symptoms and 4000 additional children per year with reduced lung function (<85% predicted FVC or FEV_1) and that $PM_{2.5}$ levels 20 μg/m^3 above such a background would be associated with 6700 additional children per year with bronchitis symptoms and 8000 additional children with reduced lung function.

Cancer

US studies suggest that cancer incidence, especially for cancer of the respiratory system, may be linked to long-term exposure to particles (See reviews by Cohen & Pope, 1995; Walters & Ayres, 1996). Cohen and Pope (1995) suggested that differences in the apparent magnitude of lung cancer risk were associated with exposure to air pollutants from different combustion sources, each producing carcinogenic and mutagenic chemicals (e.g. cigarette smoke, burning of coal, diesel, or wood, or mixtures of commercial/industrial origin). Walters and Ayres (1996) noted that some chemicals present in urban air are known carcinogens (e.g. benzene and polycyclic aromatic hydrocarbons (PAHs)), which are present in or absorb onto particles from sources as diverse as coal burning, vehicle exhaust emission or tobacco smoke. An association between air pollution and lung cancer has also been observed in Cracow, Poland (Jedrychowski, 1995), where it has been suggested that there may be a multiplicative effect between occupational and outdoor sources and tobacco smoke. However, despite the above conclusions, others have questioned the consistency of the relationship between particle exposure and cancer. COMEAP (1995a) concluded that the risk of lung cancer from exposures at ambient (nonoccupational) levels is exceedingly small.

Table 3.18 Summary of studies investigating the relationship between long-term ambient particle exposures and lung function

Study area/period	Particles measured	Mean (μg/m³)	Subjects	Results	References
North American studies					
Harvard Six Cities Study 1974–1979	TSP SO_4 particles	Range 39.3–114.1 Range 5.4–18.8	8327 Children (6–9 years at entry) asthmatics and nonasthmatics	Analysis adjusted for sex, age, height, maternal smoking and parental education FVC and FEV_1 not associated with either TSP or SO_4 particle level	Ware *et al.* (1986)
Harvard Six Cities Study 1980–1981	TSP, PM_{15}, $PM_{2.5}$, Fine SO_4 particles	Average of monthly mean TSP Range 34.1–80.0	5422 Children (10–12 years at entry) asthmatics and nonasthmatics	Adjusted for sex, height, age, parental education, maternal smoking, gas stove use, and city FVC, FEV_1, $FEV_{0.75}$ & MMEF not associated with particle level	Dockery *et al.* (1989)
24 US/Canadian regions 1988–1991			10 251 Children (8–12 years)	Analysis adjusted for age, sex, height and weight	Raizenne *et al.* (1996)
				% FVC decrement / % FEV_1 change	
	PM_{10}	23.8 (15.4–32.7)		per 17.3 μg/m³: -2.42 (CI -4.30, -0.51) / -2.09 (CI -4.00, -0.14)	
	$PM_{2.1}$	14.5 (5.8–20.7)		per 14.9 μg/m³: -3.21 (CI -4.98, -1.41) / -2.81 (CI -4.66, -0.94)	
	SO_4 particles	4.7 (0.7–7.4)		per 6.8 μg/m³: -3.06 (CI -4.50, -1.59) / -2.63 (CI -4.18, -1.05)	
	Particle strong acidity	27.5 (0.0–51.9) nmol/m³		per 53 nmol/m³: -3.45 (CI -4.87, -2.01) / -3.11 (CI -4.62, -1.58)	
California 1977–1993	PM_{10}		1391 Nonsmoking adults	Effect of PM_{10} exceeding 100 μg/m³ for 54 more days per year in area in which subject lived FEV_1 7.2% decrease in males with family history of respiratory disease Peakflow decrease of 0.6% males, 0.8% females	Abbey *et al.* (1998)
European studies					
Austrian city Winters over 5-year period	TSP	58.5 ± 19.23 mg/m³	Children (7–12 years; 7561 boys & 7484 girls)	% Increase among children with impairment* for a 2 x SD increase in level FVC 14 FEV_1 19 PEF 49 MEF_{75} 20 MEF_{50} 12 MEF_{25} 26	Neuberger *et al.* (1995)
8 Areas of Switzerland 1993	PM_{10}	21.2 (10.1–33.4)	9651 Adults (18–60 years)	Analysis adjusted for age, sex, education, height, weight, work and smoking % Change in lung function for 10 μg/m³ increase All / Current smokers / Healthy never-smokers FVC: -3.14 / -3.21 / -3.39 FEV_1: -1.03 / -1.35 / -1.59	Ackermann-Liebrich *et al.* (1997)

Table 3.18 continued

Study area/period	Particles measured	Mean (μg/m³)	Subjects	Results			References
Other study							
3 Areas of Beijing, China 1986	TSP	Annual mean Residential 389 Suburban 261 Industrial 449	1440 Adults, never smokers (40–69 years)	Multiple linear regression analysis adjusted for age, height and sex			Xu *et al.* (1991)
					FVC	FEV_1	
				Effect of per unit increase in TSP (μg/m³)	-478.7 ml	-131.4 ml	
				Effect of heating with coal	-84 ± 41 ml	-91 ± 36 ml	

* Significant impairment defined as 13 ml reduction in FVC for male or female subjects, 16 ml reduction in FEV_1 for male or female, 130 ml and 123 ml reduction in MEF_{50} for males and females respectively, 99 ml and 94 ml reduction in MEF_{75} for male and female respectively, 43 ml reduction in MEF_{50} for males or females, 39 ml or 41 ml reduction for MEF_{25} for males and females respectively

CI, Confidence interval; FVC, Forced vital capacity; FEV_1 or $_{0.75}$, Forced expiratory volume in 1 or 0.75 seconds; MMEF, Maximal midexpiratory flow; PEFR, Peak expiratory flow rate; SD, Standard deviation

Table 3.19 Summary of studies investigating the relationship between long-term ambient particle level and upper respiratory symptoms

Study area/period	Particles measured	Mean (μg/m^3)	Subjects	Results	References
European studies					
Leipzig, Germany 1991–1992	PM (unspecified)		1492 Children (9–11 years)	Analysis allowed for parental education, passive smoking, no. siblings, temperature and humidity Odds ratios for symptoms recorded by physician High daily mean PM level 1.62 (CI 1.08, 2.45) Low PM level 1.13 (CI 0.75, 1.70)	von Mutius *et al.* (1995)
10 Areas, Switzerland 1992–1993	PM_{10}	Range of annual means 10–33	4470 Children (6–14 years)	Analysis adjusted for age, sex, low birthweight, family history/education, number siblings, indoor fuel use and carpeting Relative odds for 23 μg/m^3 increase **Sneezing** in pollen season: No family history of asthma/atopy 0.59 (CI 0.24, 1.44); Family history of asthma/atopy 1.23 (CI 0.56, 2.67) **Hay fever**: 0.44 (CI 0.20, 0.94); 1.21 (CI 0.60, 2.42) **Conjunctivitis symptoms**: 1.74 (CI 0.88, 3.43); 2.43 (CI 1.20, 4.93)	Braun-Fahrlander *et al.* (1997)

CI, Confidence interval

Table 3.20 Summary of studies investigating the relationship between long-term ambient particle level and lower respiratory symptoms

Study area/period	Particles measured	Mean (μg/m³)	Subjects	Results	References
North American studies					
Harvard Six Cities Study 1974–1977	TSP	Range 39.3–114.1	8327 Children (6–9 years at entry) asthmatics and non-asthmatics	Analysis adjusted for age, sex, maternal smoking and parental education Odds ratio for 10 μg/m³ increase in TSP **Bronchitis** 1.11 **Lower respiratory symptoms** 1.08 ($p<0.05$)	Ware *et al.* (1986)
California 1977–1987	$PM_{2.5}$ (visibility based)		1868 Seventh-day Adventist adults	Odds ratio per 45 μg/m³ increase in $PM_{2.5}$ **Chronic bronchitis** 1.81 (CI 0.98, 3.25) **Asthma** 1.41 (CI 0.47, 4.06) **AOD** 1.46 (CI 0.84, 2.46)	Abbey *et al.* (1995a)
California 1977–1987	PM_{10} (TSP derived)		3914 Seventh-day Adventist adults	Analysis adjusted for sex, age and education Odds ratio for 1000 hours per year in excess of 100 μg/m³ PM_{10} for development of characteristic symptoms **Chronic bronchitis** 1.17 (CI 1.01, 1.35) **Asthma** 1.30 (CI 0.97, 1.73) **AOD** 1.17 (CI 1.02, 1.33)	Abbey *et al.* (1995b)
Harvard Six Cities Study 1980–1981	TSP, PM_{15}, $PM_{2.5}$, Fine SO_4 particles	Average of monthly mean TSP Range 34.1–80.0	5422 Children (10–12 years at entry) asthmatics and nonasthmatics	Analysis adjusted for sex, parental education, maternal smoking, gas stove use and city Odds ratio for least vs most polluted city **Bronchitis** / **no A/W**: TSP 2.0 (CI 0.9, 4.7); PM_{15} 2.2 (CI 1.1, 4.2); $PM_{2.5}$ 1.8 (CI 0.8, 4.3); Fine SO_4 1.7 (CI 0.6, 4.7) **Bronchitis** / **A/W**: TSP 3.2 (CI 0.6, 18.1); PM_{15} 3.8 (CI 0.9, 15.5); $PM_{2.5}$ 3.5 (CI 0.9, 13.2); Fine SO_4 3.1 (CI 0.6, 16.8) **Persistent wheeze***: TSP 1.1 (CI 0.5, 2.5); PM_{15} 1.2 (CI 0.5, 2.6); $PM_{2.5}$ 1.0 (CI 0.5, 2.2); Fine SO_4 1.0 (CI 0.4, 2.2) **Asthma**: TSP 0.7 (CI 0.3, 1.9); PM_{15} 0.7 (CI 0.3, 2.0); $PM_{2.5}$ 0.6 (CI 0.3, 1.4); Fine SO_4 0.6 (CI 0.3, 1.4)	Dockery *et al.* (1989)
24 US/Canadian regions 1988–1991	PM_{10} $PM_{2.1}$ $PM_{2.1}$ sulphate Particle strong acidity	23.8 ± 5.0 14.5 ± 4.2 4.7 ± 2.2 27.5 ± 16.2 nmol/m³	13 369 Children (8–12 years)	Analyses adjusted for sex, allergy history, parental education and allergy and smoking in home Odds ratio for **Asthma** / **Persistent wheeze** / **Bronchitis** / **Chronic phlegm** per 17.3 μg/m³: 0.77 (CI 0.44, 1.35); 0.75 (CI 0.53, 1.07); 1.50 (CI 0.93, 2.43); 1.05 (CI 0.64, 1.72) per 14.9 μg/m³: 0.72 (CI 0.40, 1.28); 0.80 (CI 0.55, 1.16); 1.50 (CI 0.91, 2.47); 1.02 (CI 0.61, 1.73) per 6.8 μg/m³: 0.80 (CI 0.50, 1.29); 0.96 (CI 0.70, 1.31); 1.65 (CI 1.12, 2.42); 1.29 (CI 0.84, 1.96) per 53 nmol/m³: 0.71 (CI 0.43, 1.16); 0.83 (CI 0.60, 1.15); 1.66 (CI 1.11, 2.48); 0.95 (CI 0.60, 1.49)	Dockery *et al.* (1996)

Table 3.20 continued

Study area/period	Particles measured	Mean (µg/m³)	Subjects	Results	References
European study					
10 Areas, Switzerland 1992–1993	PM_{10}	Range of annual means 10–33	4470 Children (6–14 years)	Analysis adjusted for age, sex, low birthweight, family history/education, number siblings, indoor fuel use and carpeting Relative odds for 23 µg/m³ increase **Bronchitis**: No family history of asthma/atopy 1.84 (CI 0.85, 4.00); Family history of asthma/atopy 2.79 (CI 1.14, 6.79) **Wheeze**: 1.03 (CI 0.40, 2.67); 0.99 (CI 0.44, 2.26) **Asthma**: 1.81 (CI 0.66, 5.01); 0.37 (CI 0.17, 0.81)	Braun-Fahrlander *et al.* (1997)
Other study					
3 Areas of Beijing, China 1986	Total inhalable particles	Outdoor Residential (R) 230 ± 58 Suburban (S) 151 ± 57 Industrial (I) 256 ± 76 Indoor, coal cooking R 90 ± 99; S 41 ± 57; I 152 ± 209; Indoor, gas cooking R 60 ± 69; S 25 ± 27; I 99 ± 85	1576 adults who never smoked (40–69 years)	Analysis adjusted for age, height, sex, educational level, income, number in home, occupation and passive smoking. Odds ratio (CI) **Wheeze**: High vs low outdoor particle level 2.1 (1.2, 3.9); Use of coal cooking/heating 2.7 (1.3, 5.4) **Shortness of breath**: 1.6 (0.8, 3.1); 1.7 (0.9, 3.3)	Xu & Wang (1993)

* no correction for previous history

AOD, Airway obstructive disease; A/W, pre-existing asthma or wheeze; CI, Confidence interval

Table 3.21 Summary of studies investigating the relationship between long-term ambient particle level and cough

Study area/period	Particles measured	Mean (μg/m³)	Subjects	Results	Reference
North American studies					
Harvard Six Cities Study 1974–1977	TSP	Range 39.3–114.1	8327 Children (6–9 years at entry) asthmatics and nonasthmatics	Analysis adjusted for age, sex, maternal smoking and parental education. Odds ratio for persistent cough for 10 μg/m³ increase in TSP 1.11 ($p<0.01$)	Ware *et al.* (1986)
Harvard Six Cities Study 1980–1981	TSP, PM_{15}, $PM_{2.5}$, Fine SO_4 particles	Average of monthly mean TSP Range 34.1–80.0	5422 Children (10–12 years at entry) asthmatics and nonasthmatics	Analysis adjusted for sex, parental education, maternal smoking, gas stove use and city Odds ratio for chronic cough for least vs most polluted city No A/W / A/W TSP 4.1 (CI 1.6, 10.3) / 4.0 (CI 0.2, 78.2) PM_{15} 4.1 (CI 1.9, 9.2) / 5.0 (CI 0.4, 71.6) $PM_{2.5}$ 3.0 (CI 0.9, 10.7) / 2.4 (CI 0.1, 49.5) Fine SO_4 2.9 (CI 0.6, 13.1) / 2.4 (CI 0.1, 60.6)	Dockery *et al.* (1989)
24 US/Canadian regions 1988–1991	PM_{10} $PM_{2.1}$ $PM_{2.1}$ sulphate Particle strong acidity	23.8–5.0 14.5–4.2 4.7–2.2 27.5–16.2 nmol/m³	13 369 Children (8–12 years)	Analyses adjusted for sex, allergy history, parental education and allergy, and smoking in home. Odds ratio for persistent cough per 17.3 μg/m³ 0.69 (CI 0.48, 0.99) per 14.9 μg/m³ 0.82 (CI 0.54, 1.23) per 6.8 μg/m³ 1.04 (CI 0.74, 1.47) per 53 nmol/m³ 0.92 (CI 0.64, 1.31)	Dockery *et al.* (1996)
European studies					
Romanian ferrous producing industrial area compared with control area	TSP	Range of annual means 54.2–83.9	1084 Exposed children, 715 controls (7–11 years)	Prevalence for Polluted : Control **Morning cough** 25.67% : 11.75% **Persistent cough** 25.29% : 11.05%	Cucu *et al.* (1995)
10 Areas, Switzerland 1992–1993	PM_{10}	Range of annual means 10–33	4470 Children (6–14 years)	Analysis adjusted for age, sex, low birthweight, family history/education, number siblings, indoor fuel use and carpeting Relative odds for 23 μg/m³ increase No family history of asthma/atopy 2.28 (CI 0.98, 5.32) Family history of asthma/atopy 5.00 (CI 1.87, 13.35)	Braun-Fahrlander *et al.* (1997)
Other study					
3 Areas of Beijing, China 1986	Total inhalable particles	Outdoor Residential (R) 230 ± 58, Suburban (S) 151 ± 57, Industrial (I) 256 ± 76 Indoor coal cooking R 90 ± 99, S 41 ± 57, I 152 ± 209 Indoor gas cooking R 60 ± 69, S 25 ± 27, I 99 ± 85	1576 Adults who never smoked (40–69 years)	Analysis adjusted for age, height, sex, educational level, income, number in home, occupation and passive smoking. Odds ratio High vs low outdoor particle level, 2.0 (CI 1.1, 3.5) Use of coal cooking/heating, 1.8 (CI 1.0, 3.3)	Xu & Wang (1993)

