

Particles in ambient air — a health risk assessment

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Preface

This criteria document on particles in ambient air has been prepared at the Institute of Environmental Medicine, Karolinska Institutet, at the request of the Swedish Environmental Protection Agency. Although each chapter has main authors, the work has been a joint effort, and all conclusions and recommendations have been thoroughly discussed by the group. Besides the authors, the group included Carl-Elis Boström and Titus Kyrklund from the Swedish Environmental Protection Agency. Furthermore, a draft of the document was discussed with a reference group including Bertil Forsberg, Hans-Christen Hansson, Thomas Sandström, and Katarina Victorin. The main focus of the document is on effects other than cancer since particles in the ambient air were recently evaluated as a risk factor for cancer by the Institute of Environmental Medicine. In general, literature published through 1998 is reviewed, with occasional inclusion of important work published thereafter. However, the chapter on epidemiologic studies was prepared earlier and primarily relates to reports published through 1997.

Abbreviations

General

CI	confidence interval (95% CI values used throughout)
OR	odds ratio
r	correlation coefficient
R ²	coefficient of determination
RR	relative risk
SE	standard error

Organizations, studies and areas

APHEA	Air Pollution and Health: a European Approach (study)
EPA	Environmental Protection Agency
ICRP	International Commission on Radiological Protection
ISO	International Organization for Standardization
NHANES, I & II	National Health and Nutrition Examination Survey, I and II
OECD	Organization for Economic Co-operation and Development
PEACE	Pollution Effects on Asthmatic Children in Europe
UK	United Kingdom
US	United States
SMSA	standard metropolitan statistical areas

Air pollutants and related terms

BS	black smoke
CO	carbon monoxide
CoH	coefficient of haze
H ⁺	acid particles
KM	a particulate measure of optical reflectance
NO ₂	nitrogen dioxide
NO _x	nitrogen oxides
O ₃	ozone
PM	particulate matter (general term)
PM _{1.5}	particulate matter <1.5 µm in diameter
PM _{2.5}	particulate matter <2.5 µm in diameter
PM ₇	particulate matter <7 µm in diameter
PM ₁₀	particulate matter <10 µm in diameter
PM ₁₅	particulate matter <15 µm in diameter
ΔPM ₁₀	change in PM ₁₀
SO ₂	sulfur dioxide
SO ₄	sulfate ions (SO ₄ ²⁻)
SP/SPM	suspended particles/particulate matter (≈TSP) [term used in some studies, may differ somewhat from US standardized TSP measurements]
TEOM	Tapered Element Oscillation Microbalance®
TSP	total suspended particles

Immunologic and related terms

GM-CSF	granulocyte macrophage colony stimulating factor
Ig	immunoglobulin
IFN-γ	interferon gamma

IL	interleukin
RNA	ribonucleic acid
TNF-α	tumor necrosis factor alpha

Disease categories and related terms

AMI	acute myocardial infarction, ICD-9 code 410
AP	angina pectoris, ICD-9 code 413
CDR	cardiac dysrhythmias, ICD-9 code 427
CerebroVD	cerebrovascular disease, generally all or most of the 430—438 ICD-9 codes
COPD	chronic obstructive pulmonary disease, generally all or most of the 490—492 and 493—496 ICD-9 codes
CVD	cardiovascular disease, generally all or most of the 390—459 ICD-9 codes
HD	heart disease, generally all or most of the 390—429 ICD-9 codes
HF	heart failure, ICD-9 code 428
ICD-9	International Classification of Diseases, 9th revision
IHD	ischemic heart disease, ICD-9 codes 410—414 or only 410+413
SIDS	sudden infant death syndrome
RD	respiratory disease, generally all or most of ICD-9 codes 460—519
VD	vascular disease, generally all or most of the 430—459 ICD-9 codes

Pulmonary function, respiratory symptoms and medication use

BD use	bronchodilator medication use (for asthma)
FEF _{25–75}	forced expiratory flow between 25% and 75% of the vital capacity
FEV _{1.0}	forced expiratory volume at 1 second
FEV _{0.75}	forced expiratory volume at 0.75 second
FEV _{0.25}	forced expiratory volume at 0.25 second
ΔFEV _{1.0}	change in FEV _{1.0}
FVC	forced vital capacity
ΔFVC	change in FVC
LRI	lower respiratory infection
LRS	lower respiratory symptoms (eg, wheeze, dyspnea, chest tightness, phlegm)
MMEF	maximum mid-expiratory flow (=FEF _{25–75})
PEF	peak expiratory flow
PEFR	peak expiratory flow rate (=PEF)
R _{aw}	airway resistance
RM use	regular medication use (for asthma)
TGV	thoracic gas volume, the gas volume in the lung at which airway resistance is measured
SRaw	specific airway resistance (= TGV · R _{aw})
UR	upper respiratory
URI	upper respiratory infection
URS	upper respiratory symptoms (eg, cough, sore throat, runny/stuffy nose, sneezing)
XM use	extra (symptomatic) medication use (for asthma)

Particles in the ambient atmosphere

by Hans Areskoug

Airborne particulate matter (PM) represents a broad class of chemically and physically diverse substances. The principal defining feature of airborne PM is that it consists of discrete particles in the condensed (liquid or solid) phase spanning several orders of magnitude in size, from molecular clusters of a few nanometers in diameter to coarse particles of about 100 micrometers.

Airborne particles can be either primary or secondary in nature. Primary particles are emitted directly into the atmosphere either by natural or anthropogenic processes. Secondary particles have a predominantly man-made origin and are formed in the atmosphere from the oxidation of sulfur dioxide (SO₂), nitrogen dioxide (NO₂), and volatile organic hydrocarbons and subsequent reactions.

In most European countries, industrialization and a high volume of traffic mean that anthropogenic sources dominate, especially in urban areas. The most significant sources are road traffic, power plants, combustion sources (industrial and residential), industrial fugitive dust, loading and unloading of bulk goods, mining activities, and, in some local instances, construction and demolition activities. The main natural sources are sea spray and suspended soil dust.

The major chemical constituents of airborne particles are sulfates, nitrate, carbonaceous compounds (both elemental and organic carbon compounds), acids, ammonium ions, metal compounds, water, and crustal materials.

Physical and chemical characteristics

Particle-size distribution

Size is one of the most important parameters in determining the properties and fate of atmospheric particles. The atmospheric deposition rates of particles, and, therefore, their residence time in the atmosphere is strongly dependent on particle size. Size also influences the particle deposition pattern in the lungs. Light scattering is a strong function of particle size. The scattering efficiency is greatest for particles in the size range 0.3–1.0 μm , and it decreases rapidly for particles outside this range. Therefore, the number of particles and their size distribution have a large effect on atmospheric visibility. Particles suspended in the atmosphere also affect the earth's energy budget, and thus the climate, by increasing the reflection of solar radiation back to space and indirectly by affecting the formation of clouds (1).

Although atmospheric particles are often not spherical, their size is described by an "equivalent" diame-

ter. The equivalent diameter of a particle is the diameter of a sphere having the same physical behavior as the particle in question. The aerodynamic diameter is often used to describe the size of particles. It is defined as the diameter of a spherical particle with the same settling velocity as the particle in question but with a density of 1 g/cm³.

An important feature of atmospheric aerosol size distributions is their multimodal nature. Mass (and volume) distributions are almost always bimodal, with a minimum between 1 and 3 μm (figure 1). The particles that are mostly larger than this minimum are termed coarse. Those that are mostly smaller are termed fine.

Particles are designated as primary if they are emitted directly into the air as particles or as vapors that condense to form particles without a chemical reaction. Secondary particles are formed following a chemical reaction in the atmosphere, which converts a gaseous precursor with a low enough vapor pressure.

The crushing, grinding, and abrasion of surfaces that break large pieces of material into smaller pieces form the coarse mode particles. They are then suspended by the wind or by anthropogenic activity. Energy considerations generally limit the break-up of large particles to a minimum size of about 1 μm . Mining and agricultural activities are examples of anthropogenic sources of coarse mode particles. Fungal spores, pollen, and plant and insect fragments are examples of natural bio-aerosols suspended as coarse particles.

The number distribution of the fine-mode particles reveals three modes (figure 1). The fine-mode particles are originally formed by the conversion of gases to

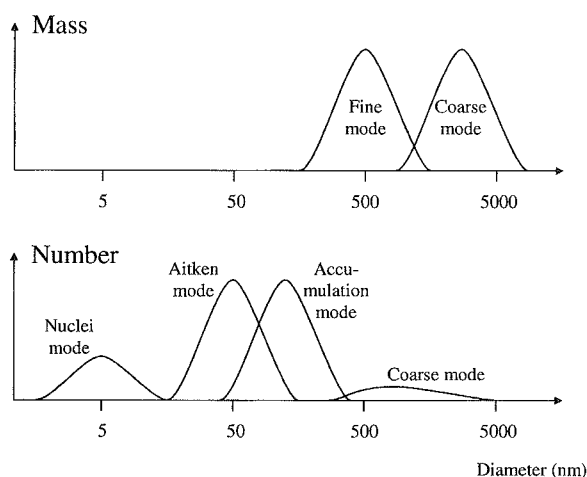


Figure 1. Conceptual description of the particle-size distribution of the ambient aerosol. The relative size of the modes gives the approximate relation between the different modes.

particles. Nuclei-mode particles are the smallest, a few nanometers to 10 nanometers in diameter, and are formed by gas phase chemistry and changes in temperature and relative humidity. Nuclei-mode particles sometimes occur at high concentrations in limited areas. Next in size is the Aitken mode between 20 and 80 nm in diameter. The source of the Aitken particles is not well known. The general assumption is that these particles originate either from primary sources or by growth of nuclei particles by coagulation or by the condensation of gases. Aitken-mode particles grow, through

Table 1. Properties of fine and coarse mode particles. Adapted from Wilson & Suh (2).