A/W, pre-existing asthma or wheeze; CI, Confidence interval

Table 3.22 Summary of studies on the potential influence of particle exposure on pregnancy and infant mortality

Exposure	Health effect		Reference
Pregnancy			
Use of coal stoves for heating, China	Odds ratio for low birth weight (<2900 g) or preterm birth 1.40 (CI 1.03, 1.91)		Xu *et al.* (1994)
TSP exposure, China	For each 100 μg/m^3 increase in TSP – reduction of 0.042 weeks in gestation length Odds ratio for preterm delivery 1.10 (CI 1.01, 1.20)		Xu *et al.* (1995)
TSP exposure, China	For each 100 μg/m^3 increase in TSP – Odds ratio for low birth weight (<2500 g) 1.10 (CI 1.05, 1.14)		Wang *et al.* (1997a)
Infant mortality			
TSP exposure for 397 090 live births in 46 districts of the Czech Republic 1986–1988		Relative risk of highest (>84.7 μg/m^3) compared with lowest (<53.6 μg/m^3) quintile of TSP	Bobak & Leon (1992)
	Death		
	Neonatal	1.17 (CI 0.99, 1.40)	
	Postneonatal	1.42 (CI 1.09, 1.84)	
	Postneonatal-respiratory	2.41 (CI 1.10, 5.28)	
PM_{10} postnatal exposure for 3 788 079 live births in USA 1989–1991	**Postnatal death**	Odds ratio for 10 μg/m^3 change in PM_{10}	Woodruff *et al.* (1997)
	Any cause	1.04 (CI 1.02, 1.07)	
	SIDS (NBW)	1.12 (CI 1.07, 1.17)	
	Respiratory (NBW)	1.20 (CI 1.06, 1.36)	
	Respiratory (LBW)	1.05 (CI 0.91, 1.22)	
	Other	1.00 (CI 0.99, 1.00)	

CI, Confidence interval; LBW, Low birth weight (<2.5 kg); NBW, Normal birth weight; SIDS, Sudden infant death syndrome

3.2.7 Other health effects

In considering the potential dangers of particle exposure, other nonrespiratory health endpoints also require consideration. For example, ETS forms a significant component of particulate exposure in homes with a smoker present, and the potential dangers of passive smoke exposure are widely recognised (e.g. Charlton, 1994; Law *et al.*, 1997; Hackshaw *et al.,* 1997). There are also indications from studies in China that ambient maternal exposure to high particle levels may have an effect during pregnancy, possibly resulting in slightly shorter gestation length and reduced birthweights, while studies in the USA and the Czech Republic indicate a possible effect on early infant mortality during the postneonatal period (Table 3.22), although it is unclear if this could be attributable to prenatal developmental effects or as a result of postnatal infant atmospheric exposure.

Such studies, although only preliminary, suggest that concern about the health effects of airborne particles should not focus entirely on the elderly, asthmatics or those with pre-existing cardiovascular or respiratory conditions. Other population subgroups, such as infants, children and pregnant women, should also be considered.

3.3 Human chamber and challenge studies

In controlled chamber or challenge studies, volunteers are given known doses of test materials or are exposed to highly controlled and characterised atmospheres, and a range of endpoints are measured including, for example, lung function, bronchial reactivity, markers of inflammation (e.g. from washings from lungs or nose), and symptoms. There are limitations on the subjects and exposures that can be used in such studies, as potentially harmful investigations among people suspected to be at greatest risk from the effects of particles (i.e. the critically ill or the young) are ethically unacceptable. In addition, for practical reasons, such studies can only be conducted over relatively short periods on small numbers of people. Furthermore, several methodological factors may affect the results of studies; these include technical difficulties in generating suitable particulate test atmospheres, variations in oral ammonia level (derived from undigested food residues) with consequent variations in inhaled acid neutralisation, the presence of buffer in the challenge solution, the effect of temperature and relative humidity on hygroscopic growth of particles, and aerosol osmolarity (COMEAP, 1995a; Walters & Ayres, 1996). Extrapolation from volunteer studies to the situations occurring in everyday life must, therefore, be approached with caution. As such, results from human volunteer studies should be regarded as providing information to aid the interpretation of epidemiological investigations; they may also have a role in identifying suitable biomarkers of effect for use in epidemiological studies.

3.3.1 Investigations of adverse effects of particulate exposure

Many experimental studies in human volunteers have attempted to identify the agents that are responsible for the adverse health effects observed in epidemiology studies. Studying human volunteers overcomes the obvious problems of extrapolation between species that occurs with animal-based models, permits a high level of control of the dosimetry and composition of the material investigated, and facilitates detailed measurement of endpoints. Delivery of controlled doses to subjects, which assists in assessing dose–response relationships, is possible, as is the inclusion of negative (undosed/placebo-dosed) controls, and both normal (asymptomatic) subjects and individuals with defined (but noncritical) disease states can be studied to provide information on differential susceptibility. However, there are limitations to such studies. Cost generally restricts the numbers of subjects, thereby raising concerns about how applicable results may be to the general population or particular subgroups, the ability to mimic the complex mixtures and interactions that occur in real-life situations is limited, and there are practical restrictions on the length of exposure and measurement periods. In addition, compared with animal models, there are practical and ethical constraints on the individuals that can be studied and the exposure levels and techniques that can be used. The results from human volunteer studies are summarised below. A more extensive discussion, including a review of studies to investigate the effects of mixtures of particulate and gaseous pollutants, can be found in COMEAP (1995a). Although beyond the scope of the current review, chamber studies on ETS have demonstrated alterations in lung function and airway reactivity that indicate there may be a subpopulation of asthmatics who are particularly susceptible to the effects of ETS (EPA, 1997); however, because of the chemical complexity of tobacco smoke, the relative importance of the particulate and gaseous phases are uncertain.

Lung function

A considerable number of studies in normal or asthmatic individuals have investigated the effects of exposure to a range of aerosols or particles (Table 3.23). As early as 1952, Amdur *et al*. reported that exposure to sulphuric acid aerosol (average diameter 1 µm) at concentrations of between 350 and 5000 µg/m^3 for 5 to 15 minutes caused reductions in maximum inspiratory and expiratory flow rates of up to 20% and increases in respiratory rate of up to 35%, in healthy male volunteers; at the lower concentrations the changes were considered to be of reflex, not voluntary, origin. Horvath *et al*. (1982) found that a 2-hour exposure to 939 µg/m^3 sulphuric acid aerosol (0.90–0.93 µm diameter), under conditions of light exercise, led to a slight, although statistically significant, reduction in FEV_1 (averaging 101 ml); and

Table 3.23 Summary of human volunteer studies investigating the effects on lung function of exposure to various particles or aerosols

Material/exposure conditions	Subjects		Reference
	Normal/asymptomatic	Asthmatic	
Sulphuric acid aerosol			
1 μm diameter; 350–5000 μg/m^3 for 5–15 minutes	Up to 20% reduction in max. inspiratory/ expiratory flow rates; up to 35% increase in respiratory rate		Amdur *et al.* (1952)
0.58 μm diameter; 1000 μg/m^3 for 2½ hours	1.4% reduction in MMEF; increased bronchial clearance		Newhouse *et al.* (1978)
<1 μm diameter; 10–1000 μg/m^3 for 10 minutes	No significant effect	No significant effect	Sackner *et al.* (1978)
0.3 μm; 100 μg/m^3 for repeated 2-hour exposures	No significant effect	No significant effect	Avol *et al.* (1979)
0.9–0.93 μm diameter; 939 μg/m^3 for 2 hours under light exercise	Average of 101 ml reduction in FEV_1		Horvath *et al.* (1982)
0.6 μm; 100 μg/m^3 for 10 minutes	NR	At rest, no significant effect; after moderate exercise, 40% increase in respiratory resistance, and reductions of 21% in V_{max50}, 29% in V_{max75} and 8% in FEV_1	Koenig *et al.* (1983)
0.6–1.0 μm diameter; 100–1000 μg/m^3 for 16 minutes	NR	At 1000 or 450 μg/m^3 significant reduction in airway conductance	Utell *et al.* (1983)
0.6–1.0 μm diameter; 100–1000 μg/m^3 for 16 minutes	At 1000 μg/m^3, increased bronchial responsiveness to carbachol challenge	Increased bronchial responsiveness to carbachol challenge at all levels	Utell *et al.* (1984)
0.6 μm; up to 410 μg/m^3 for 1 hour		No significant effect	Linn *et al.* (1986)
0.8–0.9 μm; 380–1520 μg/m^3 for 1 hour	No change in pulmonary function, bronchial response to metacholine challenge, or occurrence of irritation	No significant change in bronchial response to metacholine challenge; irritation and reduced respiratory function at exposures of 1060 or 1520 μg/m^3	Avol *et al.* (1988)
0.6 μm; 70 μg/m^3 for 40 minutes	No significant effect on FEV_1 or FVC; after exercise, 6% reduction in respiratory resistance	No significant effect on FEV_1 or FVC; after exercise, 16% increase in respiratory resistance	Koenig *et al.* (1993b)
Ammonium bisulphate			
0.6–1.0 μm diameter; up to 1000 μg/m^3 for 16 minutes	NR	At 1000 μg/m^3 only, 10% reduction in airway conductance but FEV_1 not affected	Utell *et al.* (1983)
0.6–1.0 μm diameter; up to 1000 μg/m^3 for 16 minutes	At 1000 μg/m^3, increased bronchial responsiveness to carbachol challenge	At 1000 μg/m^3, increased bronchial responsiveness to carbachol challenge	Utell *et al.* (1984)
Ammonium sulphate			
0.3 μm diameter; 100 μg/m^3 for 2 hours	No significant effect on lung function	No significant effect on lung function	Avol *et al.* (1979)
0.6–1.0 μm diameter; 10 000 μg/m^3 for 16 minutes	NR	No significant effect on lung function	Utell *et al.* (1983)

Table 3.23 continued

Material/exposure conditions	Subjects		Reference
	Normal/asymptomatic	Asthmatic	
Other particle/aerosol types			
Acetic acid (pH 4), 5.6–6.1 μm diameter for 1 min		Less bronchial response to metacholine challenge than for sodium sulphite – see below	Fine *et al.* (1987)
Ferric sulphate, 75 μg/m^3 for 2 hours	No significant effect	Marked individual differences in response but overall, no significant difference	Kleinman *et al.* (1981)
Hydrochloric acid (gaseous); 0.8–1.8 ppm for 45 minutes		No significant effect	Stevens *et al.* (1992)
Magnesium oxide, fine/ultrafine dust; 5.8–23.0 mg/m^3 for 15–120 min	No significant effect		Kuschner *et al.* (1995, 1997)
Nitric acid (gaseous); 500 μg/m^3 for 4 hours	No significant effect		Aries *et al.* (1993)
Sodium bisulphate, 0.6–1.0 μm; 100–1000 μg/m^3	NR	No significant effect on lung function	Utell *et al.* (1983)
Sodium bisulphate, 0.6–1.0 μm diameter; 100–1000 μg/m^3 for 16 min	No significant effect of carbachol challenge	No significant effect of carbachol challenge	Utell *et al.* (1984)
Sodium nitrate, 0.49 μm diameter; 7000 μg/m^3 for 16 min	No significant effect of carbachol challenge	No significant effect of carbachol challenge	Utell *et al.* (1979)
Sodium sulphite, 5.6–6.1 μm diameter at pH 4, 6.6 or 9; 0.03–10.0 mg/ml for 1 min	NR	Bronchial response to metacholine challenge less for more acidic particles	Fine *et al.* (1987)
Zinc oxide, fine/ultrafine dust; 2.76–37 mg/m^3 for 15–120 min	No significant effect		Kuschner *et al.* (1995, 1997)

FEV_1, Forced expiratory volume in 1 second; FVC, Forced vital capacity; MMEF, Maximal midexpiratory flow; V_{max50} or $_{75}$, Maximum flow calculated at 50% (or75%) of expiratory vital capacity; NR, Not reported

Newhouse *et al.* (1978) found exposure to a 1000 µg/m^3 sulphuric acid aerosol (0.58 µm diameter) for 2$^1/_2$ hours resulted in a marginal reduction (1.4%) in maximum mid-expiratory flow rate (MMEF) and significantly increased bronchial clearance, in healthy volunteers. An increased bronchial responsiveness to carbachol challenge was also noted following exposure of 14 nonasthmatic and 17 asthmatic subjects to sulphuric acid aerosol (0.6–1.0 µm diameter) at 1000 µg/m^3, in a study by Utell *et al.* (1984). At lower exposure levels (450 µg/m^3) effects were apparent only in the asthmatic subjects, while at 100 µg/m^3 only two asthmatic subjects showed any evidence of response; the asthmatic subjects in the study had discontinued bronchodilator therapy for 24 hours before exposure. However, Avol *et al.* (1979) found no significant effects on lung function, among asymptomatic or asthmatic men, following repeated 2-hour exposures to sulphuric acid aerosol (0.3 µm diameter) at 100 µg/m^3, and no effects on airway reactivity following methacholine challenge or irritant symptoms were observed in normal subjects, following 1-hour exposures to sulphuric acid aerosol at concentrations of 380 to 1520 µg/m^3 (target particle sizes of 0.8–0.9 µm diameter; Avol *et al.,* 1988).

In the study by Utell *et al.* (1984) exposure to ammonium bisulphate at 1000 µg/m^3 also increased carbachol response, though no such effect occurred at 450 µg/m^3 or below.

In other studies on several other particulates, no discernible effect on lung function or symptoms has been demonstrated in normal individuals. Studies include exposure of healthy and asthmatic men to ammonium sulphate (0.3 µm diameter) at 100 µg/m^3 for 2 hours (Avol *et al.*, 1979), ammonium bisulphate or ammonium sulphate (0.6–1 µm diameter) at up to 1000 µg/m^3 for 16 minutes (Utell *et al.,* 1983); exposure of healthy men and women to gaseous nitric acid at 500 µg/m^3 for 4 hours (Aris *et al.*, 1993); exposure of normal and asthmatic men to sodium bisulphate (0.6-1.0 µm diameter) at concentrations of between 100 and 1000 µg/m^3 for 16 minutes (Utell *et al.*, 1984); exposure of asymptomatic and asthmatic (medication discontinued for 24 hours before testing) volunteers to sodium nitrate (0.49 µm diameter) at 7000 µg/m^3 for 16 minutes (Utell *et al.*, 1979); and exposure of normal men and women to ferric sulphate aerosol at 75 µg/m^3 for 2 hours [particle size and use of medication by asthmatics not reported] (Kleinman *et al.*, 1981).

Following a 24-hour period of withdrawal of medication, lung function was unaffected in asthmatics exposed to ammonium sulphate at 1000 µg/m^3 for 16 minutes (Utell *et al.,* 1984) or sodium nitrate aerosol (0.49 µm diameter) at 7000 µg/m^3 for 16 minutes (Utell *et al.,* 1979). Similarly, exposure of asthmatics (mostly unmedicated) to gaseous hydrochloric acid at levels of between 0.8 and 1.8 ppm for 45 minutes did not effect lung function (Stevens *et al.,* 1992). However, following exposure of 18 asthmatics (no withdrawal of medication) to an aerosol (2 µm diameter) of ferric sulphate at 75 µg/m^3 for 2 hours, four individuals showed a consistent decrement in lung function, while three others showed the opposite effect, and overall no significant difference was found (Kleinman *et al.,* 1981). Ammonium bisulphate exposure of asthmatic subjects at 1000 µg/m^3 resulted in a 10% reduction in specific airway conductance but not FEV_1 while levels of 450 µg/m^3 or below were without effect (Utell *et al.,* 1983).

From the evidence presented above it is apparent that, at a high enough level of exposure, certain types of acidic particle can elicit responses of potential importance in humans. Fine *et al.* (1987) investigated the importance of pH and ionic species by exposing groups of asthmatic subjects (whose medication had been withdrawn for 12 hours prior to exposure) to nebulized sodium sulphite solutions at pH 9, 6.6 or 4, or to acetic acid solution at pH 4. The mean aerodynamic diameters of the particles generated varied between 5.6 and 6.1 µm. The bronchoconstrictive response, assessed as change in specific airway resistance following methacholine challenge, was dependent on pH for the sulphite aerosols; however, the more acidic acetic acid aerosol was much less effective. The authors therefore suggested that acidity was not in itself the key factor, but that the concentrations of specific ionic species were important.

Koenig and Peirson (1991) noted that asthmatic individuals may be more responsive to sulphuric acid aerosols than healthy subjects. In the study by Avol *et al.* (1988; see above), in contrast to normal subjects,

symptoms of irritation increased in asthmatic subjects exposed to sulphuric acid at high doses (1060 and 1520 µg/m^3), although there was no such effect at the low dose of 380 µg/m^3. It is of interest that some of the asthmatics were clinically unable to withdraw from bronchodilator use in the period before exposure. In another study, although exposure of ten asthmatic adolescents (maintained on methylzanthine medication on the day of exposure) to 100 µg/m^3 sulphuric acid aerosol for ten minutes at rest had no significant effect on lung function, when assessed after moderate exercise statistically significant changes were found, including a 40% increase in respiratory resistance (R_T) and 21, 29 and 8% reductions in maximum flow calculated at 50% and 75% of expiratory vital capacity (V_{max50}, V_{max75}) and FEV_1, respectively (Koenig *et al.*, 1983). Comparing lung function at rest and following light exercise in older (60–76 year-old) asthmatic and nonasthmatic individuals, Koenig *et al.* (1993b) found that 40 minutes exposure to 70 µg/m^3 sulphuric acid aerosol (0.6 µm diameter) had no significant effect on FEV_1 or FVC in either group; however, total respiratory resistance (R_T) increased after exposure to sulphuric acid aerosol by 16% from baseline in the asthmatic subjects and fell by 6% in the normal subjects. In contrast, Sackner *et al.* (1978) observed no significant effect on lung function among normal or asthmatic adults (medication withheld for at least 8 hours before study) exposed to sulphuric acid aerosol (<1 µm diameter) at concentrations of between 10 and 1000 µg/m^3 for 10 minutes; similarly Linn *et al.* (1986) found no significant effect on lung function among asthmatic subjects (medication withdrawn) exposed to sulphuric acid aerosol (0.6 µm) at levels of 410 µg/m^3 or below for 1 hour.

The findings of Utell *et al.* (1984) also suggest that asthmatics may be more susceptible to some particulates than normal individuals and provide some evidence that responses may be dose related. In the study, normal and asthmatic individuals were exposed to aerosols of sulphuric acid, ammonium bisulphate or sodium bisulphate at concentrations of 100, 450 or 1000 µg/m^3 for 16 minutes. Normal subjects exposed to 1000 µg/m^3 of any of the aerosols tested showed significantly potentiated bronchoconstrictor response to carbachol challenge compared with the controls. Significant effects were, however, apparent in a dose-related manner at 450 and 1000 µg/m^3 sulphate among the asthmatic subjects.

Although mechanistic studies (Section 3.4) have led some workers to suggest that activity may be particularly dependent on the ultrafine particle load, Kuschner *et al.* (1995, 1997) demonstrated that, in humans, there were no effects on pulmonary function (or other measures of effect, see below) that could be attributed to exposure to high concentrations of fine (<2.5 µm) and/or ultrafine (<0.1 µm) dusts of zinc and magnesium oxides for periods of 15 to 120 minutes.

Immunological and inflammatory function

Evidence on the immune and inflammatory effects of airborne particles is somewhat limited and inconsistent.

In one study of exposure to diesel exhaust at a high level (43 million particles/cm^3), bronchiolar lavage was performed on eight volunteers 18 hours post exposure, and increased neutrophil numbers but reduced mast cells and alveolar macrophages were observed (Rudell *et al.*, 1990). In another study on diesel exhaust, 15 healthy human volunteers were exposed for 1 hour at a level which achieved a PM_{10} concentration of 300 µg/m^3 (Salvi *et al.,* 1999). Blood samples were taken and bronchoscopy was performed 6 hours after exposure. Neutrophil and B-lymphocyte counts and levels of histamine and fibronectin in bronchoalveolar lavage (BAL) fluid were increased; neutrophil, mast cell, $CD4^+$ and $CD8^+$ lymphocyte and LFA-1+ cell counts were increased, and upregulation of the endothelial adhesion molecules ICAM-1 and VCAM-1 was observed in bronchiolar biopsy samples; neutrophil counts and platelet numbers were increased in peripheral blood. However, there were no associated changes in lung function (assessed by peak expiratory flow rate (PEFR), FVC, FEV_1, forced expiratory flow at 25–75% of vital capacity ($FEF_{25–75\%}$)). As diesel exhaust also contains many gaseous components including oxides of nitrogen, carbon and sulphur, these effects cannot necessarily be attributed to the particulate fraction. However, the authors note that another study using nitrogen dioxide alone, at levels similar to those employed in this study, did not elicit similar cellular inflammatory responses.

A markedly different response to particle exposure was noted after exposure of healthy adult men for 2 hours to sulphuric acid aerosol at 1000 µg/m^3. BAL 18 hours after exposure failed to show any effect on antimicrobial defences and there were no significant changes in cellular composition, superoxide release or influenza virus inactivation, although antibody-mediated macrophage cytotoxicity was slightly raised (Frampton *et al.,* 1992). Similarly, Aris *et al.* (1993) reported no clear evidence for an inflammatory response following exposure of normal subjects to nitric acid at 500 µg/m^3 for 4 hours. Neither BAL nor mainstem lavage revealed any change in the levels of total or differential white cell counts, lactate dehydrogenase activity (a marker of cellular injury), levels of fibronectin (a glycoprotein involved in macrophage migration, phagocytosis and platelet aggregation) or total protein (a marker of increased vascular permeability and oedema).

In volunteers exposed to fine or ultrafine metal oxide dusts, Kuschner *et al.* (1995, 1997) examined total and differential cell counts in peripheral blood and cell counts and a range of cytokine markers of inflammatory response (tumour necrosis factor-α (TNF), interleukin (IL)-1ß, IL-6, & IL-8) in BAL. Magnesium oxide dust did not produce any significant effect on either peripheral blood or BAL. In contrast, exposure to ultrafine zinc oxide dust resulted in dose-related increases in polymorphonuclear leukocytes, IL-8 and TNF and a slight (nonsignificant) change in peripheral polymorphonuclear leukocyte levels. These results suggested that the toxicity of particles is not simply determined by size characteristics but also depends on their chemical composition.

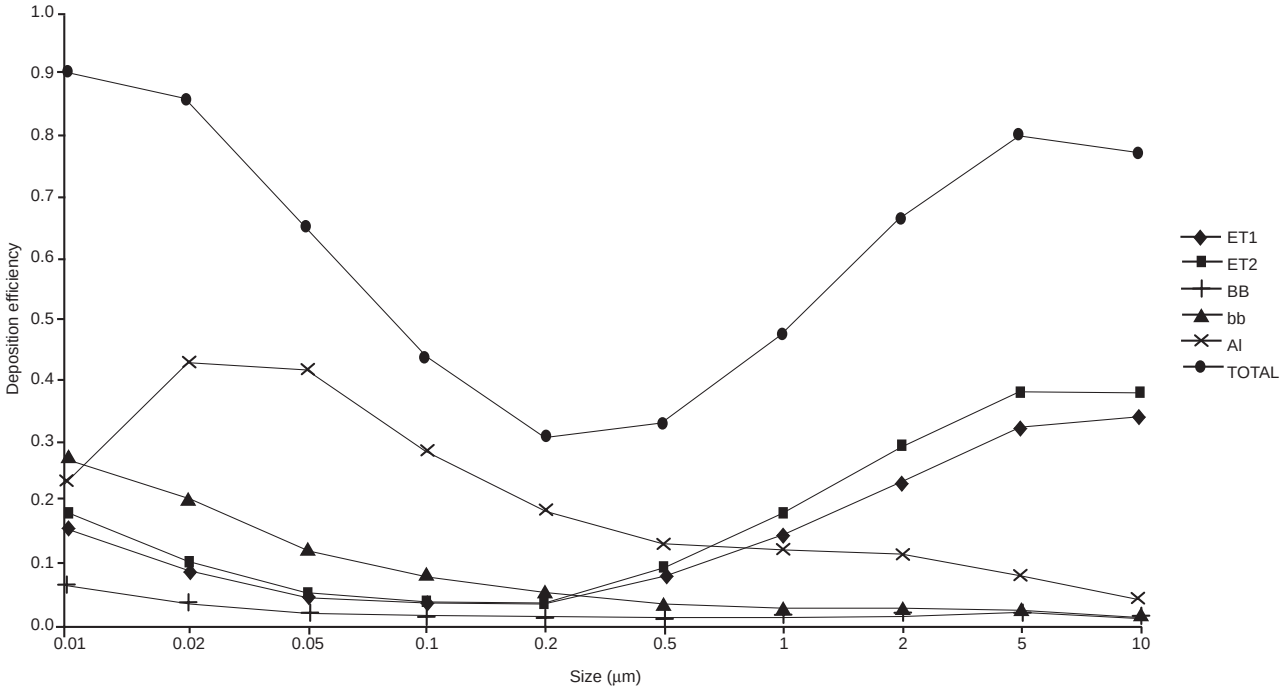
Clearance mechanisms

There are usually two distinct phases of particle clearance within the thoracic region in humans. The initial (rapid) clearance is completed within the first 24 hours and represents mucociliary clearance from the tracheobronchiolar tree. There follows a slow phase, representing clearance predominantly from the alveolar region (Roth *et al.,* 1997). There is evidence that these mechanisms can be affected by exposure to airborne particles. For example, Leikauf *et al.* (1981) studied the effects of a 1-hour exposure to sulphuric acid aerosol (0.5 µm diameter; 0, 110, 330 or 980 µg/m^3) on the clearance rate of radiolabelled ferric oxide tracer particles (7.5 µm diameter) in 10 healthy volunteers. Although subject to some inter-individual variations in response, tracheobronchiolar clearance rate at the high concentration was decreased, but at the low concentration clearance was accelerated. No significant change in respiratory pattern was noted at any exposure. The authors comment that mucociliary clearance is an important defence mechanism for the removal of pathogenic materials from the respiratory system, and that transient changes cannot be considered either beneficial or detrimental on the basis of current knowledge. However, a persistent impairment may render the individual more susceptible to the inception or progression of chronic respiratory conditions; hence repeated exposures to environmentally-relevant levels of acidic aerosol could be important. Although the effectiveness of the mucociliary clearance mechanisms is an important factor in determining overall clearance rates, other mechanisms can also be important. For example, Groth *et al.* (1997) have shown that the frequency of chronic spontaneous coughing significantly increases clearance rates in subjects with obstructive airway disease.

3.3.2 Particle deposition patterns in the respiratory tract

Based on controlled human studies using radiolabelled particles to assess regional deposition patterns, mathematical models have been developed that estimate the physical behaviour of particles in a simplified anatomical model of the lung. Examples include the models from the International Commission for Radiological Protection (ICRP) and the LUDEP dose evaluation program (Birchall *et al.*, 1991). Such models show how deposition efficiency varies for different-sized particles in various parts of the respiratory tree, as illustrated in Figure 3.1. As can be seen, there is an overall deposition minimum for particles of approximately 0.5 µm diameter, and particles less than 1 µm diameter tend to deposit to a greater extent in the lower parts of the respiratory tree. Age and sex influence the deposition pattern although the influence is different in different regions of the respiratory tree (Figures 3.2–3.4). Overall, these findings suggest that there will be enhanced

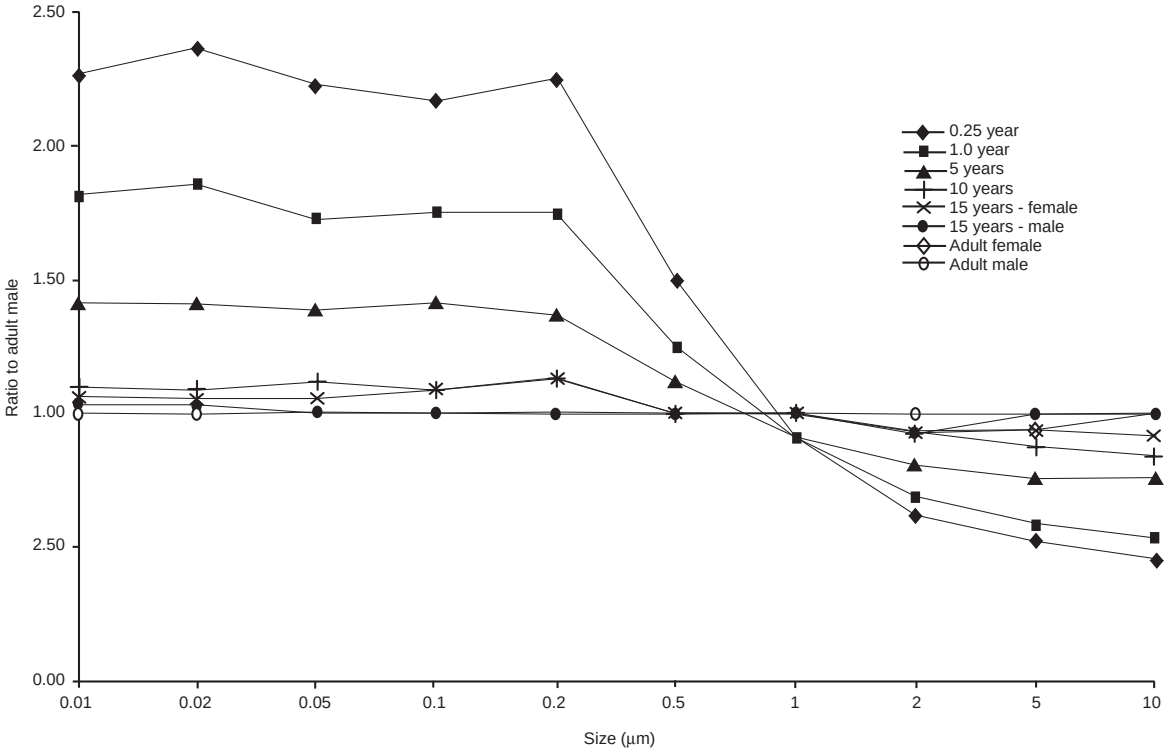
Figure 3.1 The effect of particle size on deposition efficiency in different regions of the lung



Data from ICRP (1994)

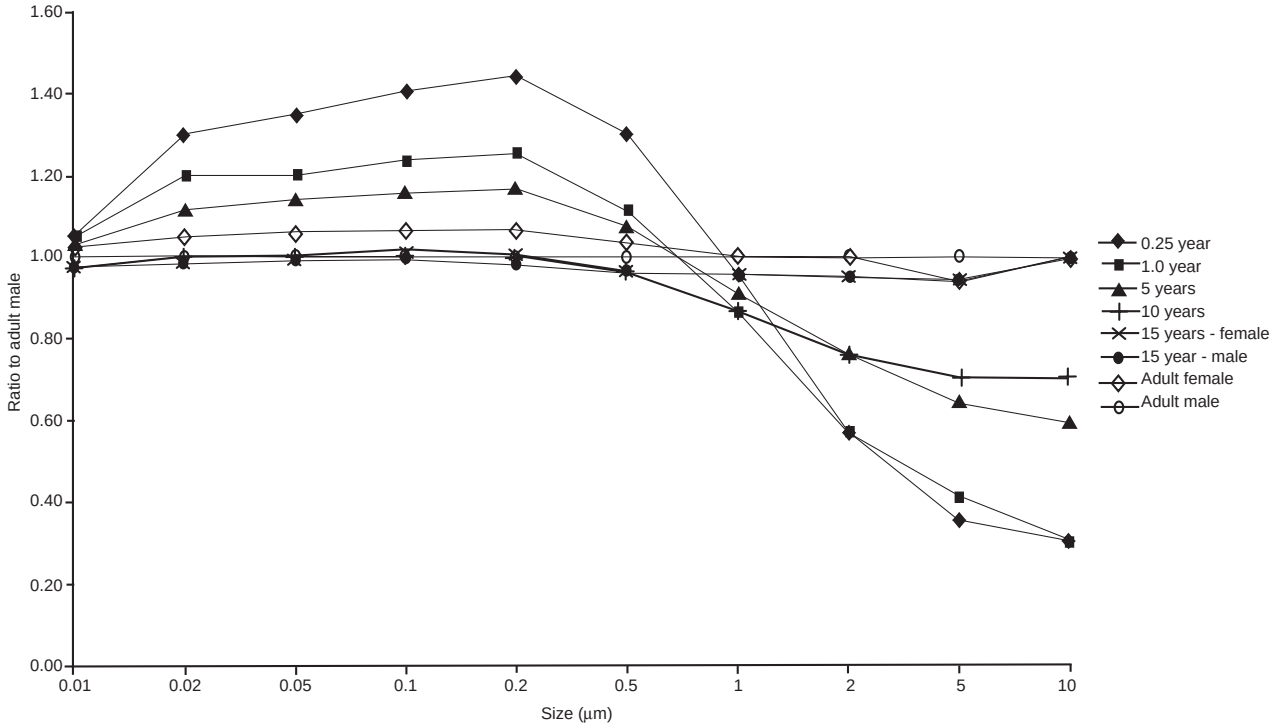
ET1, anterior nasal passages; ET2, nose, mouth and throat to larynx; BB, bronchial region, comprising trachea and 8-generation branching structure; bb, bronchiolar region, comprising small conducting bronchioles to terminal bronchioles; AI, alveolar region, comprising respiratory bronchioles and alveolar sacs