	Fine mode ($<2.5 \mu\text{m}$)	Coarse mode ($>1.0 \mu\text{m}$)
Formed from	Gases	Large solids or droplets
Formed by	Chemical reactions	Mechanical disruption (eg, crushing, grinding, abrasion of surfaces)
	Nucleation	Evaporation of sprays
	Condensation	Suspension of dust
	Coagulation	
	Evaporation of fog and cloud droplets in which gases have dissolved and reacted	
Composition	Sulfate, sulfate ion (SO_4^{2-})	Resuspended dust (eg, soil dust, road dust)
	Nitrate, nitrate ion (NO_3^-)	Coal and fly ash
	Ammonium, ammonium ion (NH_4^+)	Metal oxides of crustal elements (silicon, aluminum, titanium, iron)
	Hydrogen ion (H^+)	Calcium carbonate, sodium chloride, sea salt
	Elemental carbon	Pollen, mold, fungal spores
	Organic compounds (eg, polycyclic aromatic hydrocarbons, PNA).	Plant or animal fragments
	Metals (eg, lead, cadmium, nickel, copper, zinc, manganese, iron)	
	Particle bound water	
Sources	Combustion of coal, oil, gasoline, diesel and wood	Resuspension of industrial dust and soil tracked onto roads and streets
	Atmospheric transformation products of nitrogen oxides, sulfur dioxide and organic compounds including biogenic organic species (eg, terpenes)	Suspension from disturbed soil (eg, farming, mining, unpaved roads)
	High temperature processes, smelters, steel mills, etc	Biological sources
		Construction and demolition, coal and oil combustion.
		Sea spray
Atmospheric life-time	Days to weeks	Minutes to hours

liquid-phase chemistry in clouds, to the size range called the accumulation mode, which is 100 to about 1000 nm. These particles are active in forming cloud droplets and are therefore removed from the atmosphere by precipitation.

Fine-mode particles can be of primary or secondary origin. The dominant anthropogenic fine-mode primary particle source is the combustion of coal, gasoline, diesel, and wood. Atmospheric transformation products of SO_2 , NO_2 , and organic compounds form secondary fine-mode particles. The source gases can be anthropogenic or natural.

The gas-to-particle conversion processes in a stack or a tail pipe of a car are similar to those in the atmosphere. The particle-size distribution in the atmosphere is therefore fairly stable despite vastly different source types.

The fine- and coarse-mode particles have substantially different properties, as they are formed in different processes (and are different sizes). A comparison of the two modes is given in table 1.

Generally, particles in the Aitken and accumulation mode dominate the number concentration of particles, while the particles in the accumulation and coarse mode dominate the mass. As the coarse mode is usually dependent on wind speed, ground conditions, and other dust-generating activities, its mass concentration can vary strongly. Another parameter of possible interest is the particle surface. The particles with the largest total particle surface area are those in the accumulation mode.

It should be noted that there is no general consensus among aerosol physicists on the subdivisions of fine-mode particles. Sometimes the nuclei mode, as defined in this report, and the Aitken mode are grouped together and named the nuclei mode. The mode denoted nuclei in this report are then called ultrafine nuclei.

In the terminology of health scientists ultrafine is often used to characterize any size distribution with a mass mean diameter below $0.1 \mu\text{m}$. Ultrafine particles, in reference to health effects, are closely related to the nuclei and Aitken mode. In this document ultrafine is used in its biological context.

Chemical composition

The processes that form the particles in the different modes also affect the chemistry and morphology of these particles.

The smallest particles (ie, nuclei mode) are believed to be formed by the bimolecular nucleation of gaseous sulfuric acid and water vapor. It is likely that gaseous ammonia is involved in the nucleation process, and it neutralizes the particles at least to some extent. However, it is probable that other gases (eg, organic) can also form nuclei particles. The composition of Aitken-mode particles is not well known due to analytical difficulties

and the poor theoretical understanding of the source of this mode. However, indirect methods indicate that the composition is similar to that of accumulation-mode particles (3). The chemical composition of accumulation-mode particles has been investigated in numerous studies. The composition of the urban and nonurban continental fine-particle mode is roughly the same (table 2). Sulfate and carbon compounds make up about 65% of the mass, and ammonium and nitrate about 15%. The carbon compounds are more abundant in urban aerosol (40%) than in the nonurban aerosol (30%), while the opposite is true for sulfate. Only 10% to 20% of organic carbon compounds have been identified in terms of molecular structure (5). Identified compounds include n-alkanes, n-alkanolic acids, aliphatic dicarbocyclic acids, diterpenoid acids, polycyclic aromatic hydrocarbons, and the like (6).

The main feature of the fine-mode particle composition in remote marine regions is the large fraction of crustal and marine components such as silicon, chlorine, calcium, iron, and undetermined compounds. The fraction of elemental carbon, one of the best tracers of anthropogenic emissions, is very low.

In contrast, major components of coarse particles are aluminosilicates and other oxides of crustal elements (eg, iron, calcium) in soil dust; fugitive dust from roads, industry, agriculture, construction and demolition; fly ash from the combustion of oil and coal; and additional contributions from plant and animal material.

Particle size as a function of relative humidity

The interaction between particles and water vapor is important in the atmosphere and has thus been investigated in several studies (3, 7). This interaction is also important in the human lung.

The amount of water absorbed by particles is related to relative humidity in the atmosphere, as well as in the respiratory system. The theoretical growth ratio of sodium chloride particles larger than 100 nm is 5 to 6 when the relative humidity is above 99.5% (figure 2). The smaller the dry size of particles, the lower the growth ratio. The theoretical growth ratios have been confirmed in experiments simulating the humidification process in the human lung (8).

The lower growth for particles less than 100 nm may be important with respect to the biological effect of water-soluble particles. It implies that hygroscopic accumulation-mode particles are more diluted when exposed to humidification in the lungs than nuclei- and Aitken-mode particles are.

The growth of a particle in humid air can also be used as an indirect measurement of the chemical composition of a particle (ie, how much hygroscopic material it contains). In the ambient accumulation mode, two

types of particles are observed (9, 10). One type adsorbs very little water when humidity increases, while the other can adsorb considerable amounts. The less hygroscopic particles grow only by about 5% in diameter at 85% relative humidity, and therefore these particles evidently contain about 95% hydrophobic material, probably soot and organic components. The more hygroscopic particles grow about 40% at 85% relative humidity, and this phenomenon indicates that the particles are predominately inorganic salts such as sulfates, nitrates, and chlorides. However, the growth is far from what is expected for pure salts (see the preceding text), probably because a significant fraction of hygroscopically inactive material is mixed with the inorganic salts. The less hygroscopic particles are more abundant, up to 70%, in urban areas, while in remote regions the relation between the two types is often reversed.

The different growth of the two particle types in a humid environment, like the human lung, leads to different aerodynamic properties, and thus the two particle types deposit in different parts of the respiratory system.

Table 2. Average chemical composition (%) of fine mode particles (<1 μm) in different regions of the world. Adapted from Heintzenberg (4). [C(e) = C (elemental), C(o) = C (organic), NH_4^+ = ammonium ion, NO_3^- = nitrate ion, SO_4^{2-} = sulfate ion]

Region	C(e)	C(o)	NH_4^+	NO_3^-	SO_4^{2-}	Other
Remote ^a	0.3	11	7	3	22	56
Nonurban continental	5	24	11	4	37	18
Urban	9	31	8	6	28	18

^a Mainly data from islands and ship cruises in the Atlantic and Pacific oceans.

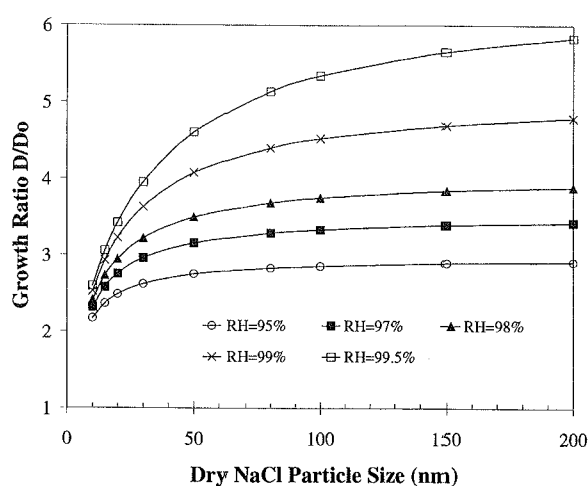


Figure 2. Theoretical predictions of growth of sodium chloride (NaCl) particles at relative humidity between 95% and 100%.

Measurement methods

PM, unlike other air pollutants, tends to be classified by the measurement method used. Thus PM₁₀, PM_{2.5}, black smoke (BS), and total suspended particles (TSP) are all terms used to characterize the concentration of airborne PM, and they give an indication of the measurement method used. These terms and the health-related sampling conventions formulated in an international standard by the International Organization for Standardization (ISO) are defined below (11) as follows:

Inhalable fraction (IF): the mass fraction of total airborne particles that is inhaled through the nose or mouth. For ambient atmospheres the fraction is given by:

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

where D is the aerodynamic diameter (m) of the particle and U is the wind speed (m/s).

Thoracic fraction: the mass fraction of inhaled particles that penetrate the respiratory system beyond the larynx. As a function of total airborne particles, it is given by a cumulative lognormal curve, with a median of 10 µm and a geometric standard deviation of 1.5.

Respirable fraction: the mass fraction of inhaled particles that penetrate to the alveolar region of the lung. As a function of total airborne particles, it is given by a cumulative lognormal curve, with a median of 4 µm and a geometric standard deviation of 1.5.

"High-risk" respirable fraction: the respirable fraction for the sick and infirm or children. As a function of total airborne particles, it is given by a cumulative lognormal curve, with a median of 2.5 µm and a geometric standard deviation of 1.5.

Total suspended particulate (TSP): a term describing the gravimetrically determined mass loading of airborne particles, most commonly associated with the use of the United States (US) high-volume sampler in which particles are collected for weighing. The sampler has a cut point¹ that varies between 25 and 40 µm depending on wind speed and direction.

PM₁₀: particles measured by a sampler that contains a size fractionator of defined characteristics with a 50% sampling efficiency at an aerodynamic diameter of 10 µm. This measurement includes the fine-mode particles and part of the coarse-mode particles and is an indicator for thoracic particles.

PM_{2.5}: particles measured by a sampler that contains a size fractionator of defined characteristics with a 50%

sampling efficiency at an aerodynamic diameter of 2.5 µm. The cut point is primarily chosen to sample the fine-mode particles, but mimics also the "high-risk" respirable fraction as defined by ISO.

Black smoke (BS): nonreflective (dark) PM, associated with the smoke-stain measurement method. Sampled particles are collected on a filter. The quantity of dust is calculated by converting the light reflectance from the surface of the filter using a calibration curve.

The majority of reliable instruments currently available are for the PM₁₀ fraction. They generally make use of a validated sampling head to select the PM₁₀ fraction, the collected particles being collected for analysis with primarily the following two types of instruments: (i) gravimetric, cumulative samplers in which the amount of particles deposited over a sampling period, normally 24 hours, is determined by weighing and (ii) direct-reading monitors in which the particles are either deposited on a filter, with continuous assessment of the change in a property of the filter due to their presence, or passed through an optical sensing unit. The PM_{2.5} fraction can be measured using the same analyzers if an appropriate sampling head is used.

Gravimetric PM₁₀ samplers

Several gravimetric, cumulative samplers are available. The main difference between them is the flow rate, which ranges from 16.7 to 1130 l/min. The samplers with a high flow rate have the advantage of providing a sufficient sample for both gravimetric and chemical analysis, but they are larger than those with a low flow rate. Gravimetric-type samplers constitute the reference in the United States and are also the proposed European reference.

In the proposed European reference method, the filter is equilibrated for 48 hours before and after the sampling at 20±1°C and a relative humidity of 50±5%. This process is supposed to remove most of the particle-bound water, but may also lead to some loss of volatile compounds, including volatile hydrocarbons and ammonium nitrate. More importantly, the ambient conditions of temperature and humidity that the sample is exposed to both during and after collection (before removal from the sampler) are completely uncontrolled and can lead to additional variability in the amount of PM.

Direct-reading PM₁₀ samplers

The direct-reading samplers normally use a low-flow PM₁₀ or PM_{2.5} inlet. Several different instruments are

¹ When used in the context of sampling, cut point is a term to describe the separation efficiency curve of samplers. The cut point is typically described by the aerodynamic diameter at which the sampler achieves 50% collection efficiency.

available, and they can be categorized into the following three main categories: optical, beta particle, and resonance oscillation.

The optical instruments use the interaction between airborne particles and visible light in a sensing region to determine the amount of particles. As the response is dependent on the size distribution, shape, and refractive index, the instruments require calibration to give results in terms of mass. The calibration only holds if the particle properties do not change, and hence measurements obtained in the ambient atmosphere can be very uncertain.

In the beta-particle instruments, the attenuation of the intensity of beta particles passing through a dust-laden filter is measured. The change in attenuation reflects the amount of particles collected. As the change is not only dependent on the mass of the particles, but also on the elemental composition, the instrument must be calibrated, and hence the results, as for the optical samplers, are uncertain.

TEOM® sampler. The Tapered Element Oscillating Microbalance (TEOM) is the only direct-reading monitor in which the output is directly dependent on mass. The sample air passes a filter on top of the narrow end of a hollow tapered glass tube. As particles collect on the filter, the mass, and thus the natural frequency of oscillation of the tube, changes. The frequency change is directly proportional to the added mass. The sampling inlet including the sensing unit is heated to 30°C or 50°C to drive off any sampled water.

Several researchers have reported that the modification of the aerosol by the elevated operating temperature appears to have a significant effect (loss) on mass concentrations under certain conditions (ie, a high concentration of ammonium nitrate and volatile organic hydrocarbons). Meyer et al (12) co-located a TEOM with a gravimetric PM₁₀ sampler in Mammoth Lakes, in the United States, during a winter heating season (heavy wood stove usage). The regression between the two samplers had a strong correlation ($r^2 > 0.98$), but the TEOM results were 35% and 45% low for operation at 30°C and 50°C, respectively. The negative bias of the TEOM was attributed primarily to a loss of semivolatile organics from the filter. A WESTAR (13) council report summarizes the relationship between TEOM monitors and cumulative gravimetric samplers in at least 10 states in the western part of the United States. The report concludes that, on the average, the TEOM sampler showed 22% lower concentrations than other co-located PM₁₀ samplers at concentrations above 50 µg/m³. On the other hand, several studies (eg, reference 14) have reported a consistent and linear relationship between the TEOM sampler and gravimetric samplers.

As already noted, a loss of volatile PM can occur also with gravimetric filter methods. The loss can vary greatly, due to the uncontrolled conditions during and after the sampling, but it is, in general, lower than for TEOM samplers. Whether the sometimes lower, but well-defined (in terms of sampling conditions) TEOM results are to be preferred before the perhaps more realistic, but also more variable results obtained by the gravimetric filter methods is an open question. The discussion highlights the problems of particle sampling and raises the question of whether the sampling conditions should be tightly controlled in the reference methods as suggested by, for example, Smith et al (15). However, the possible difference between the TEOM sampler and the gravimetric filter methods should be kept in mind when data obtained with the TEOM sampler are used to determine compliance with air quality standards for PM₁₀. These standards are often based on PM₁₀ data obtained with gravimetric filter methods or by the conversion of BS or TSP data to PM₁₀ using conversion factors obtained in a comparison of TSP and BS with gravimetric filter methods.

Other particle-sampling methods

BS sampler. BS is determined in Sweden by a version of the method introduced by the OECD (Organization for Economic Co-operation and Development) in 1964. Air is drawn through an inverted funnel and a few meters of plastic tubing. The cut point of the method is about 4 to 7 µm at low wind speeds, but lower at high wind speeds. The collected particles are deposited on white filter paper. The mass concentration of BS is calculated by converting the light reflectance from the surface of the filter using a calibration curve. Soot particles composed of elemental carbon, found in incomplete fossil-fuel combustion products, typically contribute most to the darkness of the particles. Thus the amount of elemental carbon, but not organic carbon, correlates the best with the reflectance. Other nonblack, noncarbon particles also have optical properties that can affect reflectance, although their contribution is usually negligible.

Since the relative proportion of atmospheric carbon and noncarbon particles can vary greatly from time to time and site to site, the same reflectance can be associated with markedly different amounts of collected particles or even with markedly different amounts of carbon. The calibration curves used in the OECD method are based on a European standard for soot from the time of the introduction of the method. At that time, coal was the predominant fuel used for heating. As the properties of particles have changed during the years depending on changing combustion and cleaning techniques, the mass concentrations given by the OECD method

cannot be compared over time or between different locations without considerable caution (16).

Several studies have found varying (site- and season-dependent) ratios for TSP and PM_{10} to BS. In the European study Pollution Effects on Asthmatic Children in Europe (PEACE), gravimetric PM_{10} samplers and BS samplers were collocated at 28 sites in 10 countries in the winter of 1993–1994 (17). Four Swedish sites were included, two in the southern and two in the northern part of the country. The correlation between PM_{10} and BS measured at the same site was high at most sites, but the median PM_{10} to BS ratio varied from 0.67 to 3.67. The average ratio was 1.97. The ratios varied less, from 2.45 to 3.67, at the Swedish sites.