Figure 3.2 The effects of particle size and age of subject on particle deposition characteristics in bronchial regions of the lung



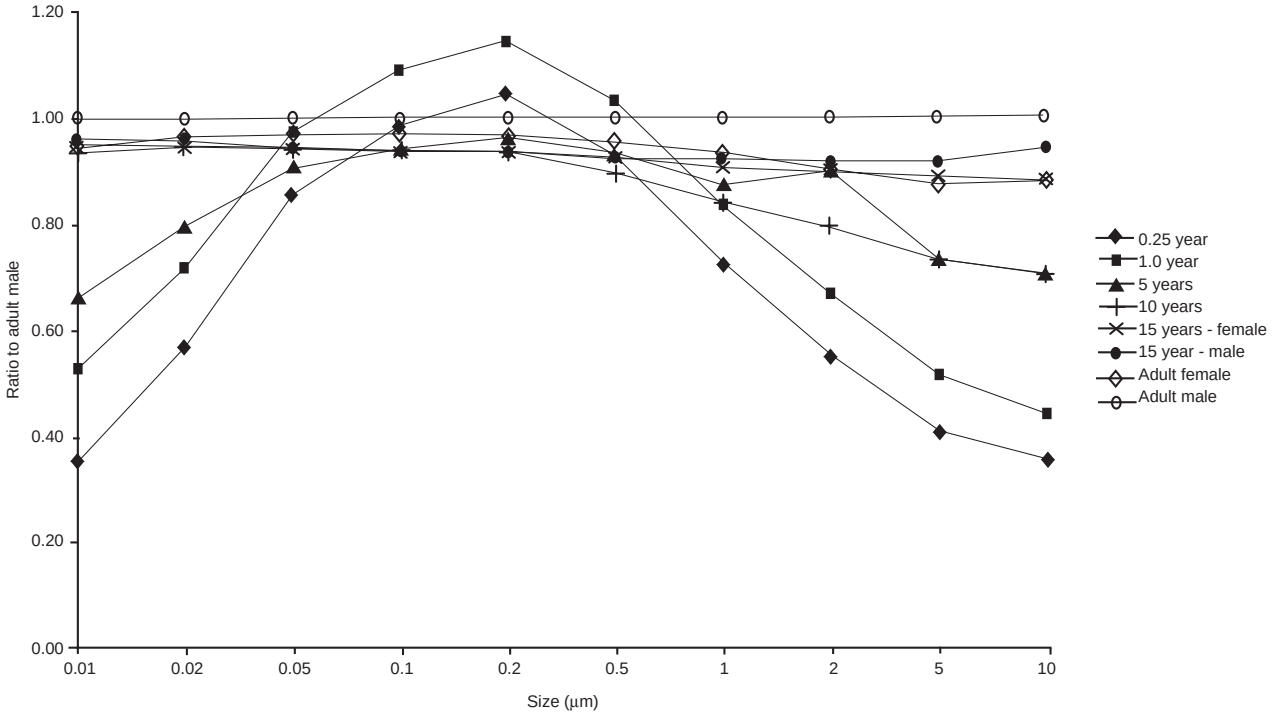
Data from ICRP (1994)

Figure 3.3 The effects of particle size and age of subject on particle deposition characteristics in bronchiolar regions of the lung



Data from ICRP (1994)

Figure 3.4 The effects of particle size and age of subject on particle deposition characteristics in alveolar regions of the lung



Data from ICRP (1994)

deposition of the small particles in the lower regions of the lungs of children compared with adults. Such models also offer the possibility of predicting the influence of changes in the pattern of the respiratory tree such as might arise, for example, as a result of chronic respiratory disease. The results from such models should, however, be treated with a degree of caution since they represent idealised conditions, and hence do not allow for the inter-subject variability that arises in real life, principally as a result of physiological and anatomical differences (COMEAP, 1995a).

Human volunteer studies have been conducted to investigate the differences between population subgroups. As for the human volunteer studies on adverse effects described above, these only provide information of relevance to short-term exposure situations. However, together with the output from the modelling studies, such information can assist in understanding the factors that may underlie the apparently high susceptibility of certain population subgroups observed in some epidemiological studies.

Becquemin *et al*. (1991) compared nasal deposition and resistance in 12 children aged 5.5–11.5 years, eight children aged 12–15 years and 10 adults, at rest and during exercise, by analysing the aerosol concentration of polystyrene beads in inhaled and exhaled air when breathing through the mouth or nose. Although showing some variation with particle size, the percentage nasal deposition was lower in children than adults (Table 3.24). In contrast, in a study of respiratory tract deposition rates for radiolabelled ferric oxide particles (4.5 µm diameter) using gamma camera analysis, the percentage of extrathoracic deposition (%ED) among 13 adolescent children and 25 adults with mild cystic fibrosis (CF), and eight normal adults, was greatest in CF children (%ED in CF children 30.7 ± 15.3, in CF adults 20.1 ± 14.7, in normal adults 16.0 ± 7.2), although total deposition was similar in each group (Bennett *et al.,* 1997).

In a study by Chong *et al*. (1995) of bolus administration of monodisperse aerosols (1, 3 and 5 µm diameter) in 11 men and 11 women, the total deposition fraction was consistently greater in the women regardless of particle size or flow rate. In a study by Anderson *et al.* (1990), respiratory tract deposition was assessed for inhaled, ultrafine, nonhygroscopic particles of various diameters (0.02 to 0.24 µm) in five subjects with obstructive lung disease, three subjects with restrictive lung disease and 10 healthy adults. The total respiratory tract deposition was similar in normal subjects and those with restrictive lung disease but was significantly increased in volunteers with obstructive disorders, at each of the particle diameters investigated (e.g. for 0.02 µm particles, deposition fractions were 0.47 for normal adults, 0.45 for those with restrictive disorder and 0.54 for those with obstructive disorders). Respiratory monitoring identified abnormalities in the breathing patterns of subjects with obstructive but not restrictive disorders that may explain these differences. Possible causes suggested by the authors included prolongation of the time of the final expiratory phase, onset of flow limitation during this phase, decrease in airway calibre and increase in airway secretions. Bennett *et al.* (1996) showed that the rate of deposition of 2 µm diameter monodisperse wax particles in moderate/severely affected COPD patents was nearly $2^1/_2$ times greater than in normal individuals when measured at rest.

Thus, there is considerable evidence suggesting that respiratory tract deposition patterns vary among age groups, and that sex and chronic respiratory disease can also influence the location of deposition and dose received, for the same environmental exposure. Such differences in dosimetry could be of clinical importance.

Table 3.24 Percentage nasal deposition in adults and different age ranges of children

Particle size	Rest			Exercise		
	Adults	>12 years	<12 years	Adults	>12 years	<12 years
1 µm	15.6 ± 9.7	11.7 ± 6.1	12.9 ± 6.1	29.2 ± 12.3	15.9 ± 7.1	17.8 ± 8.4
2.05 µm	21.6 ± 10.9	15.9 ± 11.1	13.3 ± 6.2	34.7 ± 11.1	18.4 ± 8.6	21.3 ± 5.7
2.8 µm	20.0 ± 11.1	17.7 ± 12.7	11.0 ± 5.3	36.8 ± 10.4	16.1 ± 8.6	16.0 ± 6.2

From Becquemin *et al.* (1991)

3.4 Mechanisms of action

Although human volunteer studies have identified some effects in humans exposed for short durations to high levels of certain particles (Section 3.3.1) and associations between exposure and health effects have been identified in epidemiological studies (Section 3.2), establishing a causal relationship between exposure and effect would be greatly strengthened by the identification of a plausible mechanism by which particles could exert toxicity at the measured levels. In assessing the plausibility of a mechanism, the complex nature of ambient air and the possibility of interactions between various components of the gaseous and particulate phases has to be recognised (MAAPE, 1995).

Both *in vivo* and *in vitro* studies have contributed significantly to current understanding, although the available models are limited. *In vivo* studies have generally been conducted at high exposures, frequently in the rat, and extrapolation to humans presents some challenges. The differences in inhalation processes between species (e.g. rats are obligate nasal breathers) and the range of possible cellular targets and differences in bioactivational or protective mechanisms all increase the difficulty in extrapolating between species (MAAPE, 1995). The deposition pattern is also subject to species–specific factors such as the length of the various parts of the respiratory tract, lung size, tracheobronchial branching pattern, airway diameter and breathing pattern (Schlesinger, 1985). Indeed species differences extend to the cellular level. For example, human and, to a lesser extent, nonhuman primate alveolar macrophages are markedly larger than those of rodents (Krombach *et al.,* 1997), nitric oxide production is elicited by lipopolysaccharide or interferon-γ treatment in rats but not hamsters, monkeys or humans (Jesch *et al.,* 1997), and the oxidative capacity of rat and hamster macrophages differ markedly (Dorger *et al.,* 1997). Indeed, even in man various types of macrophage have markedly different functions, and it has been shown that exposure to different particles may have different effects on different cell types (Holian *et al.,* 1997), underlining the difficulties that exist in extrapolating between species and different exposure conditions, and thus in predicting the effects in man of the complex mixtures found in ambient air.

A further question concerning the validity of current *in vivo* models is their relevance to those groups of humans identified as at greatest risk, that is asthmatics, COPD patients or those with pre-existing cardiopulmonary conditions. Although extremely useful for elucidating cellular processes and cell-to-cell interactions, there are also limitations in extrapolating from *in vitro* models, especially given that complex physiological processes may play an important role *in vivo*. Despite these limitations, there has been significant progress towards understanding the toxic processes that may underlie the observed associations between exposure to airborne particles and ill health, although the relative importance of the processes remains an area of much discussion.

3.4.1 Factors affecting particle activity

The site of deposition and the fate of the inhaled particles within the respiratory tract may be important in dictating toxicity (COMEAP, 1995a); deposition and fate can be influenced by the physicochemical and electrostatic properties of the particles, their surface characteristics and their size. Chemical or metallic elements integral to the particles or adsorbed onto their surface may also have some effect.

Possible sites of particle interaction

Once a particle has deposited within the respiratory system its fate will be influenced by the extent of its solubility and the extent to which it is physically cleared by the lung's defence mechanisms. A key element of the initial clearance process from the airways is the mucociliary escalator. To function adequately this depends on several factors: adequate functioning of the respiratory cilia; presence of the right quantity of periciliary fluid; maintenance of appropriate physicochemical properties of the mucus; and the integrity of the ciliary epithelium (Schlesinger, 1990). If not readily removed from the system there is the possibility that the particle, or chemicals released from it, will adversely effect the respiratory epithelium and/or

evoke an inflammatory response which could result in significant adverse local and systemic effects. Thus, the epithelial lining cells, pulmonary alveolar macrophages (PAM) and other cells of the inflammatory system are the first cell types to be exposed to deposited particles and so are particular targets for toxicity. There is also evidence that the fluid lining the respiratory system also plays an important role in determining the impact of the particles on the body. In the upper respiratory tract, solid particles trapped in the mucus are raised into the gel layer component of the lining fluid and are propelled to the nasopharynx by ciliary action (Gehr *et al.*, 1996). Regional differences in the surface tension of the fluid lining the respiratory tree may promote the transport of particles towards the upper regions of the respiratory tract (Yager *et al.*, 1994), and pulmonary surfactant may modify the viscosity of the mucus and thereby increase the velocity of transport (Gerber *et al.,* 1996).

The epithelial lining fluid

As noted above, the interaction between particles and epithelial lining fluid (ELF) may be an important mediator of toxicity (review by Gehr *et al.*, 1996). The aqueous layer covering the airways varies in thickness in different parts of the respiratory tree (Yager *et al.*, 1994), and is thought to consist of two phases (a sol phase in which cilia beat and a more viscous gel phase, the mucus blanket) separated by surfactant-based osmophilic membranes (Kilburn, 1968; Widdicombe, 1985; Gehr *et al.*, 1996). There is experimental evidence that deposition of particles in the intrapulmonary conducting airways triggers rapid responses in the cells producing the mucus (the epithelial goblet cells and submucosal glands), although the mechanisms by which this occurs are not yet elucidated. For example, Green *et al.* (1995) demonstrated that intratracheal injection of airborne dust samples increased the thickness of the mucus layer within five minutes while, using *in vitro* techniques, Lee *et al.* (1995) demonstrated changes in tracheal surface tension and particle displacement within the mucus, for rats exposed to sulphuric acid aerosol for 30 minutes before sacrifice. The effects of such changes would include thickening of the surfactant-based osmophilic membrane and dilution of particle concentrations. In contrast to the upper respiratory tree, within the lower respiratory tree, surface and line tension forces in the surfactant layer are sufficient to pull the particles depositing at this level of the respiratory tract into the aqueous layer and bring them into close physical contact with epithelial cells; the magnitude of the effect depends on the surface tension in the film, the surface chemistry of the particle and its diameter (Gehr *et al.*, 1996). Although negligible for relatively large particles, such an effect becomes significant for particles less than 10 µm diameter (Schürch *et al.,* 1992*)* and could lead to delayed clearance owing to, for example, physical contact with and uptake by the epithelial or airway Langerhans (dendritic) cells (Gehr *et al.*, 1996). Enhanced interactions between the cells and particles could have important consequences, and could contribute to the greater than expected toxicity shown by small diameter particles.

In addition to its role in physically mediating interactions with particles, the ELF has a range of other biological activities reflecting its complex chemical composition. For example, it has significant antioxidant properties (e.g. Putman *et al.*, 1997; Matalon *et al.,* 1990), which offer protection against endogenous or exogenous oxidants. The phospholipid component (mainly dipalmitoylphosphatidylcholine, DPPC), although largely involved in surface tension functions, also has immunomodulating properties (Gehr *et al.,* 1996). ELF proteins have a number of immune functions, including acting as opsonins during alveolar macrophage phagocytosis, stimulation of macrophage oxygen radical production (van Iwaarden *et al.*, 1991) and migratory activity (Hoffman *et al.*, 1987), and regulation of cytokine release from alveolar Type II cells (Blau *et al.,* 1994). The fluid composition varies between parts of the respiratory tree with, for example, the upper regions having higher antioxidant levels and hence being better protected. Differences in the composition of ELF between species may contribute to interspecies differences in susceptibility to particles (Putman *et al.*, 1997).

The macrophage and other inflammatory cells

Particulate material deposited in the conducting airways of the respiratory tree is normally rapidly cleared by the mucociliary escalator. Removal of particles from the lower regions requires dissolution and absorption of the material and/or phagocytosis by PAMs before movement of the PAMs onto the mucociliary escalator (Pepelko,

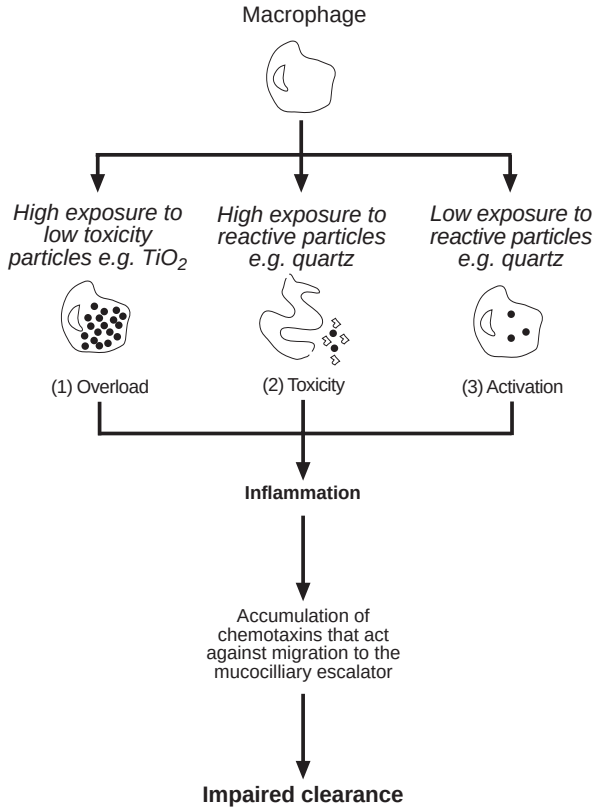
1987; Schlesinger, 1990). At low levels, even poorly soluble particles are generally rapidly removed by the actions of the PAMs.