In another study, results from three collocated BS and PM_{10} samplers at three English sites also correlated well at each site (18). The correlation was stronger in winter than in summer, indicating the larger contribution of black motor-vehicle-derived PM_{10} in winter and the larger contribution of secondary noncarbon PM_{10} in summer. The PM_{10} and BS concentrations were about the same in winter, but during summer the PM_{10} concentrations were systematically higher. The calculated regression coefficients for BS as a function of PM_{10} were also site-specific and, therefore, reflect the contribution of the different sources to the observed concentrations of PM at each site.

Coefficient of haze. A particle sampler for the coefficient of haze (CoH) has been employed for routine monitoring in many cities in the United States. The sampler collects particles with a 50% cut point of about 5 μm . The sampled particles are collected on a filter-paper tape that is periodically advanced to allow accumulation of another stain. The opacity of the stain is determined by the transmittance of light through the deposited material. The results are expressed in terms of optical density or the CoH per 1000 linear feet of air sampled (rather than in mass units). The CoH sampler is somewhat more responsive to noncarbon particles than the BS sampler is, but, again, any attempt to relate the CoH to micrograms per cubic meter requires site-specific calibration by a collocated gravimetric sampler.

Conversion to PM_{10} from other particulate measures

A variety of measures of airborne PM has been used in epidemiologic studies. If the health effects are to be related to a common measure (eg, PM_{10}) conversion factors from other measures have to be applied. Dockery & Pope (19) have suggested conversion factors of $PM_{10} = PM_{15} = BS = PM_{2.5}/0.6 = CoH \times 55 = TSP \times 0.55 = (\text{particulate sulfate}) \times 4$. These factors are used in the section on epidemiologic studies in this document. As already described, conversion factors are both site- and

time-dependent, making them highly variable, especially the factors that convert the optical measures BS and CoH. For example, the assumption that BS concentrations are equal to PM_{10} is based on studies in the United States. This relation does not seem to be valid in Sweden, where PM_{10} are two to four times the BS concentration; see the preceding discussion. The conversion factors for the gravimetric measures ($PM_{2.5}$, PM_{15} , TSP, and particulate sulfate) are probably more accurate in most cases.

Main sources of particulate matter

In comparison with sources of other air pollutants there are two features of PM that increase the difficulty and uncertainty to estimate its emission. The first is that the sources that emit particles not only include fuel use, but also fugitive sources, whose scale and activity rates are poorly known. The other is the varying definitions of PM used in emission estimates. Sometimes the estimates refer to the total amount of suspended particles emitted, sometimes to the PM_{10} particles. Moreover, in most cases, no information is available on the size distribution of the emitted particles. Another difficulty is that emission inventories for particles in general contain no information on sources of secondary particles, which in many areas can make up a significant proportion of ambient concentrations.

Natural sources

On a global scale, several natural sources, such as suspension of soil dust, sea salt, volcanic activities, forest and other wild fires, and an ingress of extraterrestrial particles, are significant sources of particles emitted into the atmosphere.

The action of the wind on dry loose surfaces leads to particles blowing into the air. This phenomenon is most obvious during sand and dust storms in the world's deserts. These processes do, however, extend to other regions of the globe, although their magnitude is reduced where soils are moist and have vegetation cover.

Breaking waves on the sea cause the ejection of tiny droplets into the atmosphere. When the droplets evaporate, they leave mostly coarse, sea salt particles in the air. However, some of the particles are small enough to have an appreciable atmospheric lifetime. All parts of Sweden are influenced to some extent by sea salt particles. Coastal areas are obviously affected the most, especially the west coast of Sweden, where the salinity of sea water is substantially higher than in the Baltic Sea.

Secondary particles are formed naturally (i) by the oxidation of sulfur gases from oceans, wetlands, volcanoes and forest fires, (ii) by the oxidation of nitrogen

oxides (NO_x) produced by soils, forest fires and lightning, (iii) by the emission of ammonia from wild animals and undisturbed soil, and (iv) by the oxidation of hydrocarbons emitted from vegetation (terpenes, waxes) and wild fires.

A comparison of the global natural and anthropogenic emissions of particles is given in table 3. Overall the natural emissions are about 10 times the anthropogenic levels. However, the emission of fine particles is dominated by anthropogenic sources. In the densely populated parts of the Northern Hemisphere, including Sweden, natural sources are less important in comparison with the particles arising from human activities. The concentrations of PM₁₀ in Scandinavia are 10–50 times the estimated natural levels (21).

Table 3. Global emission estimates for major aerosol types in the 1980s. Source: Kiehl & Rodhe (20).

Source	Estimated flux (million tons per year)		
	Fine particles ^a	Coarse particles ^a	Comments
Natural			
Primary			
Soil dust	1000—3000 ^b		Mainly coarse
Sea salt	-	1000—10 000	
Volcanic dust	-	4—10 000	
Biological debris	-	26—80	
Secondary			
Sulfates from biogenic gases	80—150	-	
Sulfates from volcanic sulfur dioxide	5—60	-	
Organic matter from biogenic volatile organic compounds	40—200	-	
Nitrates from nitrogen oxides	15—50 ^b		Fine and coarse
Total natural	130—435 ^c	2000—23 100 ^{c, d}	
Anthropogenic			
Primary			
Industrial dust, etc	4—130 ^b		Mainly coarse
Soot	5—20	-	
Secondary			
Sulfates from sulfur dioxide	170—250	-	
Biomass burning	60—150	-	
Nitrates from nitrogen oxides	25—65 ^b		Mainly coarse
Organics from anthropogenic volatile organic compounds	40—200	-	
Total anthropogenic	275—650	30—200 ^a	
Total	400—1 100	2030—23 300	

^a Coarse and fine size categories refer to mean particle diameter above and below 1 µm, respectively.

^b The sum of fine and coarse modes

^c Includes 50% of the nitrates formed from natural emissions of nitrogen oxides.

^d Includes all soil dust.

^e Includes all industrial dust and all nitrates formed from anthropogenic emissions of nitrogen oxides.

Anthropogenic sources of primary particles

Emissions from mobile sources. All mobile vehicle sources emit particles formed by the incomplete combustion of fuel and lubricating oil. Road transport also generates particles due to the wear of brakes and tires. The produced particles are generally smaller than 10 µm (table 4). Road transport can also generate high concentrations of particles in the vicinity of roads by the resuspension of particles deposited on road surfaces.

Particles form in high-temperature combustion processes in diesel and gasoline engines. Initially only soot particles are formed, while the other compounds are in the vapor phase. The hydrocarbons and, in the case of diesel, sulfate (which results from the fuel sulfur) condense as the temperature drops and form particles with a carbon core and a coating of hydrocarbons and sulfate. The particles grow by coagulation, condensation, and adsorption, predominantly after the gas has left the exhaust pipe, as the residence time is too short and the temperature too high for adsorption and coagulation.

The particle emission from diesel vehicles is more than a hundred times as high as the emission from gasoline-driven cars equipped with a three-way catalyst, while the emission from cars without a catalyst is about 10 times the emission from a catalyst car (table 5). The emission factors are calculated from standardized

Table 4. Size fraction of particulate matter emission from road transport. Source: US EPA (22).

	Mass percentage in size fraction	
	<2.5 µm	<10 µm
Gasoline engines		
Leaded — no catalyst	67	80
Unleaded — no catalyst	70	90
Three-way catalyst	90	97
Diesel engines		
	92	100
Tire wear	39	55
Brake lining	39	98

Table 5. Estimated emission factors for particles for gasoline-fueled light-duty vehicles, with and without a 3-way catalyst (TWC) (23, 24) and for diesel fueled-heavy-duty vehicles using an environmental class 1 (MK1) fuel and a nonclassified diesel fuel (MK3) (25).

	Estimated emission factors for particles (mg/km)
Gasoline passenger cars	
Light-duty without TWC, model 1993	20
Light-duty with TWC, model 1993	2.4
Diesel vehicles	
Heavy-duty vehicle MK1	299
Heavy-duty vehicle MK3	336

driving cycles for diesel- and gasoline-fueled vehicles. The gasoline-fueled vehicles are tested according to the federal test procedure of 1973, the diesel vehicles in a transient driving cycle simulating public transportation within a city area.

Emission factors are dependent on several factors (eg, weather conditions, speed, and engine conditions), and it is therefore difficult to make emission estimates based on them. However, when traffic frequency is taken into account, the annual exhaust particle emissions in Sweden from heavy and light duty diesel vehicles are estimated to be 6600 and 560 t/year, respectively (K Andersson, Swedish EPA, personal communication). The particle emission from gasoline-fueled cars with and without a catalyst is estimated to be 280 and 1360 t/year, respectively.

The movement of vehicles on streets results in the resuspension of road dust. The road dust deposit available for resuspension originates from the mechanical wear of, and dirt on, vehicles (including tire and brake lining wear), debris from loads on vehicles, influx of soil material, and the like. Data from the US Environmental Protection Agency (EPA) indicate that the resuspended dust mainly consists of coarse particles. About 20% of the particles are less than 10 μm in diameter, and about 9% have a diameter of less than 2.5 μm (26).

In Scandinavia, the use of studded tires in winter on paved roads without snow or ice cover may wear the road surface to such an extent that the resulting particle deposit on the road becomes the dominating source of resuspended particles (27). Sanding and salting to prevent slippery roads because of snow and ice are also important sources.

The amount of resuspended particles is thus dependent on many parameters (eg, traffic density and the ratio between the number of cars and buses or trucks, humidity, temperature, precipitation amount and duration of dry periods, frequency of sanding and salting, etc).

A model to calculate the PM_{10} concentrations due to local emissions, including resuspension, has been developed at the Swedish Meteorological and Hydrological Institute (28). The model has been applied to a central street in Stockholm (Hornsgatan, 33 000 vehicles/day, 93% cars) for two winter seasons (1 October—31 March, 1994—1995 and 1996—1997) and one summer (1 April—30 September 1995). The results showed that resuspension was the dominating source of PM_{10} during the winter season and generally accounts for between 20% and 50% during the rest of the year (29). The model was also applied for the winter season 1995—1996 to an area of about 15×20 km, including the central parts of Stockholm. The resuspension of particles contributed, on the average, 15—20% of the total PM_{10} concentration, which is about the same contribution as direct emissions from mobile sources.

It is tempting to try to estimate the total Swedish emission of resuspended particles by extrapolating the findings from Stockholm. However, it is not possible, as the parameters that control resuspension can differ markedly between the regions of Sweden (eg, the frequency of sanding and salting, ice and snow cover on roads, etc). Moreover, the Stockholm results are based on model estimates for the winter. The model findings must be further validated by measurements before they can be used for general assessments of emissions. However, the emission of PM_{10} particles due to resuspension may be of the same order of magnitude as the direct emissions from cars and trucks.

There are several other mobile sources that emit particles. The annual emissions from ships on Swedish territorial waters have been estimated to be 2000 t (30). Cargo ships are responsible for about 15%, ferries for about 23%, and pleasure boats for the rest. The large emissions from pleasure boats are due to the frequent use of 2-stroke engines, which only combust 75% of the fuel.

The emissions from airplanes consist of very small particles (<2.5 μm), soot, and engine wear. The magnitude of the emissions has been estimated from fuel-related emission factors. They are not significant emissions on a national scale, but may be of importance locally. The emissions during landing and take-off in the Stockholm area (including the largest civil airport in Sweden, Arlanda) are estimated to be 26 t/year (29).

Emissions from motorized tools and work machines are not regulated. This is a broad category that includes a variety of domestic, commercial, agricultural and forest sources, such as air compressors, snowmobiles, and lawnmowers. As they are often operated during long periods, the emissions of particles may be significant, especially at road and construction sites. The annual emissions in Sweden are estimated to be 6780 t, almost as much as the direct emissions from diesel and gasoline vehicles (K Andersson, Swedish EPA, personal communication).

Emissions from stationary combustion. The emission of particles due to the use of fossil fuel for heating is very important in the cold season. The emission factors for a residential heating unit and a large central heating unit for a shopping center fueled with oil have been estimated to be 140 and 100 mg of particles per kilogram of fuel, respectively (31). This level is lower than the emission factors for diesel vehicles; see the preceding discussion. The annual Swedish emission from residential heating has been estimated to be 580 t by Hansson et al (21).

Heavy oil is mainly burned in large power plants that are used at high consumption peaks, generally during cold winter days. The annual emissions are thus strong-

ly dependent on the meteorology. The total emission in 1994 is estimated to have been 5000 t, based on an oil consumption of 3.28 million cubic meters and using an emission factor of 1.5 grams of particles per kilogram of fuel (21). The emission from coal and charcoal combustion is estimated to be 1180 t/year (21).

In addition to fossil fuels, wood is burned for residential heating and occasionally in forest fires. Forest fires are significant particle sources on a global level, but is normally of less importance in the humid climate of Sweden. However, emissions from fuel wood for heating are a major source locally, especially during the cold part of the year.

Emissions from wood combustion consist mainly of PM, tar, and volatile compounds. As the combustion is often inefficient, large quantities of particles and organic matter are emitted. The composition of the particles is not known in detail. Tar is made up of a great number of condensable organic compounds, among which the polycyclic aromatic hydrocarbons are an important group. The annual Swedish emission of particles due to wood combustion is estimated to be in the broad interval of 8600–65 000 t (21).

Industrial processes. Industrial emissions can be a significant source of particulate emission in certain areas, depending on the location of the industry and the abatement technology used. Although many studies have been conducted to characterize emissions from industrial sources, for example, steel works, information on small emitters such as metallurgical processes and small factories is more limited. Particles emitted from these sources have been found to be in the size range of 0.5 to some 100 µm, depending on the nature of the source.

For precise emission estimates, detailed information is needed from each emitter. Such information is normally not available, and thus the estimates are very imprecise. Kindbom et al (32) have estimated the particulate emission for 1990–1995 to be 9000 t/year. A large fraction of the particles are likely to be larger than 10 µm.

Dust from construction sources. The amount of dust emission from a construction site depends on the size of the site and the amount of construction activity.

The annual emission of the PM₁₀ fraction of construction dust in the United Kingdom has been estimated to be 500–8300 t (18). The estimate is based on an American study around the construction site of an apartment and shopping center. By taking into account the size of the American study area, the amount of construction in the United Kingdom and the more humid climate in the United Kingdom, the emission range was calculated.

By further extrapolation to Sweden, on the assumption of the climate being about the same and the amount

of construction being proportional to the population (United Kingdom 57 million, Sweden 9 million), the Swedish emissions can be estimated to be 80–1300 t/year. Although this estimate is very rough — one could expect that the colder climate in Sweden than in the United Kingdom would reduce the Swedish emissions to some extent — the estimate shows that construction dust is a minor source on the national level, but may be important locally.

Summary of emission estimates for primary particles

The estimates given are summarized in table 6. They are essentially the same as those given by Hansson et al (21). They differ in that: (i) dust emissions from construction sites are included and (ii) new data on emissions from industrial sources (excluding combustion) are used.

Wood combustion is probably the major source, although the emission estimate is very uncertain. A better estimate requires better knowledge of wood consumption, emission factors, and also factors determining the combustion efficiency (eg, type of stove and condition of the wood fuel).

When the magnitudes of different sources are compared, one should be aware that the emissions from traffic, direct exhaust emissions, dust resuspension, and emissions from residential heating, especially wood combustion, generally occur close to the ground and in areas where people spend much of their time. Thus these

Table 6. Estimates of annual particle emissions in Sweden, 1995. (TWC = 3-way catalyst)

Source category	Particles (t/year)	Comments
Mobile sources		
Road transport		
Engine emissions		
Heavy-duty diesel	6600	
Light-duty diesel	560	
Petrol with TWC	280	
Petrol without TWC	1360	
Resuspension	5–10 000	Probably in the same order of magnitude as engine emissions from mobile sources
Other mobile sources		
Working machines	6780	
Ships	2000	On Swedish territorial waters
Air craft	<100	Insignificant on a national level
Stationary combustion		
Heavy oil	5000	
Domestic oil	580	
Coal and charcoal	1180	
Wood	8600–65 000	
Industrial processes	9000	
Construction	80–1,300	
Total	49 000–112 000	

sources are normally more important than the remaining sources from a health point of view. The strength of the sources can also vary considerably over time. For example, the resuspension of road dust can differ substantially depending on the road surface being wet or dry.

Sources of secondary particulate matter

Secondary PM is an important contributor to suspended particulate mass. Sulfate is formed by the oxidation of SO₂, nitrate by the oxidation of NO₂, ammonium from ammonia and aerosol organic carbon species by the oxidation of a large number of precursors. Thus the formation rate of a substantial fraction of the PM is given by a complex function of both emission rates of precursor gases and the rate of chemical processes in the atmosphere.

To be able to use precursor emission estimates to model the formation of secondary particles, detailed knowledge of the conversion processes is needed. While the mechanism for forming inorganic secondary particles is fairly well known, that for organic secondary aerosol is not well understood.

The emission of the precursor gases SO₂, NO_x, ammonia, and nonmethane hydrocarbons in Sweden in 1995 is estimated to be 94, 355, 61, and 458 thousand tonnes, respectively. These values cannot directly be translated into production rates of particles. While, for example, the chemical oxidation of SO₂ leads quantitatively to the formation of sulfate, the formation of aerosol from the oxidation of nonmethane hydrocarbons is much less because only a small fraction reacts to form particles.

Dry deposition and precipitation scavenging of some of the precursor gases may occur before the gases are transformed to aerosols. In addition, a large fraction of the gases is transported out of Sweden before being oxidized. Likewise, oxidation products formed from precursor gases emitted in countries outside Sweden constitute a considerable fraction of the airborne PM in Sweden.

This "import-export" of airborne PM can be illustrated by model calculations made within the Co-operative Program for Monitoring and Evaluation of the Long-range Transmission of Air Pollutants in Europe

Table 7. Import-export budgets of oxidized sulfur (kt/year) and oxidized and reduced nitrogen (kt/year) for Sweden, average 1985–1994. Source: Barrett et al (33).

Constituent	Emissions	Export	Deposition	Import ^a
Oxidized sulfur	85	65	219	199
Oxidized nitrogen	124	109	120	105
Reduced nitrogen	58	27	80	51

^a Import = deposition in Sweden originating from non-Swedish sources.