As the quantity of particles increases, the numbers phagocytosed by each macrophage rise and chemical mediators promoting an inflammatory response are released from the macrophage. Alveolar macrophages are the primary source of the family of proinflammatory proteins, the cytokines, which include TNF-α, IL-1, and chemokines, such as IL-8, which are involved in the recruitment and activation of inflammatory cells. Some cytokines in turn stimulate the production of further cytokines from other pulmonary cells. IL-8 and the macrophage inflammatory protein MIP-2 (both produced by several cell types including macrophages) possess neutrophil stimulatory and chemotactic activity. Their release leads to the recruitment of polymorphonuclear neutrophils (PMN) with subsequent development of a pulmonary inflammatory response. Other chemicals released by inflammatory macrophages include leukotriene LTB_4, fibronectin and the growth factor cytokines, such as platelet derived growth factor (PDG), transforming growth factor-ß (TGF-ß), fibroblast growth factor (FGF), and interferons IFN-α and IFN-ß.

Failure of the alveolar macrophage clearance system could have important consequences; several mechanisms by which particles of different types can impair alveolar macrophage clearance are shown in Figure 3.5.

One of the most highly investigated areas of particle toxicity has been the effect of long-term high-level exposure to insoluble low toxicity particles, in the so-called 'overload' studies. Under such conditions, clearance mechanisms are likely to be overwhelmed (see Mechanism 1; Figure 3.5). It is hypothesised that when there are very high numbers of particles deposited in the lung the alveolar macrophages may reach the limit of their ability to phagocytose particles or to migrate to the mucociliary escalator; that is, the classical overload situation develops (Mauderly & McCunney, 1996; Mauderly, 1996). It has been calculated, on the basis of lung burden and numbers of macrophages in the lung, that such effects start at phagocytosed particle volumes of greater than approximately 60 μm^3 per cell, with

Figure 3.5 Possible mechanisms responsible for impairment of alveolar clearance



TiO_2, titanium dioxide

virtual cessation of particle-mediated clearance at a volume of 600 μm^3 per cell (Morrow, 1988; Oberdörster *et al.,* 1992). Various underlying mechanisms have been suggested for the phenomenon of overload in the macrophage, such as excessive particle-cell and cell-cell chemical interaction, or limitations on availability of surface membrane and cytoskeleton components (Morrow, 1988).

Impaired clearance of more biologically-active particles, such as crystalline silica, can be explained by their cytotoxicity to alveolar macrophages (Mechanism 2, Figure 3.5). If sufficient numbers of particles are present or if particles have sufficient toxicity, resultant lysis of the phagolysosome or other chemically-induced toxicity could result in necrosis or apoptosis of the cell (Hext, 1994; Leigh *et al.*, 1997). This would result in release into the lung of cellular components and the free particles; the process would be perpetuated by reingestion by other inflammatory cells, with the overall result of increasing quantities of particles within the lung together with biologically active cellular debris (Hext, 1994).

Similarly, the presence of reactive particles, such as asbestos, low levels of quartz or sulphuric acid aerosol (Mechanism 3, Figure 3.5) is known to stimulate the inflammatory functions of macrophages (Naumann & Schlesinger, 1986; Kleinman *et al.*, 1995; Driscoll, 1996; Driscoll *et al.,* 1996; Lim *et al.*, 1997). The response varies depending on the nature of the particle. For example, reactive dusts such as crystalline silica or asbestos cause rat alveolar macrophages to release TNF-α, but this response is not elicited by inert latex beads (Hext, 1994).

Whatever the mechanism, the overall result of high-level exposure to particles is to enhance the pulmonary inflammatory response, with continued recruitment and localisation of inflammatory cells (such as PMN) in response to chemotactic substances released by the activated macrophages (Damgård Nielsen *et al.*, 1995). In the case of the death of phagocytic cells, insoluble particles would be repeatedly rephagocytosed, further promoting a cyclic process of increasing dose, with effective inhibition of particle clearance (Hext, 1994). This has been modelled mathematically (e.g. Tran *et al.,* 1997). Under normal environmental conditions, levels of exposure to particles are too low for classical macrophage overload to occur in humans. However, the possibility that Mechanisms 2 and/or 3 above could operate warrants consideration, especially given the experimental evidence (discussed below) suggesting that responses to particles depend on several factors, including chemical composition, size, surface area, and number.

Removal of particles that penetrate to the pulmonary interstitium will be slow as such particles can no longer be cleared through the normal airway clearance mechanisms described above. Interstitial macrophages will attempt to engulf the interstitial particles and transport them to local lymph nodes (Schlesinger, 1990) although the rate of clearance in the interstitium is likely to be less than that of the airway clearance mechanisms. Acute interstitial inflammation and pulmonary oedema may result (Ferin, 1994; Abbey *et al.*, 1996).

Particle composition

There is evidence that the chemical composition of particles is important in determining the biological outcome of exposure. For example, although pulmonary lesions consistent with an overload of pulmonary clearance occur in rats following long-term exposure to a concentration of 250 mg/m^3 of titanium dioxide (TiO_2) particles (1.5–1.7 μm diameter), a material that has no intrinsic toxicity associated with its chemistry, exposure to only 1 mg/m^3 of similarly-sized particles of crystalline silica (mean diameter 1.4 μm), a material known to be toxic to rat alveolar macrophages, produces similar effects (Muhle *et al.*, 1991; Lee *et al.*, 1985). Thus, the particle burden that can be tolerated by macrophages and other lung cells without adverse effect appears to be related to the biological activity of the particles.

Physical properties of particles

There is also evidence that the physical properties of particles are important in determining toxicity. Particle size *per se* may be of great importance. For example, in rats subchronically exposed to identical gravimetric doses of 0.25 μm and 0.02 μm diameter particles of TiO_2, the smaller particles were slower to clear, had greater interstitial translocation and caused a greater inflammatory response (Oberdörster *et al.*, 1994). Theoretical consideration of macrophage volume occupied by the particles, suggests that effects on clearance occurred at a much lower volume for the small particles (i.e. at 2.6% of cell volume for 0.020 μm diameter TiO_2 particles compared with 9% for particles of 0.25 μm diameter). The higher activity of small particles may thus be a reflection of their relatively greater surface area (Oberdörster & Yu, 1990; Oberdörster *et al.*, 1994). Indeed, when related to the surface area of particles in the lung, the inflammatory responses for the different diameter particles show similar dose–effect curves, suggesting that surface area, at least in part, determines toxicity to cells or cellular components (Oberdörster *et al.*, 1994).

Others have suggested that it is the actual number of particles to which the macrophage is exposed that is important. That is, for a given mass concentration, the size of the particles would determine the numbers of particles to which the cells were exposed. Chen *et al.* (1995) proposed that this would explain the results of studies in guinea pigs in which equal mass concentrations of differently sized sulphuric acid

aerosols (0.3 and 0.04 µm diameter) had different toxicities to alveolar macrophages, with the smaller particles being more toxic, as the number of particles present would be greater for the smaller sized particles. Further evidence for the importance of numbers of particles is provided by a study in which particles with a 0.026 µm mean diameter, derived from the thermodegredation products of polytetrafluoroethylene (PTFE), caused rapid mortality in rats after short-term exposure at a mass concentration of only 40–60 µg/m^3 (Oberdörster *et al.,* 1995). Abnormalities were consistent with acute haemorrhagic inflammatory oedema and the effect was attributed to the high particle numbers. The authors proposed that environmentally-relevant low concentrations (by mass) of inhaled singlet particles of less than 0.05 µm diameter may be important for acute effects in humans, especially where there is pre-existing lung disease. However, the role of residual free radical chemistry at the surface of the deposited PTFE particles has not been excluded (Johnston *et al.,* 1996). In addition, as noted in Section 3.3.1, pulmonary clearance occurs in two phases (rapid and slow), and study of clearance rates in rats following tracheal instillation of particles of 0.022–0.03 µm, 1.4 µm and 3 µm diameter has demonstrated a size-dependent effect on slow phase clearance (Patrick, 1998). That is, both the fraction subject to slow clearance and the rate of clearance are reduced as particle size decreases.

Oxidative activity of particles

Several studies have shown that reactive oxygen species (ROS) may play a key role in the development of pulmonary disease (see below). Mammalian cells have an elaborate system of enzymatic (e.g. manganese-containing superoxide dismutase) and nonenzymic (e.g. glutathione) antioxidants to scavenge ROS. Normally a balance exists between the formation of ROS and the antioxidant defences. However, conditions of oxidative stress can arise where excessive accumulation of ROS outweighs the antioxidant defence or where there are deficiencies in the functioning of the antioxidant systems. Under these conditions, oxidant-mediated injury to cellular components (e.g. DNA, proteins and other macromolecules) may ensue.

Factors associated with the physical proximity to small particles can damage a wide range of cell types. For example, Razzaboni and Bolsaitis (1990) showed that silica caused haemolysis of red blood cells and suggested that this was, at least in part, related to oxidative reactions at the particle's surface. *In vitro* exposure of fibroblasts to finely ground hydroxyapatite also causes damage to cells when the cells and particles are in physical contact but not when they are separated by a microporous membrane. Such an effect of proximity appears to operate only for particles less than 5 µm in diameter. The demonstration of lysis of erythrocytes suggests that the effect is on the cell membrane rather than related to phagocytosis (Evans & Smith, 1991), while exposure of human epithelial cells to residual oil fly ash (ROFA) is known to induce the expression of the pro-inflammatory cytokine IL-6 (Devlin *et al.*, 1998).

Aust and Smith (1996), using *in vitro* systems to determine the iron mobilisation potential of crocidolite asbestos particles and their ability to induce strand breaks in ØX 174 RFI DNA, noted that generation of oxygen radicals, lipid peroxidation and DNA damage by crocidolite asbestos was attributable to the iron in the fibres, and demonstrated that iron from particles from urban air could be taken up by human pulmonary epithelial cells and cause similar effects.

Li *et al.* (1996) suggested that the exact composition of airborne particles might not be critical in causing adverse pulmonary effects and proposed that PM_{10} may possess an intrinsic oxidative activity, related to the size of the particles, that might cause a pulmonary inflammatory response. These workers compared the effects of intratracheal administration of PM_{10} (obtained from ambient air samples collected in Edinburgh) with those of 0.2–0.25 µm diameter and 0.02 µm diameter carbon black in rats. Analysis of BAL samples taken 6 hours after instillation of PM_{10} showed an increased influx of neutrophils, increased production of TNF-α and nitric oxide by leukocytes, lowered GSH but not GSSG levels, depletion of supercoiled plasmid DNA bands (a marker for induction of free radical mediated damage to plasmid DNA), and increased air space epithelial permeability (not associated with cell injury). The 0.02 µm diameter, but not the 0.2–0.25 µm diameter,

carbon black particles caused similar but more marked changes. The authors concluded that the effects on plasmid DNA scission supported the hypothesis that free radical activity was responsible for the inflammatory and epithelial responses in the lung. They also noted other evidence suggesting that iron, through Fenton reactions, was responsible for hydroxyl radical production and haemolysis during pneumoconiosis and that the free radical activity of PM_{10} could be abolished in the presence of the iron chelator desferrioxamine. However, the finding that ultrafine carbon black elicits similar but more marked effects to PM_{10} suggests that the size of the particle, not just its iron content, may be of importance.

In further work, Gilmour *et al*. (1997) demonstrated that PM_{10} and TiO_2 particles less than 0.1 µm diameter possess hydroxyl radical activity and suggested that the fraction of PM_{10} of less than 0.1 µm diameter was particularly important, with effects being mediated by iron. Thus, there is strong support for the idea that iron from particles may catalyse an oxidative reaction through the Fenton reaction:

$$O_2^{-\bullet} + Fe^{3+} \rightarrow Fe^{2+} + O_2$$
$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + HO^{\bullet} + OH^- \quad \textbf{\textit{Fenton Reaction}}$$

However, the production of oxygen radicals need not be solely dependent on iron. Other transition metals such as vanadium, nickel and copper are present in various environmentally-relevant particulates, and are also capable of cycling between valence states to generate radicals in the presence of appropriate reductants (Abbey *et al.*, 1996). The relative activity and importance of the various elements is, as yet, uncertain. For example, although *in vitro* studies of rat epithelial response to nickel or vanadium indicate that vanadium is the more toxic, studies involving *in vivo* intratracheal administration suggest the opposite (Kodavanti *et al.*, 1998). Friedlander and Yeh (1996) have also suggested that submicron atmospheric aerosols may carry short-lived, reactive species, including hydrogen peroxide and organic peroxides. Particles in the lung may also accumulate endogenous iron that can become redox active (Eborn & Aust, 1995; Ghio *et al.,* 1994); this may explain the relationship noted between toxicity and the surface area of particles in the lung.

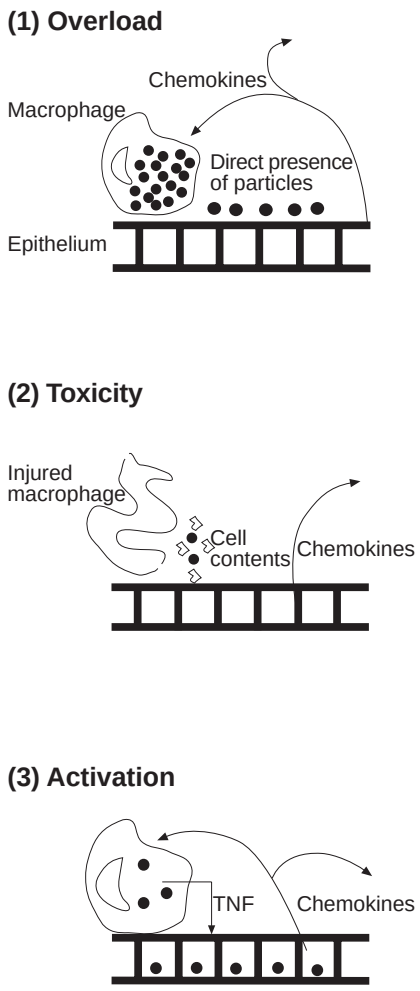
It is possible that oxygen radical production may not be the only mechanism by which transition metals in particles can effect the inflammatory process. ROFA is known to induce inflammatory effects in rats, and Samet *et al*. (1997) have shown that ROFA, or the soluble ions of vanadium (but not nickel or iron) from it, can affect protein tyrosine phosphate metabolism in human bronchial epithelium cells. However, the activity remained even in the presence of an oxidant scavenger suggesting that, in this case, activity did not involve reactive oxygen intermediates.

Other pulmonary cell types and chemical mediation

Where alveolar macrophages are unable to clear particles adequately, there is the opportunity for prolonged interactions between nonphagocytosed particles and epithelial cells. Indeed, as noted above, in the case of small particles, surface tension forces in the ELF may act to promote close contact. Depending upon the particle type, this may be sufficient to stimulate the epithelial cells directly to produce chemokines (such as MIP-2, cytokine-induced neutrophil chemoattractant, CINL, and IL-8), which promote further development of an inflammatory response (Mechanism 1, Figure 3.6), in addition to potentially effecting epithelial proliferation and facilitating the interstitialisation of the particles (Mauderly, 1996; Driscoll *et al.*, 1997). The Type II pulmonary cells and Clara cells are both suggested to be of particular importance (Finkelstein *et al.*, 1997). The presence of cellular contents and re-released particles from injured or dead macrophages (Mechanism 2, Figure 3.6) might also be expected to exert a similar stimulatory effect on the epithelial cells or on other macrophages present in the area (Hext, 1994). One important chemical mediator is TNF-α, which is known to stimulate chemokine production by the epithelium and other cells (Mechanism 3, Figure 3.6; e.g. Hext, 1994; Driscoll *et al.,* 1997). Epithelial cells also show other responses to the presence of particles, such as increased epithelial permeability (Li *et al.*, 1996), which may have important biological consequences.

Other cell types are also involved in interactions with, or respond to, chemical signals from the macrophages. For example, fibroblasts, smooth muscle and endothelial

Figure 3.6 Stimulation of chemical mediators by particles in the lung



cells produce IL-8 in response to IL-1 release by macrophages (Damgård Nielsen *et al.*, 1995). However, not all responses to particles may be mediated via the macrophages. For example, Ikeda *et al.* (1995) have reported that *in vitro* suspensions of diesel exhaust particles could directly inhibit production of nitric oxide by blood vessel endothelium cells, which could have deleterious consequences for vasodilation, platelet aggregation, blood vessel permeability and inflammation. Thus, although the macrophage and other inflammatory cells are the prime mediators of the body's response to particles, other cell types are involved and complex cell-to-cell interactions can occur.

3.4.2 Possible outcomes of the biological response to particles

As described above, some particles could potentially elicit inflammatory responses at relatively low levels. Several mechanisms by which such an inflammatory response could lead to significant adverse local or systemic effects in humans have been suggested (summarised in Figure 3.7).