(table 7). Sweden is a net importer of oxidized sulfur and reduced nitrogen and a net exporter of oxidized nitrogen, but it exports the major part of the SO₂ and NO_x emitted by domestic sources and about half of the emitted reduced nitrogen.

Long-range transport

The long-range transport of particles can be viewed as a separate source when the importance of Swedish control measures to reduce the particle emissions are being assessed.

The long-range transport of particles to Scandinavia is totally dominated by anthropogenic fine-mode particles, which have an atmospheric life-time long enough to be transported thousands of kilometers. Moreover, the fine-mode generating sources in northern Europe are almost solely anthropogenic. A major fraction of these particles is probably secondary particles.

Long-range transport dominates the concentrations of particles and other pollutants in remote areas of Sweden not influenced by any nearby sources. Persson et al (34) estimated that long-range transport constitutes an average of about 50% of the airborne particles in southern Sweden and, on the average, is the dominating source in the north. Tarrasón & Tsyro (35) estimated that the contribution to the concentration of inorganic PM_{2.5} particles due to sources abroad averages 90% for Sweden. The model results should be treated with caution, as the model did not consider primary particles. Moreover, elemental and organic carbon was not considered by Tarrasón & Tsyro, and it was calculated in a simplified way by Persson et al.

Ambient concentrations

Regular monitoring of the health-related particle sizes (ie, PM₁₀ and PM_{2.5}) in Sweden did not commence until the beginning of the 1990s. Data are still sparse, especially PM_{2.5} data, as the measurements are made mainly in a few large towns, mostly in the southern part of the country. Most of the available data are from measurements at roof level in city centers. Data on the concentrations at street level are primarily from short-term campaigns. The rural, background concentration is monitored at one station 100 km south of Stockholm. Unfortunately, no data on the concentrations in a residential area where wood burning is used for heating is available. A summary of all available data on PM₁₀ in Swedish cities is shown in table 8 (roof level) and table 9 (street level).

Roof level (urban background) PM₁₀ concentrations

The annual mean concentration of PM₁₀ at roof level is 12–20 µg/m³. The 98th percentiles of the daily mean

values are in the range of 30–40 $\mu\text{g}/\text{m}^3$, the maximum daily mean concentrations being in the range of 50–100 $\mu\text{g}/\text{m}^3$. The ratios between the 98th percentile and the mean are 2.3–2.7.

The variation of roof-level PM_{10} concentrations between the cities is strikingly small. The main reason is the strong influence of the long-range transport of particles in southern Sweden. Consequently, the difference between the concentrations at roof level in the towns and the concentrations in rural air is also small. The average concentration at roof level in central Stockholm in 1994–1997 was 15 $\mu\text{g}/\text{m}^3$ compared with 10 at a rural background station about 100 km from the town center. The 98th percentile of the daily means in the city was 36; at the background station it was 30 $\mu\text{g}/\text{m}^3$.

Table 8. Summary of PM_{10} concentrations at roof level in Swedish cities. Data from the local environment and health protection administrations. (Summer = 1 April – 30 September, Winter = 1 October – 31 March, 98%-day, max-day, 98%-hour, max-hour: 98th percentile and maximum of daily and hourly averages, respectively)

Station	Period	Aver age	98%- day	Max- day	98%- hour	Max- hour
Göteborg, Femman	Summer 90	14	..	52	..	..
Malmö, Kalendegatan	Summer 90	8	..	60	..	..
Göteborg, Femman	Winter 90–91	17	..	59	..	..
Malmö, Kalendegatan	Winter 90–91	20	..	90	..	..
Göteborg, Femman	Summer 91	14	..	44	..	..
Malmö, Kalendegatan	Summer 91	7	..	43	..	..
Göteborg, Femman	Winter 91–92	15	..	70	51	211
Malmö, Kalendegatan	Winter 91–92	11	..	80	..	..
Göteborg, Femman	Summer 92	15	..	53	..	..
Malmö, Kalendegatan	Summer 92	6	..	42	..	..
Göteborg, Femman	Winter 92–93	15	..	53	48	260
Malmö, Kalendegatan	Winter 92–93	8	..	116	..	..
Norrköping, Lindö	Winter 92–93	12	28	..	34	58
Göteborg, Femman	Summer 93	15	..	64	..	..
Stockholm, Torkel K	Summer 93	12	..	22	..	..
Göteborg, Femman	Winter 93–94	17	..	65	58	275
Stockholm, Torkel K	Winter 93–94	15	..	34	..	..
Göteborg, Femman	Summer 94	14	..	31	..	..
Malmö, Kalendegatan	Summer 94	26	..	78	..	..
Stockholm, Torkel K	Year 1994	14	38	48	..	..
Göteborg, Femman	Winter 94–95	15	..	45	43	162
Malmö, Kalendegatan	Winter 94–95	12	..	45	..	..
Norrköping, Rosen	Winter 94–95	13	..	43	..	..
Oxelösund, vattentornet	Winter 94–95	13	..	56	..	..
Göteborg, Femman	Summer 95	13	..	50	..	..
Norrköping, Rosen	Summer 95	14	..	42	..	..
Stockholm, Torkel	Year 1995	15	34	..	..	..
Göteborg, Femman	Winter 95–96	17	..	53	..	..
Norrköping, Rosen	Winter 95–96	15	41	..	47	167
Oxelösund, vattentornet	Winter 95–96	16	..	60	..	..
Göteborg, Femman	Summer 96	16	..	55	..	..
Malmö, Kalendegatan	Summer 96	16	..	44	..	..
Stockholm, Rosenlund	Year 1996	16	38	49	..	..
Göteborg, Femman	Winter 96–97	13	..	47	..	..
Malmö, Kalendegatan	Winter 96–97	16	..	59	..	..
Malmö, Kalendegatan	Summer 97	16	..	49	45	97
Stockholm, Rosenlund	Year 1997	15	36	..	..	..
Malmö, Kalendegatan	Winter 97–98	14	..	47	39	100

Street level PM_{10} concentrations

The concentrations at street level in the major cities in southern Sweden vary considerably more; this variation can be explained by varying traffic density and type of street (eg, street canyon versus street without surrounding buildings). The mean concentrations are in the range of 20–40 $\mu\text{g}/\text{m}^3$, the 98th percentile of the daily means being 50–100 $\mu\text{g}/\text{m}^3$. The ratios between the 98th percentile and the mean extend from 2.2 to 3.0. The maximum daily concentrations are in the range of 100 to 150 $\mu\text{g}/\text{m}^3$, and the hourly mean concentrations can be up to 300 $\mu\text{g}/\text{m}^3$.

PM_{10} and black smoke in northern Sweden

Very little data on PM_{10} are available from northern Sweden. However, soot levels in several small municipalities in the inland of northern Sweden in general were about the same as in the major cities in southern Sweden (36, 37). Soot levels in six small northern municipalities in January to March 1990 were substantially elevated during cold periods (38), possibly because of the low dispersion during the stable conditions often prevailing during cold weather. In addition, low temperatures directly influence the emissions of soot (and PM_{10}) through the need for increased house heating. Wood burning for residential heating is widespread in this area

Table 9. Summary of PM_{10} concentrations at street levels in Swedish cities. Data from the local environment and health protection administrations. (Summer = 1 April – 30 September, Winter = 1 October – 31 March, 98%-day, max-day, 98%-hour, max-hour: 98th percentile and maximum of daily and hourly averages, respectively)

Station	Period	Aver age	98%- day	Max- day	98%- hour	Max- hour
Göteborg, Riddargatan	May 94	15	..	37	..	..
Göteborg, Artillerigatan	Winter 94–95	18	..	86	..	..
Stockholm, Hornsgatan	Winter 91–92	42	..	133	..	..
Stockholm, Hornsgatan	Summer 92	27	..	51	..	..
Stockholm, Hornsgatan	April - June 94	38	..	127	129	..
Stockholm, Hornsgatan	April - June 95	35	..	..	112	..
Stockholm, Hornsgatan	April - June 96	39	..	..	122	..
Stockholm, Hornsgatan	April - June 97	36	..	..	113	..
Stockholm, Hornsgatan	April - June 98	40	..	..	149	..
Sundsvall, Skolhusallén	Winter 97–98	20	85	..	..	..
Norrköping	Feb - May 93	25	63	..	80	242
Umeå, Storgatan	Jan 94 - Jun 95	13	..	105	..	..
Sollentuna, Kanalvägen	Winter 95–96	36	93	97	106	259
Sollentuna, Kanalvägen	Summer 96	35	71	86	123	347
Sollentuna, Pommern- vägen	Summer 96	29	..	77	81	197
Sollentuna, Pommern- vägen	Winter 96–97	26	62	64	89	189
Sollentuna, Pommern- vägen	Summer 97	21	45	45	55	180
Sollentuna, Pommern- vägen	Winter 97–98	24	69	90	84	249
Sollentuna, Pommern- vägen	Summer 98	25	78	95	89	189

of Sweden. PM_{10} and $PM_{2.5}$ were studied in Lycksele, a small city in the inland area of northern Sweden and in Göteborg during 1 month in March–April 1997 (37). Similar concentrations were recorded at the two sites; the average PM_{10} concentration was 26 and 28 $\mu\text{g}/\text{m}^3$ in Lycksele and Göteborg, respectively, the average $PM_{2.5}$ concentration being 13 and 15 $\mu\text{g}/\text{m}^3$, respectively.

In summary, the concentrations of particles in the cities and municipalities in northern Sweden may be about the same as in the southern part. The influence of long-range transport is strong in the south, but decreases with latitude, while the importance of low dispersion during inversions increase with latitude.

Comparison with guidelines and limit values

There is no limit value for the concentration of PM_{10} in urban air in Sweden. However, there are guidelines stating that the 98th percentile of the 24-hour mean should be less than 110 $\mu\text{g}/\text{m}^3$ and the mean of the winter season (1 October — 31 March) should be less than 50 $\mu\text{g}/\text{m}^3$. All reported data are below the guideline levels. Limit values for PM_{10} have recently been introduced in the European Union. In the first step, to be reached before 2005, the 90th percentile of the 24-hour means should be less than 50 $\mu\text{g}/\text{m}^3$ and the annual mean less

than 40 $\mu\text{g}/\text{m}^3$. In the planned second step, to be reached in 2010, the 98th percentile of 24-hour means should be less than 50 $\mu\text{g}/\text{m}^3$ and the annual mean less than 20 $\mu\text{g}/\text{m}^3$. It is evident that the present concentrations at street levels in Swedish cities (see the preceding text) are higher than the limit values that are planned for introduction in 2010. However, the second step may be changed due to a revision that will take place in 2003.

Rural background PM_{10} concentrations

As already noted, the rural background concentration of PM_{10} in the Stockholm region is about 10 $\mu\text{g}/\text{m}^3$. A summary of the PM_{10} results obtained at a rural background site is shown in table 10. There are no data from other parts of the country. However, the concentrations of PM_{15} and $PM_{2.5}$ at a rural site in northern Finland during 1992–1994 was 5.3 $\mu\text{g}/\text{m}^3$ and 3.7 $\mu\text{g}/\text{m}^3$, respectively (39). As $PM_{2.5}$ made up almost 80% of the PM_{15} and as the conditions in northern Finland are similar to the ones in northern Sweden, the PM_{10} concentration in northern Sweden is estimated to be 4–5 $\mu\text{g}/\text{m}^3$. In Aspvreten, at the rural station 100 km from Stockholm, the concentration of particulate sulfate was about 75% of the levels found in Vavihill, the location of a background site near Malmö. On the assumption that the same relation is valid for PM_{10} , the background concentrations of PM_{10} in the far south of Sweden can be estimated to be 13–14 $\mu\text{g}/\text{m}^3$.

Seasonal variation

The seasonal variation (ie, the difference between the highest and lowest monthly means) in PM_{10} is rather small at roof level (figure 3). In Göteborg, the highest concentrations have been measured in February through May. In contrast, no seasonality is apparent at the rural site Aspvreten. The increased difference between the two stations in spring may be explained by the high contribution of resuspended road dust in the city in spring. The increased resuspension is due to the build-up of particles on the road surface during sanding and salting, as well as to road wear from studded tires in the winter season.

Comparison with PM_{10} concentrations in other countries

Different sampling methods and sampling site criteria make it difficult to compare PM_{10} data obtained in different parts of the world. Roof-level measurements are used in Sweden to estimate the urban background, while ground-level measurements located away from any direct sources are often used elsewhere. The TEOM sampler is totally dominant in Sweden at present, but gravimetric methods are used in other countries.

Table 10. Statistical summary of PM_{10} daily average concentrations at Aspvreten. (N = number of daily averages used in the calculations)

Year	Mean ($\mu\text{g}/\text{m}^3$)	Median ($\mu\text{g}/\text{m}^3$)	98th percentile	Maximum ($\mu\text{g}/\text{m}^3$)	N
1990	13.6	9.7	55.6	>100.0	219
1991	12.1	9.2	37.3	61.4	262
1992	12	9.2	33.6	54.6	229
1993	11.8	9.2	33.8	50.4	270
1994	10.4	8.9	28.0	33.9	321
1995	10.5	8.4	29.3	39.2	284
1996	9.5	7.2	33.2	48.1	318

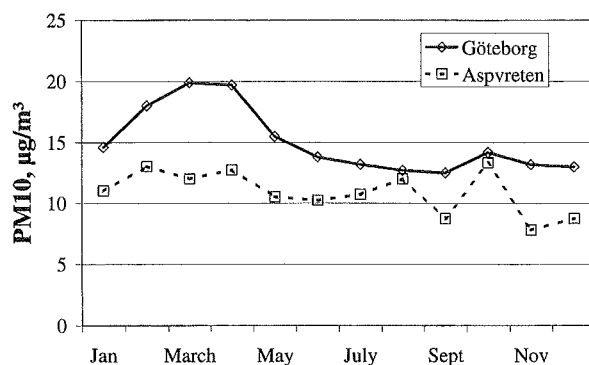


Figure 3. Seasonal variation of PM_{10} (particulate matter <10 μm in diameter) in a town, Göteborg, and at a rural site, Aspvreten, in southern Sweden — average 1990–1998.

Table 11. Summary of concentrations of PM₁₀ and PM_{2.5} in various parts of Europe and the United States. (90th percentile values = daily means).

Area	PM ₁₀		PM _{2.5}		Location	Study period	Number of sites	Method	Reference
	Mean or median	90th percentile	Mean or median	90th percentile					
The Netherlands	41	88	..	..	Urban background	Winter 1992—1993, Winter 1993—1994	1	Filter	40
The Netherlands	34	91	..	..	Nonurban	Winter 1992—1993, Winter 1993—1994	1	Filter	40
The Netherlands	29	51	14	38	Urban background	Winter 1994—1995	1	Filter	40
The Netherlands	24	44	15	34	Nonurban	Winter 1994—1995	1	Filter	40
Scandinavia	13—23	25—40	..	..	Urban background	Winter 1993—1994	4	Filter	17
Central Europe	40—75	80—150	..	..	Urban background	Winter 1993—1994	6	Filter	17
Scandinavia	11—16	20—30	..	..	Rural	Winter 1993—1994	4	Filter	17
Central Europe	40—75	60—100	..	..	Rural	Winter 1993—1994	6	Filter	17
United Kingdom	20—30	..	..	..	Urban background	1993—1994	16	TEOM	18
Canada	28	47	14	26	Urban background	1984—1993	11	Filter	41
Canada	11—30	..	7—17	..	Rural	1984—1993	4	Filter	41
Western United States	6—20	..	3—6	..	Rural	1988—1993	28	Filter	42
Eastern United States	10—20	..	8—14	..	Rural	1988—1993	11	Filter	42
Alaska	4	..	2	..	Rural	1988—1993	1	Filter	42
Northeast United States	17—29	..	10—15	..	Urban background	1988—1994	>100	Filter	5
New York, city center	50—60	70—100	20—30	50—80	Urban background	1988—1994	1	Filter	5
Sweden	10—20	..	..	..	Urban background	1990—1998	6	TEOM	This report
Sweden	11	22	8	14	Rural	1990—1998 ^a	1	TEOM	This report

^a PM_{2.5}: 1998.

Therefore, the reported PM₁₀ concentrations in Sweden tend to be lower than concentrations reported from other parts of Europe (table 11). In western Europe, the average daily concentrations are 20—35 µg/m³ in the urban background air. In central and eastern Europe, the average concentration in major urban areas is 40—75 µg/m³, the 90th percentiles of the daily means being 80—150 µg/m³. The difference between rural and urban background concentrations in central Europe averages less than 25% and thus illustrates the importance of long-range transport on the PM₁₀ levels. The urban concentrations in Canada and in humid areas of the United States are similar to the ones found in western Europe.

PM_{2.5} concentrations

Data on PM_{2.5} are very sparse. About 1 year of measurements in Stockholm and at a rural site 100 km south of Stockholm indicate that the PM_{2.5} fraction of PM₁₀ is 40—50% at street level and about 70—80% at roof level and in background air. These findings confirm results from studies in Canada, the United States, and The Netherlands (table 11).

Time trends of PM₁₀

The results given in table 9 do not indicate any time trend for PM₁₀ in the urban background (roof level) in

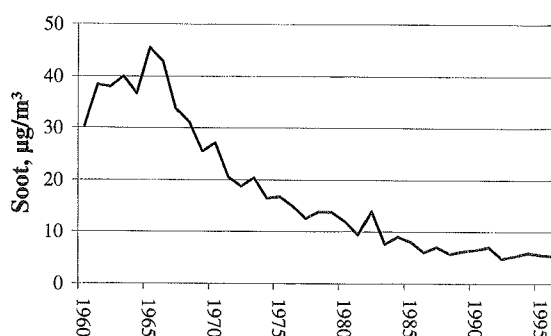


Figure 4. Concentrations of soot (black smoke) (annual mean, µg/m³) in central Göteborg in 1960—1996. Source: Göteborgs stads miljöförvaltning, 1997 (43).

the 1990s. Very few data are available before 1990. However, PM₁₀ concentrations in Göteborg have decreased from about 60 to about 15 µg/m³ since 1975 (43). The observed trend should be treated with caution, as the sampling method and site have changed during the period. The concentration of soot (BS), which can be seen as an indirect measurement of particles, has decreased substantially in Göteborg, from 45 to 5 µg/m³, since the beginning of the 1960s (figure 4). The remarkable decrease reflects the large efforts that have been made in Sweden to reduce the emission of several pollutants during the last few decades. For example, the Swedish emission of SO₂ in 1995 was 80% less than the

emission in 1980. Similar reductions have taken place in other parts of western Europe. As the ratio between soot and PM₁₀ concentrations is time and site dependent, the observed trend cannot be directly translated to PM₁₀. However, it is clear that the PM₁₀ levels have also decreased substantially.