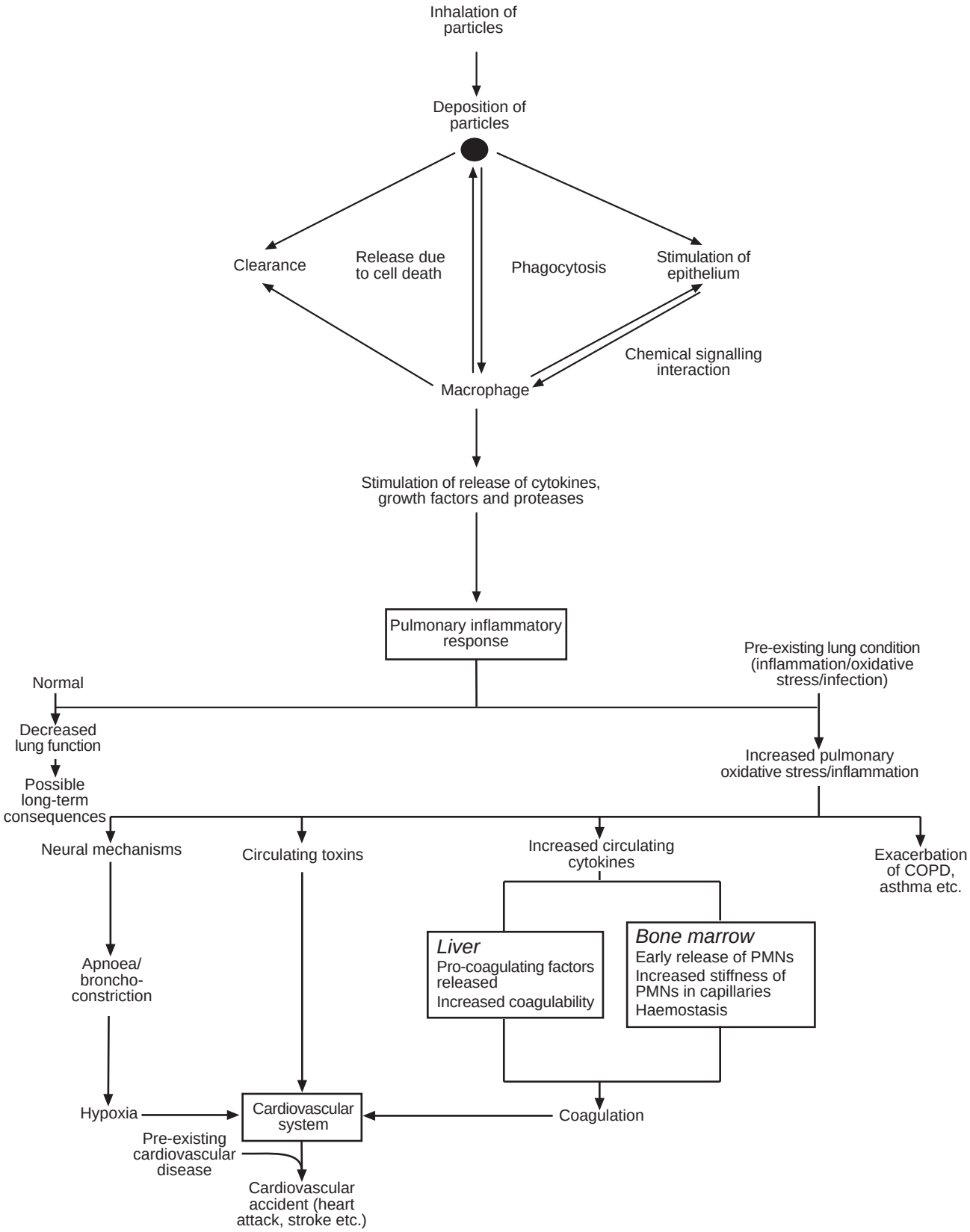
Exacerbation of pulmonary disease states

Exposure to particles could, potentially, initiate or amplify localised inflammatory processes within the lung, although the underlying mechanisms are still open to dispute. However, the observed effects of particles may be difficult to interpret, as their influence on the oxidative activity of macrophages can be difficult to predict. For example, slightly elevated superoxide production during respiratory burst occurs when rats are exposed to low levels of sulphate or road dust, but activity is depressed at high-level exposures (Kleinman *et al.*, 1995). The reason for this is uncertain, but could be a consequence of a reduced capacity of the macrophages to mount a respiratory burst to generate superoxide and, presumably, other biocidal compounds, under high exposure conditions. In healthy individuals with only low levels of pulmonary inflammatory activity and high functional reserves, effects associated with particle exposure are unlikely to be of clinical significance. However, in an individual already suffering from pre-existing pulmonary inflammation (e.g. asthma or COPD), particles could exacerbate the condition. An increased release of cytotoxic and inflammatory mediators could exacerbate bronchial damage and mucus hypersecretion, and decrease the alveolar lumen (which will in turn influence lung compliance), while interactions with the epithelial layers may result in altered bronchomotor tone and changes in permeability (Damgård Nielsen *et al.*, 1995; Kleinman *et al.*, 1995).

Asthma

In addition to considering the role of airborne particles in pulmonary impairment, the potential significance of

Figure 3.7 Possible mechanisms for the propagation of local and systemic effects of particle inhalation



particle exposure in asthmatics requires mention. Particles of biological origin and ETS are well established agents in the induction and exacerbation of asthma (e.g. IEH, 1996; EPA, 1997). While ETS is a major source of particle pollution in homes with a smoker (see Section 2), it must also be appreciated that the PM_{10} fraction of both indoor and outdoor air includes allergenic components of biological origin (e.g. fungal spores of a few μm diameter) and that spore and pollen fragments may be inhaled either directly or following their adherence to other particles (COMEAP, 1995b). Endotoxins (lipopolysaccharides) of bacterial origin are also present in the particulate fraction of ambient air and may be a contributory factor in sensitive individuals (Abbey *et al.,* 1996). The role of biological particles and ETS, and details of the ongoing attempts to elucidate the mechanisms underlying the development and pathology of asthma, are largely outside the scope of the current document.

There are also indications from epidemiological studies that exposure to particles of non-ETS or nonbiological origin may exacerbate asthma, but there is little to support an effect on asthma induction.

Some particle types may have biological activity of relevance to asthma. For example, Gorski and Tarkowski (1992) have shown that diesel exhaust particles have an adjuvant effect on IgE production in mice, and suggest that diesel exhaust may be a factor involved in human sensitisation. COMEAP (1995b) also noted that diesel exhaust particles can directly effect T and B cells. A possible role was also identified for sulphuric acid aerosols by COMEAP (1995b) who noted that exposure of rabbits and guinea pigs results in a transitory increase in responsiveness to acetylcholine challenge, but does not appear to cause gross epithelial damage or inflammatory cell influx. COMEAP suggested that the mode of action of acidic particles may involve direct, transitory effects on mast cells, airway cells and other tissue components (possibly mediated via H_3-histamine receptor interactions or by alterations in pH influencing the release of mediators of bronchoconstriction, such as prostaglandin E_2). However, the intracellular mechanisms involved are unclear. Experimental work in ferrets has also indicated that short-term inhalation of sulphuric acid aerosol at a concentration of 1.0 mg/m^3 significantly increased pulmonary clearance rates (Mannix *et al.,* 1991) while chronic exposure to a concentration of 125 μg/m^3 resulted in increased numbers of secretory cells in the small airway (Schlesinger *et al.,* 1992).

Possible interactions between biological materials and small particles in the air have been suggested by Schinko *et al.* (1994); small atmospheric particulates (<5 μm diameter) were found on the surface of pollen grains, which could result in simultaneous exposure of the respiratory tract to toxic and allergenic stimuli, leading to possible synergistic effects. Behrendt *et al.* (1997) have also noted that pollen exposed to aqueous extracts of airborne particles *in vitro* shows dose and time-dependent increases in protein release, suggesting that inhalation of such particle-pollen combinations might enhance exposure to allergenic substances.

Other inflammatory and immune function effects

Immune/inflammatory responses other than asthma might also be affected by airborne particles. In a meeting report on the cellular and molecular responses to inhaled particles, Shasby and Williams (1994) cited examples of possible effects: macrophage function and numbers were altered in hamsters following exposure to 6 μm diameter polystyrene particles; phagocytic capacity of macrophages was decreased in rats exposed to concentrated samples of ambient air particles; oxygen radical production by macrophages was increased in response to particles of Fe_3O_4 or TiO_2; and, in response to extracts of airborne particles, histamine release from basophils was stimulated as was the release of elastase, leukotrienes and interleukin from neutrophils.

Interactions between particles and the immune system may be complex and difficult to predict. For example, subchronic exposure of rats to ammonium sulphate (0.2 μm diameter; 70 or 20 μg/m^3) or ammonium nitrate (0.6 μm diameter; 90 or 350 μg/m^3) aerosol, or to road dust (5 μm diameter; 300 or 900 μg/m^3) resulted in a reduced ability to mount Fc-receptor mediated macrophage phagocytosis of antigenic material (sheep red blood cells), the greatest effect occurred with the low concentration of sulphate (Kleinman *et al.,* 1995). In a study in which rats were exposed to carbon black

(2.4 ± 2.75 µm diameter) at a concentration of 10 mg/m^3, 4 hours per day for 4 days, Jakab (1993) found no change in PAM or PMN numbers but decreased numbers of lymphocytes in BAL fluid. Pulmonary challenge subsequent to carbon black exposure with *Staphylococcus aureus* (a marker for PAM phagocytosis), *Proteus mirabilis* (alveolar macrophage; AM & PMN functions), *Listeria monocytogenes* (lymphokine-mediated, acquired cellular immune response) or A/PR8/34 influenza virus (cytotoxic T-cell immunity) showed no effect on defence mechanisms. Exposure to acrolein was also found to be without effect; however, combined exposure to carbon black and acrolein resulted in the reduced elimination of *S. aureus, L. monocytogenes* and influenza virus but enhanced killing of *P. mirabilis*. This demonstrates that mixtures of air pollutants may have markedly different properties from their individual constituents, including different effects on immune function. The difficulties in extrapolating from experimental to normal environmental situations are again apparent.

Systemic effects

In addition to the localised pulmonary inflammatory or immune responses to particles described above, mechanisms have been proposed that would explain the occurrence of wider systemic changes and why certain population subgroups might be at particular risk from exposure to ambient particles.

Pre-existing cardiopulmonary disease may be an important risk factor. Preliminary work by Costa *et al.* (1994), using two rat models of hypertension (monocrotaline-induced primary hypertension and secondary hypertension arising from elastase-induced emphysema), showed enhancement of inflammatory response and increased death rate following exposure to particles. Subsequently, Costa and Dreher (1997) studied the effects of intratracheal administration of ROFA, domestic oil fly ash, coal fly ash and TSP, collected from three North American cities and one German city, on acute lung injury and inflammation in normal rats and rats with monocrotaline-induced primary hypertension. Measurement of BAL protein and albumin content, lactate dehydrogenase activity and macrophage, neutrophil and eosinophil numbers demonstrated a close correlation between biological response and the bioavailability of absorbed transition metals (as determined by analysis of the extractability of the metals from the particles, under aqueous and acidic conditions). The effects were greatest in hypertensive animals, including the death of many animals, apparently from altered cardiac function. The authors noted that, theoretically, lung inflammation could result in release of superoxide and labile hydrogen peroxide from lung cells, which have been shown *in vitro* to react with lipids yielding more oxidants and, furthermore, that it was unclear if the cardiac damage observed was a primary effect or secondary to pulmonary failure.

Godleski *et al.* (1996) compared the effect of exposing normal rats or rats with chronic bronchitis (induced by exposure to sulphur dioxide at 250 ppm for 5 hours per day, 5 days per week for 6 weeks) to concentrated samples of ambient air particles (0.1–2.5 µm diameter) for 5 hours per day, 5 days per week, over 6 weeks. The mass levels in the concentrated particles ranged from 190.5–317.1 µg/m^3 compared with ambient levels of 7.9–11.3 µg/m^3. Deaths only occurred among the bronchitic rats exposed to concentrated particles; neither the exposed healthy rats nor the unexposed bronchitic rats died. In rats with pre-existing disease, pulmonary inflammation was present prior to particle exposure, but when the bronchitic rats were exposed to concentrated particles significant bronchoconstriction also occurred. BAL analysis showed that, compared with healthy rats, those with chronic bronchitis had elevated neutrophils, the number of which more than doubled following exposure to the concentrated particles. The authors concluded that there may be substantial synergistic effects between pre-existing disease and inhaled particles.

Seaton *et al.* (1995) have proposed an hypothesis to explain an increased health risk associated with exposure to airborne particles during air pollution episodes among people with cardiopulmonary disease relative to the general population. The hypothesis takes into account the extent of particle deposition in the lung during air pollution episodes, the uneven deposition of particles in the lung among those with chronic lung disease, and the characteristics of airborne particles in the urban environment.

- Particle deposition — The authors calculated that in humans each lung acinus receives on average 30 million particles and each alveolus approximately 1500 particles, every 24 hours during pollution episodes. Of these, about 50% will be deposited. This calculation was based on measured levels of 0.05 µm particles in Birmingham in the range 1000 to 50 000/cm^3, rising to 100 000/cm^3 during pollution episodes.

- Deposition in chronic lung disease — There is experimental evidence to suggest that deposition of particles within the lung would be uneven among people with chronic lung disease. For example, among rats exposed to a radiolabelled insoluble aerosol of ^{99M}Tc-sulphur colloid (0.45 µm average diameter; mass concentration 50 ± 5 mg/m^3), although the total quantity of particles in the lung was similar for healthy rats and rats with chronic bronchitis (induced by prolonged inhalation of sulphur dioxide), the distribution in rats with bronchitis was much more heterogeneous, with the highest deposits in the larger airways (Sweeney *et al.*, 1995).

- Characteristics of urban particles — The authors noted that in urban areas in the UK a considerable fraction of PM_{10} is composed of particles less than 2.5 µm diameter. This fraction is approximately 50% carbon (mainly derived from combustion sources, and contains absorbed/adherent chemicals) and 50% salts (mainly ammonium sulphate). A substantial fraction is actually less than 1 µm diameter, and therefore readily able to penetrate buildings.

The authors suggested that high exposures to particles of up to 0.05 µm diameter might result in failure of particle removal by alveolar macrophages, with a consequent airspace inflammatory response, although it is possible for pro-inflammatory effects to arise even in the absence of overload (see Figure 3.5 above). Given that many of the factors involved in the inflammatory process are also mediators of blood coagulation and plasma viscosity (e.g. fibrinogen, factor VII and plasminogen activator inhibitor), the authors also suggested that certain chemicals, such as IL-6, could pass to the liver and exert systemic effects on blood coagulants. The secondary changes in blood coagulability would then predispose to acute cardiovascular events. Such a mechanism was supported by a review of the incidence of ischaemic heart disease in different occupational groups (Sjögren, 1997) which showed that those exposed to high levels of organic or inorganic dusts had increased risk of ischaemic heart disease, associated with lung function impairment/respiratory symptoms and increased levels of IL-6 and/or fibrinogen. In addition, a study monitoring blood viscosity over a pollution episode conducted in Augsburg, Germany during the winter of 1984–1985, demonstrated increased risk of raised plasma viscosity with rising particle levels (odds ratios for 100 µg/m^3 rise in total suspended particles: men 1.75, CI 0.79, 3.89; women 2.30, CI 0.92, 5.79); correlations with sulphur dioxide and carbon monoxide levels were also apparent (Peters *et al.*, 1997).

The validity of the hypothesis of Seaton and colleagues has, however, been questioned. COMEAP (1995a) calculated that for a concentration of 1000 particles/cm^3 of 0.5 µm diameter (based on data for Birmingham, UK) the adult daily exposure was only 270 particles per alveolus, a level that would not be expected to cause macrophage overload.

Another mechanism by which inflammation could cause adverse local or systemic effects is by interference with oxidant–antioxidant balance. Indeed, there is some evidence of relevant systemic changes in susceptible human groups. For example, in a study of normal (nonsmoking) and smoking volunteers and asthma or COPD sufferers, Rahman *et al.* (1996) found a marked oxidant–antioxidant imbalance in favour of oxidant stress in the plasma of chronic smokers and in patients with stable but chronic asthma or with acute exacerbation of COPD, but not in clinically stable COPD patients. Associated changes in levels of lipid peroxidation products in the blood were also apparent.

Terashima *et al.* (1997) have proposed another mechanism by which circulatory effects could be induced. Instillation of colloidal carbon (average <1 µm diameter) into the lower lungs of rabbits was found to promote the release of immature PMNs from bone marrow. This was thought to be mediated by release of inflammatory mediators from pulmonary PMNs into the systemic circulation. The authors speculated that the immature PMNs released from the bone marrow would be slower than mature cells at crossing the pulmonary capillaries to sites of inflammation, and that their presence in lung capillaries, and potentially the heart, might result in localised alterations in haemodynamics and cytotoxicity (through their inflammatory activity). This

could contribute to the cardiopulmonary impairment seen following exposure to particulates, and might explain why individuals with pre-existing cardiopulmonary conditions were at particular risk.

A possible neuronal involvement has also been proposed. The lung contains different types of afferent and efferent neurones capable of influencing factors such as vasodilation and vascular permeability, respiratory rates and interactions with the immune system. Stimulation of receptors in the respiratory tree, either directly or via chemicals such as prostaglandins, might affect the central nervous system, causing responses such as apnoea, bronchoconstriction or altered circulatory muscle tone, with potential adverse cardiopulmonary consequences (Damgård Nielsen *et al.*, 1995; Godleski *et al.*, 1996).

Neoplasia

A few epidemiological studies have suggested a possible association between ambient particle exposure and cancer (Section 3.2.6) and there is also *in vivo* and *in vitro* evidence supporting particle-induced neoplasia.

Some airborne particles (e.g. diesel exhaust) are coated with carcinogens (e.g. PAHs and some nitro-PAHs) and are mutagenic (Rosenkranz, 1996); some other environmentally-relevant particles are genotoxic. For example, increased sister-chromatid exchange occurred in human BEAS-2B epithelium cells and in rat or hamster tracheal epithelium cells exposed to particles from the air of a German city (Hornberg *et al.*, 1997); TSP or PM_{10} fractions from Mexico City gave positive results in the Ames test (Villalobos-Pietrini *et al.*, 1995); and increased promoter activity (interference with intercellular gap-junctional communication) was observed in V79 cells and primary cultures of alveolar Type II cells exposed to indoor and outdoor air extracts (Heusssen & Alink, 1994).

In vivo, pulmonary neoplasia has frequently been reported in rats after high exposures to some particles. Two tumour types occur:

- bronchoalveolar tumours — adenomatous and carcinomatous lesions arising from hyperplasia and hypertrophy of alveolar Type II epithelial cells; and
- epidermoid/squamous cell tumours — possibly arising from areas of bronchiolisation/ squamous metaplasia in terminal bronchioles and alveoli (Lee *et al.*, 1985).

It appears that pulmonary neoplasia in the rat will only occur if certain conditions are met. The particles must be insoluble, exposures must be continuous throughout the majority of the life span, deposition rate must exceed clearance (i.e. overload), and a prolonged inflammatory response must be maintained. It has been suggested that the neoplasia is due to chronic inflammation causing high rates of cell proliferation, thus increasing the chance of cellular transformation, rather than being a result of direct particle-induced genotoxic damage (Hext, 1994). Driscoll (1996), however, has proposed a mechanism whereby genome damage could result from oxidants produced by phagocytes during the inflammatory process. Thus neoplasia may be a secondary consequence of the inflammatory effect; a threshold dose, below which biological defences could clear particles, thus avoiding the consequences of macrophage overload, is implicit in such a process.

Although particle overload and associated nonneoplastic lesions have been shown for other species (including man), particle-induced pulmonary neoplasia appears to be restricted to the rat (see Table 3.25; Hext, 1994; Levy, 1995). *In vivo* studies in mice and hamsters have not shown lung neoplasia even when clearance is impaired (Hext, 1994). Primates also appear relatively unresponsive to particles. For example, following exposure of rats and monkeys to diesel exhaust and/or coal dust, the incidence and severity of treatment-related histopathology (including hyperplasia, inflammation and fibrosis) was much greater in rats, and some lesions only occurred in the rats, despite the monkeys having the greatest particle load. The deposition patterns were also different; rats retained a greater proportion of particles in the alveolar duct and lumen than did the monkeys (Nikula *et al.*, 1997). The significance of rat lung neoplasia is further called into question by the finding that long-term exposure of rats to diesel exhaust or carbon black has no effect on the mutation rates of several oncogenes (p53, *K-ras* or *mdm2*) normally associated with murine or human pulmonary neoplasia (Swafford *et al.,* 1995; Belinsky *et al.*, 1995).

Table 3.25 Summary of responses to poorly soluble low-toxicity particles

Response	Rat	Mouse	Hamster	Human (Coal workers)
Impaired particle clearance	++	++	++	(+)
Inflammation	++	+	(+)	+
Cell proliferation	++	+	(+)	+
Fibrotic foci	++	±	(+)	+
Local emphysema	+	–	(–)	+
Tumours	++	–	–	–

From Levy (1995)

++, Clear positive evidence; +, Positive evidence; (+), Possibly positive; ±, Equivocal; (–), Possibly negative; –, Negative evidence

Overall, it is possible that the deposition patterns in other species permit continued clearance even at high lung burdens (Snipes, 1996) and that they may show inherently lower inflammatory and fibrotic responses and have lower susceptibility to cellular transformation than the rat (Hext, 1994). Thus, Nikula *et al*. (1997) suggest there may be inherent interspecies differences in responsiveness and it may be that, particularly for particles of low toxicity, the rat is a poor predictor of pulmonary effects in primates. Hence the relevance of *in vitro* and rat carcinogenesis data to humans is open to question (Rosenkranz, 1996; Mauderly, 1996), and a firm mechanistic basis to support any neoplastic effect of particles to humans under normal conditions is lacking.

3.4.3 Experimental models for susceptible groups

There is concern that the potentially unique susceptibility of the rat to long-term, high-level particle exposure limits the relevance to humans of data obtained in the rat. There are also uncertainties about the applicability of experimental models to the potentially susceptible subpopulations (e.g. the elderly, those with cardiopulmonary impairment and asthmatics) identified from epidemiological studies. A number of workers have reported animal models that attempt to mimic the lung impairment of, for example, COPD patients (e.g. Costa *et al.*, 1994; Godleski *et al.,* 1996; Costa & Dreher, 1997); these studies clearly show a markedly greater sensitivity in health-impaired animals compared with normal animals. This suggests that it may be appropriate to concentrate efforts on firmly establishing models capable of mimicking the range of disease conditions found in susceptible subgroups within the human population. If the reported effects during pregnancy or on infant survival (Section 3.2.7) are substantiated, the suitability of available animal models to address these aspects will also require consideration.

3.5 Evaluation of the literature on the health effects of particles

3.5.1 Epidemiological studies

The evidence

Epidemiological studies have demonstrated consistent and often statistically significant associations between short-term elevations in ambient (outdoor) levels of particles measured using a variety of endpoints (e.g. TSP, PM_{10}, $PM_{2.5}$, black smoke) and the incidence of mortality (Tables 3.2–3.4) or morbidity (Tables 3.5–3.10), with cardiopulmonary impairment being the predominant effect. The elderly or infirm appear at particular risk (e.g. Schwartz, 1994c; Anderson *et al.,* 1995; Schwartz *et al.,* 1996), especially if suffering from pre-existing chronic conditions, and it should be noted that the effect of particles may be smaller in Europe than the US (COMEAP, 1998).

Short-term effects on pulmonary function (Table 3.11) and respiratory symptoms (Tables 3.12–3.14) have been reported in adults and children with, irrespective of age, asthmatics appearing to be particularly susceptible (Pope *et al.,* 1995a; Ostro *et al*., 1996; Scarlett *et al.,* 1996; Timonen & Pekkanen, 1997). However, specific causative agents (whether specific constituents of particles or co-pollutants) or mechanisms have not been indentified. NILU (1996) suggested that asthmatics might be more susceptible to lower respiratory tract symptoms and, although recognising the limited data, estimated that a 10 $\mu g/m^3$ increase in PM_{10} might increase exacerbation of asthma symptoms by 5%. A further possible association is with upper respiratory tract symptoms in children (von Mutius *et al.,* 1995; Bräun-Fahrlander *et al.,* 1997).

Although less well established and despite the need for better quantitative risk estimates of long-term exposure (Pope *et al*., 1995a & b), associations between long-term ambient particle level and mortality (Table 3.16) and morbidity rates (Table 3.17), lung function (Table 3.18) and respiratory symptom incidences (Tables 3.19–3.21) have also been noted; cardiopulmonary disease has again been highlighted as of particular concern.

The rates of some cancers have also been suggested to be associated with ambient particle exposure although the relevance of this has been questioned (COMEAP, 1995a; NILU, 1996).

Other potential causes for concern arise from a few studies suggesting that high maternal or post-natal exposure to particles may be associated with small reductions in the duration of pregnancy, low birth weight, and an increased risk of death during infancy (Table 3.22).

The available data therefore suggest that raised outdoor particle exposure may be affecting public health; even a small change in the distribution of an effect across a population could result in clinically significant changes in some 'at risk' individuals. In particular, it has been estimated that in the UK a 10 $\mu g/m^3$ increase in 24-hour mean PM_{10} may be associated with an increase in deaths from all causes of 0.75% and in hospital admissions for respiratory causes of 0.8%, and that, for the UK population, life long exposure to 25 $\mu g/m^3$ PM_{10} may result in a 1-year loss in life expectancy.

Confounding factors

The interpretation and comparison of the epidemiology data are not straightforward because of the differing approaches taken to both the classification and monitoring of airborne particles and the recording of health outcomes. Concerns have been expressed that the associations found could reflect unidentified confounding factors which could be independently associated with both exposure and disease (Dockery & Pope, 1994; Pope *et al*., 1995a & b). For example, Valberg and Watson (1996b) have suggested that there is a firmer basis for attributing effects to exposure to bioaerosols, indoor allergens and, perhaps, ETS than to ambient particulate matter (see Box 1). However, for the short-term studies, many of the major factors that influence health (e.g. smoking, hypertension and age) are unlikely to vary with daily fluctuations in ambient level, and in several studies associations have persisted even after adjustment for weather, temperature and season.

Box 1 Valberg and Watson hypothesis

According to the hypothesis of Valberg and Watson (1996b) extreme weather conditions cause the physical effects of cold or heat which in turn modify behaviour patterns (e.g. increase the time indoors). For example, in cold weather outdoor particle levels would be raised because of increased use of vehicles and in-house heating or air conditioning systems. The increased use of heating and air conditioning systems would also generate or recirculate pollutants, including bioaerosols (e.g. viruses, bacteria and fungal spores) in the indoor air. In addition, since more time would be spent indoors, those occupying homes with smokers would experience increased ETS exposure.

Comment — The hypothesis is partially based on the wide use, in the USA, of air conditioning systems and humidifiers, which are known to serve as reservoirs for microbiological contaminants. Although such systems are much less widely used in UK homes, windows are likely to be closed in the UK in winter; ventilation rates would, therefore, be low, allowing build-up of pollutants from tobacco smoke and cooking or heating appliances. In contrast, during summer, despite house ventilation rates being higher, the levels of bacteria, fungi and house dust mites indoors are known to be at their highest (Berry *et al.*, 1996). Thus, elements of the hypothesis of Valberg and Watson appear to be applicable to the UK situation.

Relevance of indoor sources

For all the potential health effects described above, from mortality to pregnancy outcome, there is very little information on the possible role of indoor or personal particle exposures, although some studies have attempted to adjust for smoking history.

There are several potential indoor sources of biologically-important particles. In any assessment of indoor air the role of ETS must be recognised, although detailed consideration of its effects is beyond the scope of the present review. As noted in Section 2, ETS is a major contributor to indoor particle levels in those homes with one or more smokers. ETS has been implicated in many health effects including those also associated with particles (see Box 2).

A further potential source of indoor particles outside the remit of this report are those of biological origin possessing allergenic activity. There have been few epidemiological studies investigating whether particles found in the home can induce allergic states (Ayres, 1995), although conditions such as extrinsic allergic alveolitides (hypersensitivities of the lung, such as farmer's lung and humidifier fever) have been associated with exposure to allergenic organic dusts smaller than 5 μm diameter (Edwards *et al.*, 1992).

There is also evidence that where heating or cooking generates relatively high particle levels, this can have adverse effects on respiratory disease and lung function (e.g. Hosein & Corey, 1986; Xu & Wang, 1993; Robin *et al.,* 1996). This is supplemented by a considerable body of literature (not reviewed here) that has identified the use of biomass cooking fuels in the under-developed world as being of concern (see Leslie, 1995). Within the UK, the lack of data on links between health effects and indoor (home) particle levels, and the relative importance of the various indoor sources are of concern, particularly since pollution levels in the home might be expected to be of greatest relevance to 'at risk' groups (e.g. elderly people, the infirm, children).

In summary, associations have been shown between ambient particles and short- and long-term health effects. Alterations in the rates of death or hospitalisation in response to short-term fluctuations in particle level have been seen in a range of geographical regions for various measures of particle exposure. With the exception of hospitalisation for asthma, these generally relate to cardiopulmonary disease in the elderly or infirm. Of great interest are the reports on the relationship between cardiopulmonary effects and the smaller-sized particles, although the data are as yet insufficient to establish the relative importance of different size particles. Short-term changes in lung function and alterations in respiratory symptoms have also been noted, especially in asthmatics and children. The possibility that particle exposure may effect pregnancy or the infant is also an area that requires further investigation.

Box 2 Health impact of ETS

In a recent review, the EPA (1997) noted the causal link between the exposure of nonsmokers to ETS and the following adverse conditions, and estimated their associated relative risks (RR): death from heart disease (RR 1.3); lung cancer (RR 1.2); nasal sinus cancers (RR 1.7–3.0) and, in children, low birth weight (RR 1.2–1.4); sudden infant death syndrome (SIDS; RR 3.5); asthma induction (RR 1.75–2.25) and exacerbation (RR 1.6–2); middle ear infection (RR 1.62) and lower respiratory disease (RR 1.5–2). Although the relative risk for some of the conditions is small, the diseases are common, and the overall impact on public health is potentially quite large. In addition, the available evidence was considered to suggest that a number of other effects may be causally linked to ETS exposure, including spontaneous abortion, impaired cognitive and behavioural development, exacerbation of cystic fibrosis, decreased pulmonary function and cervical cancer. A series of meta-analyses published during 1997 and 1998 also demonstrated a number of effects of ETS. These included, for maternal smoking, increased risk of SIDS (prenatal odds ratio [OR] 2.08, CI 1.83–2.38; postnatal OR 1.94, CI 1.55–2.43), bronchial hyperreactivity (OR 1.29, CI 1.10–1.50), wheeze-associated illness (OR 1.31, CI 1.22–1.41, to age 6 years) and asthma (OR 1.37, CI 1.15–1.64). For children with smoking parents, increased risks comprised lower respiratory-tract disease (OR 1.57, CI 1.42–1.74), asthma (OR 1.21, CI 1.10–1.34), wheeze (OR 1.24, CI 1.17–1.31), cough (OR 1.40, CI 1.27–1.53), phlegm (OR 1.35, CI 1.13–1.62), breathlessness (OR 1.31, CI 1.08–1.59), recurrent otitis media (1.48, CI 1.08–2.04) and middle ear effusion (OR 1.38, CI 1.23–1.55). A small but significant impairment in lung function was also shown for children of smoking mothers (Cook & Strachan, 1997; Strachan & Cook, 1997; Anderson & Cook, 1998; Cook & Strachan, 1998; Cook *et al.*, 1998; Strachan & Cook, 1998a,b,c). ETS is a highly complex mixture of chemicals present in both particle and gaseous forms, and the relative contribution of the various constituents of ETS to these health effects is uncertain. Given the overlap of possibly-implicated diseases, interpretation of the role of non ETS-derived indoor particles in situations where co-exposure to ETS occurs is likely to be difficult and the possibility of confounding may be great.

3.5.2 Human chamber and challenge studies

Experimental studies on human volunteers have been used to investigate the possible effects of different types of airborne particle on humans, and to provide data on which to base mathematical models of the physical behaviour of particles within the respiratory tree.

Lung function

Despite the limitations inherent in controlled studies in human volunteers (described in Section 3.3), biologically-important responses have been found following exposure to some types of non ETS-derived particles. Principal among these are the changes in lung function and bronchial responsiveness seen in normal and asthmatic individuals following exposure to acidic particles, especially the sulphates and sulphuric acid (COMEAP, 1995a). However, the effects are small and only elicited at exposures substantially above those normally experienced in outdoor or nonoccupational indoor environments. In a review of chamber studies to investigate adverse effects associated with various combinations of aerosols or particles and gases, the Advisory Group on the Medical Aspects of Air Pollution Episodes (MAAPE, 1995) concluded that ozone exerts the greatest effect, but that particles and aerosols could also elicit such effects. COMEAP (1995a & b) also noted experimental evidence that some groups (e.g. asthmatics) may be more sensitive than the normal healthy adult population.

Models

Mathematical models, developed using data from human volunteer studies, have demonstrated that there are differences in deposition patterns and dosimetry for various population subgroups (e.g. those between children and adults), which will result in different doses and sites of deposition under identical atmospheric concentrations. Such differences may, to some extent, explain the differential susceptibilities shown by certain groups.

3.5.3 Mechanisms of action

Experimental studies *in vitro* and *in vivo* have confirmed the intrinsic biological activity of some types of particle; both the physical and chemical characteristics of particles may be important determinants of activity, but no one factor is as yet generally accepted as causal. *In vitro* studies have shown that the presence of transition metals on particles may facilitate Fenton reactions leading to the production of oxidative radicals.

Despite the limitations of extrapolating from *in vivo* studies to humans, *in vivo* studies in rats have provided evidence supporting possible nonneoplastic effects of some particle types in humans at normal exposure levels. The principle mediator of such effects is thought to be the initiation or promotion of an inflammatory response, although other processes (such as interactions with the epithelial lining fluid, the epithelial cells and, possibly, the blood vessel endothelium) may contribute to the overall outcome.

A number of mechanisms have been proposed to explain both how a localised pulmonary inflammatory response to low-level particle exposure could provide sufficient stimulus to cause adverse effects either in the lung or systemically, and how individuals with pre-existing cardiopulmonary impairment could be at particular risk.

- The release of chemical mediators of inflammation from the lungs into the systemic circulation may stimulate increased hepatic release of blood coagulation factors or the release of immature PMNs from bone marrow. (Such changes could cause an increased risk of blood clots and hence cardiovascular accidents.)
- Circulating chemicals released during the inflammatory response may be cytotoxic to the heart.
- The systemic oxidant–antioxidant balance may be altered.
- Stimulation of neural receptors in the lung may cause the central nervous system to alter bronchial tone, respiratory rate or other physiological parameters.

The validity and/or relative importance of any of these processes in humans under normal environmental conditions are as yet uncertain.

Widely-recognised interspecies differences in anatomy, physiology and deposition pattern affect the interpretation of mechanistic studies and extrapolation from experimental animals to humans. Thus the possible mechanisms described above should be regarded as hypotheses rather than as firmly established as operating in humans. Indeed, much of the available *in vivo* data relate to high-level long-term exposure of rats. The mechanisms identified as operating in such a model, especially with respect to neoplasia, may not be applicable to the normal human exposure situation and, given these concerns, there is a need to consider the suitability of available *in vivo* models. The recognition from epidemiological studies that there are subpopulations at particular risk (e.g. the elderly and people suffering from COPD or asthma) also emphasises the need to consider the development of suitable animal models for these conditions.

4 Conclusions and recommendations

4.1 Assessment of current knowledge

Potential indoor sources of particles include cooking, certain heating appliances, and human activity. Although outside the scope of the current review, the major indoor source of particles is environmental tobacco smoke (ETS), and the role of allergenic (biological) particles must also be recognised.

Indoor particle levels (measured as a mass concentration) are generally lower than, but correlated with, outdoor levels, except when a significant indoor source is present. However, personal exposure levels are generally higher than either indoor or outdoor concentrations.

There is considerable epidemiological evidence that airborne particles may adversely affect human health. Short-term elevations in ambient particle levels have been strongly associated with increases in mortality, morbidity, and/or hospital or emergency room (ER) admissions: acute cardiopulmonary impairment is the predominant effect, and the elderly or infirm are particularly at risk. Short-term changes in pulmonary function and respiratory symptoms have also been detected, particularly in people with asthma. Long-term exposure to particles may increase mortality and morbidity rates and levels of respiratory symptoms, and impair pulmonary function, although the evidence for adverse effects being associated with long-term exposure is less certain.

There is a degree of mechanistic explanation for the observed toxicity of particles. Attention is increasingly being focused on the role of particles in the initiation or promotion of pulmonary inflammation. Several mechanisms by which pulmonary inflammation could lead to systemic effects have been proposed. Inflammatory mediators released from the lungs into the systemic circulation could promote the release of blood coagulation factors and white blood cells from their sites of production and thereby increase the risk of blood clotting, cardiotoxic chemicals could be released during the inflammatory response, the systemic oxidant–antioxidant balance could be changed, or the central nervous system could be affected through stimulation of neural receptors in the lung. The validity and/or relative importance in humans of these hypothetical mechanisms at normal exposure levels is, as yet, uncertain.

Personal exposure is of considerable importance as it is the key determinant of the particle dose received by an individual and will thus directly influence any impact on health. As indoor sources have been shown to raise personal exposure levels substantially, and the population subgroups most at risk from particle exposure are likely to spend the majority of their time indoors, it is considered possible that indoor sources of particles could play an important role in any health effects attributable to particle exposure, although information on the relative contribution of these sources is currently limited. Control of indoor sources could be a valuable component of possible remedial strategies to reduce total personal exposure.

The following gaps in knowledge have been identified.

- Identification of susceptible groups
  As noted above, current epidemiological evidence suggests a strong relationship between ambient particle levels and health effects only for some subgroups (i.e. the elderly, infirm and, probably, asthmatics), with others in the population appearing at lower risk of harm under normal exposure conditions. However, there may be other groups 'at risk', such as (as has been suggested) pregnant women and infants.

- Long-term exposures and chronic effects
  Although the relationships between short-term changes in particle level and health effects are reasonably well established, the situation is less certain when long-term effects of exposure are considered.

- Seasonal factors
  Little is known about the influence of seasonal factors on the relationship between health and outdoor particle levels.

- Importance of indoor and personal exposure
  For all the suggested health effects, there is very little information available on the importance, for the effects observed, of indoor particle levels and the composition of the personal cloud, especially with reference to UK conditions. This is partly a reflection of the technical limitations of the currently available sampling devices, and of the difficulties in comparing data collected using different devices. The compositions of indoor air and the personal cloud are likely to be of much greater importance than outside air quality, since pollution levels in the home would be expected to be of greatest relevance for the groups identified as at particular risk.

- Characterisation of particles indoors and source apportionment
  At present, both the characterisation of particles arising from indoor sources and methods to determine whether particular airborne particles originate from outdoor or from indoor sources are poorly developed. This inability to distinguish sources hampers the interpretation of studies on the composition of indoor air and the identification of the types of particle that are most associated with observed health effects.

- Mechanisms of toxicity
  The mechanisms by which particles elicit adverse health effects at normal exposure levels are not well established. The data are not yet sufficient to attribute causality to particles of a particular size, and other metrics of particle exposure (e.g. number, surface area, composition, presence of transition metals) have been suggested as important. Thus, the mechanism of particle toxicity remains an outstanding area of considerable uncertainty.

- Experimental models
  The relevance to humans of the widely-used chronic, high-level exposure rat model is being questioned. Also, there are few animal models of relevance to the subgroups identified as being at particular risk (e.g. elderly, COPD sufferers, asthmatics).

4.2 Summary conclusion

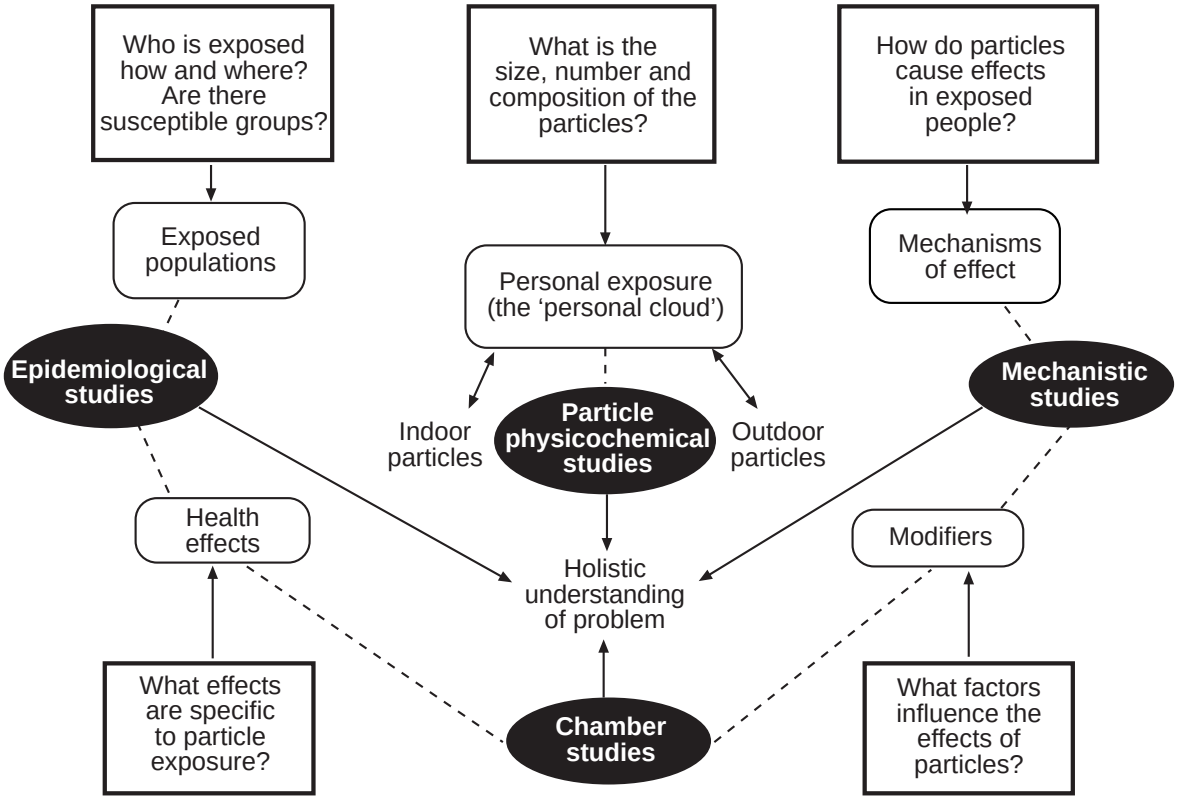
There is evidence to suggest that exposure to airborne particles may have an adverse impact on human health, with those suffering from chronic obstructive pulmonary disease or other cardiopulmonary conditions and patients with asthma being at greatest risk. However, the mechanisms underlying the observed effects are at present far from certain. The relative importance of indoor sources of particles is not known but, as these have the potential to elevate personal exposures, it is important to advance understanding about their role and contribution to adverse human health impacts.

4.3 Future direction of research

As a result of this review a number of important topics for future research, with direct relevance to the UK, have been identified. Future research should focus on identifying the particle sources that influence the personal exposure of those groups identified as at particular risk. In order to maximise the public health benefits resulting from any regulatory or remedial action it is important to clarify the type(s) of particle of importance, their sources and behaviour, and the interactions between (and factors affecting) the indoor, outdoor and personal exposure compartments.

A multidisciplinary approach, involving epidemiology, human and nonhuman mechanistic studies and exposure monitoring, is likely to be the best way to answer the outstanding questions. A possible multidisciplinary strategy is presented in Figure 4.1. Susceptible groups would be identified using epidemiological methods, and their exposure patterns to particles, the types of particle to which they are exposed, and the relevant sources would be identified subsequently through focused monitoring, linking outdoor, indoor and personal compartments. Once the types and levels of particle were better characterised, mechanistic studies could be undertaken in an attempt to identify the biological activities of the particles and to determine how exposures might be associated with adverse health effects. On the basis of current knowledge, a number of specific research activities having particular relevance to the UK (and which could be integrated into a multidisciplinary approach) can be identified (see Section 4.4).

Figure 4.1 Investigating the health effects of indoor particles



4.4 Specific research recommendations

A number of specific research topics of relevance to the UK have been identified. Although the need to adopt an integrated multidisciplinary approach to such research cannot be over-emphasised, the research topics are presented for convenience under the following categories: exposure assessment, epidemiology and human volunteer studies, and mechanistic studies.

4.4.1 Exposure assessment

The relationship between measurements derived from outdoor fixed-site monitors and indoor and personal exposures is still uncertain. To clarify this, it will be necessary to develop exposure models of the interrelationships between the outdoor, indoor and personal exposure compartments, to characterise and determine the relative importance of indoor particle sources, and to investigate the composition of the personal cloud. In support of this objective, a number of key areas for research have been identified.

- To facilitate investigations of human exposure to particles it is important to develop monitoring devices to measure outdoor, indoor and personal particle composition in a comparable and consistent manner.
- There is a need to characterise the size, number and composition of particles in the indoor air and the personal cloud, and their relationship to ambient (outdoor) air composition. Special effort will be needed to characterise the various sources of particles (for example, it may be appropriate to characterise any differences between gas and electric cooking) and the influence of the heterogeneous UK building stock.
- Because of its key role in determining individual exposure, there is a need to understand better the composition of, and factors affecting, the personal cloud.
- The spatial variations in particle level, composition, and dispersion and deposition patterns within representative homes should be studied.
- Investigations are required into the movement of particles of indoor and outdoor origin into and out of representative homes, so as to determine the relative importance of indoor and outdoor sources.
- Modelling studies should be undertaken to assist the characterisation of the interrelationships between indoor, outdoor and personal air, and the effects of activity patterns and other factors.
- The influence of seasonal and behavioural factors on indoor to outdoor ratios for UK residences requires clarification, with special reference to the living conditions and habits of ‘at risk’ groups.
- Biomarkers need to be developed to facilitate identification of the different types of particle to which an individual has been exposed. Such markers would be of great assistance in exposure monitoring.
- The effectiveness of strategies to reduce particle exposure indoors (e.g. improvements in home ventilation, use of air filters or cooker hoods) should be assessed, so as to inform the debate regarding the most appropriate measures to undertake to improve public health.

4.4.2 Epidemiology and human volunteer studies

Future epidemiological and human volunteer studies should seek to confirm the health effects attributable to particle exposure and to define better the groups most at risk. In particular, in the context of this review there is a need to investigate the relative importance of indoor sources of particle exposure. The following research needs have been identified.

- Epidemiological studies, focusing on identified ‘at risk’ groups, are required to clarify the strength of the relationships between health endpoints and particle size, number and composition. In particular, there is a need to investigate the relative importance of small (<2.5 μm) diameter particles.
- The association between various indoor combustion sources and identified health effects should be systematically investigated for UK homes.
- The influence of indoor/outdoor activity and behaviour patterns should be investigated for ‘at risk’ groups.
- Experimental studies are required to investigate the influence on biologically-important endpoints (e.g. antioxidant status, blood coagulatability) of cooking activities, cooker fuel type and other relevant indoor particle sources.
- Information should be collected on the geographical variations in health effects in relation to the composition of the particles to which individuals are exposed.

- Research approaches should be developed and implemented that focus on chronic rather than shorter-term health endpoints.

4.4.3 Mechanistic studies

The significance of particle composition, size and number in determining the observed human health effects still needs clarification, and will require study of the relationship between composition and innate toxicity. However, mechanistic research should be directed towards elucidating processes relevant to normal human exposures, and therefore should take account of findings from investigations of the size, number and composition of indoor and outdoor air particles. The following research needs have been identified.

- Methods should be developed that are capable of collecting or generating environmentally-relevant samples of particles in sufficiently large amounts to be used to provide the test materials for *in vivo* studies; until such particulate material is widely available in sufficient quantities, mechanistic research on particles should remain focused on *in vitro* techniques.
- Investigations of proposed mechanisms of particle toxicity (e.g. transition metal effects) should be extended to particle size ranges, compositions and levels of relevance to normal human exposures.
- The bioavailability of biologically-active chemicals (e.g. PAHs and metals) present on or in particles should be investigated.
- Models should be developed to investigate the differences in response to particles that may exist between normal and susceptible humans. This would be of value in assessing the likely relevance of proposed mechanisms of particle toxicity.

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Indoor Air Quality in the Home (2): Carbon Monoxide	Assessment A5 (1998)

Special reports

Understanding Asthma (1995)

Health Effects of Ozone and Nitrogen Dioxide in an Integrated Assessment of Air Pollution (1997)

Fibrous Materials in the Environment (1997)

Organophosphorus Esters: An Evaluation of Chronic Neurotoxic Effects (1998)

Joint Research Programmes on Outdoor and Indoor Air Pollution (A Review of Progress, 1999) (2000)

Risk Assessment and Toxicology Steering Committee reports

Developing New Approaches to Assessing Risk to Human Health from Chemicals	cr1 (1999)
Risk Assessment Approaches Used by UK Government for Evaluating Human Health Effects from Chemicals	cr2 (1999)
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