As already noted, there are no trends for urban background. However, at the rural site in Aspöreten, the annual mean PM₁₀ concentrations decreased about 25% from 1990 to 1996 (table 10).

Future trends

Predicting the future trend for the concentrations of aerosols in the air depends on judgments and assumptions regarding future changes in the emissions of the sources that contribute most to the particle levels found in air today.

In Sweden, long-range transport is the predominant source of PM₁₀ in rural areas, as well as in the urban background, in southern Sweden. The contribution from locally emitted particles to the PM₁₀ concentration is estimated to be 3–7 µg/m³ in the urban background air. In street canyons, road traffic (direct emissions and re-suspension of road dust) add, on the average, another 10–30 µg/m³. However, the addition varies greatly, as especially the amount of re-suspended dust varies substantially. The highest concentrations are generally found in spring when re-suspension is greatest. Wood combustion for residential heating may be a very important source in certain areas, but no estimation of its contribution is available.

The future contribution from the long-range transport of particles depends on the trend of emissions in Europe. Tarrasón & Tsyro (35) have calculated the concentrations of inorganic PM_{2.5} particles in Europe for 2010, on the assumption that the emission of precursor gases in 2010 will be in accordance with the current European emission reduction plans. Although the particle concentrations will decrease by 25–30% in central Europe, the concentrations will be essentially unchanged in most of Sweden. The planned emission reductions in countries of western Europe will be counteracted by increased emissions in eastern Europe.

It has been estimated that the emissions of primary particles per vehicle from gasoline and diesel vehicles will decrease in the future due to the continuing introduction of cars equipped with catalysts and improved diesel engines. However, the reductions in PM emissions envisaged as a result of improved technology could be in danger if the percentage of diesel cars, which emit considerably more than gasoline cars, increases too much. The share of diesel-fueled cars among new cars in Sweden has increased from about 1% in 1990 to more than 10% at present (44).

The future emission of particles from the burning of wood for residential heating depends on several factors. If modern technology is introduced, the emission of PM will decrease substantially. As the life-time of boilers is normally 25–40 years, the shift from old to new technology is expected to be slow. An increase in the use of wood and other biomasses as fuel due to higher prices for oil and electricity will counteract the reduced emissions due to better combustion technology.

The emission of coarse particles due to the resuspension of road dust will probably not change in the future. The emissions due to studded tires may decrease if the use of new stud-free winter tires increases. Better and more frequent cleaning of the streets, particularly in spring, would also reduce the amount of dust available for resuspension. Less frequent sanding and salting would produce the same effect, although it might have other unwanted consequences.

In summary, emission trends are difficult to predict for the future, as they depend on several factors. However, it seems unlikely that there will be any dramatic changes during the next 10–15 years.

Human exposure

When relating human health effects to exposure to PM (as in epidemiologic studies) time-weighted-average ambient concentrations are often used as a surrogate for personal exposure because, under normal circumstances, only fragmentary data are available on true personal exposures. Further extrapolation to the dose is impossible in practice, as individual ventilation rates and the pulmonary deposition rates are affected by unmeasured individual physiological parameters. Moreover, the deposition is dependent on the normally unknown particle-size distribution in the air actually inhaled by each person.

The personal exposure (ie, the total PM exposure of a person during a specific time period) is composed of exposure to many different particles from various sources in different microenvironments. A microenvironment can be defined as a volume in space, during a specific time interval, during which the variance of concentration within the volume is significantly less than the variance between that microenvironment and its surrounding microenvironments (45). Microenvironments can be of very different sizes in both space and time. They are normally small in both time and space near a source (eg, a smoker) and increase in size spatially and temporally in the absence of any nearby sources.

A person can pass through a large number of microenvironments during a day (normally the shortest time period used in epidemiologic studies); however, differ-

ent microenvironments can be divided into the following four general classes: indoor, ambient-outdoor, occupational, and in-traffic. The relation between indoor and ambient-outdoor concentrations of particles is especially important as people in industrialized countries spend most of their time indoors. A time budget survey in the United States showed that US residents spend 87.2% of their time indoors (mainly at home or at work), 7.2% in other nonambient environments (eg, in vehicles in transit), and only 5.6% outdoors (46). A time-budget examination in Sweden, including 160 children in the age range of 7–12 years, gave similar results. The children spent an average of 9% of their time outdoors (47). However, as the amount of physical activity outdoors is usually larger than that indoors, the ventilation rate, and thus the dose (the amount of deposited particles in the respiratory tract), is proportionally more important than the time spent outdoors.

The US EPA (5) has evaluated several mainly US studies in determining the relative contributions of ambient-outdoor and nonambient (indoor) particles to total human exposures. The key conclusions were as follows:

- The ambient environment can be a major source of indoor particles due to air exchange and infiltration. Whether it is the dominant source depends on the relative magnitude of the indoor sources of particles.
- The largest identified indoor source of particles in both homes and other buildings is cigarette smoke. The $PM_{2.5}$ concentration in homes with smokers has a 24-hour average increment ranging between 25 and 45 $\mu g/m^3$. The second largest identified source is cooking. In homes with cooking, the PM_{10} 24-hour average concentrations increase by 10 to 20 $\mu g/m^3$.
- Indoor air concentrations of PM_{10} and $PM_{2.5}$ generally exceed outdoor concentrations except in areas where outdoor concentrations are high.
- The regression of daily indoor PM_{10} and $PM_{2.5}$ concentrations on the corresponding daily outdoor concentrations generally explains less than one-half of the variance ($r^2 < 0.5$) if the regressions are carried out for all homes in the study. However, the regression for a single home (in cases in which homes were measured repeatedly) often has a better indoor-outdoor relationship (r^2 up to 0.9). Since many epidemiologic studies deal with repeated measurements over time, "longitudinal" regressions by individual homes may be more relevant to these studies than "cross-sectional" regressions across all homes.
- For PM, studies have detected a "personal cloud" related to the activities of a person who may generate significant levels of particles in his or her vicinity. The

personal exposure is thus often higher than the indoor and ambient concentrations.

- When a cross-sectional analysis is performed that compares ambient PM_{10} with individual personal exposures for a group of subjects, the correlation often goes towards zero, because of the large influence of indoor sources and sinks that vary *between* individuals. However, because of the relative consistency *within* any given residence for the indoor sources and sinks of PM_{10} , the longitudinal (time-series) correlation of personal exposure of a specific person to the total indoor PM_{10} (from outdoor *and* indoor sources) and ambient PM_{10} can be very high. Two analyses involving a limited number of subjects yielded correlation coefficients (R^2) above 0.9 when indoor sources were consistent from day-to-day.
- Both fine and coarse particles enter indoors. However, because coarse particles are rapidly removed by deposition, the indoor concentration of ambient fine particles is more representative of the outdoor, ambient, fine particle levels. Thus, in turn, a centrally located ambient monitor may provide a fine-particle concentration that is representative of community exposure (indoor and outdoor) to ambient fine particles, but not a representative sample for coarse particles.
- Indoor sources do not generate fine-mode particles of the same composition as the most common particles of outdoor origin (eg, sulfates, metals, etc). Moreover, the production of indoor-generated particles is controlled by daily indoor activities. Therefore, the exposure to indoor-generated particles will not correlate with the concentration of ambient (outdoor-generated particles), and time-series epidemiology based on ambient measurements will not identify health effects of indoor-generated particles.
- Therefore, the measurement of *daily* variation of *ambient* concentrations of PM, as used in time-series epidemiology studies, has a plausible link to the daily variations of human exposure to particles from ambient sources, for the people represented by the ambient monitoring stations. This link should be better for indicators of fine particles ($PM_{2.5}$) than for indicators of fine plus coarse particles (PM_{10} or TSP), which in turn should be better than indicators for coarse particles ($PM_{10} - PM_{2.5}$).

Ultrafine particles

Recent work has suggested that very small particles (less than about 0.1 μm) may be responsible for some of the health effects associated with exposure to PM. (See the

section on ultrafine particles in this volume.) The hypothesis for explaining the health effects of these small particles is based on the number, composition, and size of the particles rather than on the mass, as they contribute very little to, for example, the PM_{10} concentrations.

The number of particles is a good measure of the load of these particles as the number concentration in ambient air is dominated by particles <0.1 μm . Particle concentrations vary widely from 100/cm³ in marine aerosol and around 1000/cm³ in clean continental backgrounds to over 100 000/cm³ in polluted urban aerosols. The average residence time of these particles is strongly dependent on the number concentration as the probability to interact (coagulate, condense) with other particles increases when the number concentration increases. Thus the less the number concentration, the longer the residence time. The residence time of 10 and 100 nm particles is 1 and 10 days, respectively, in clean air (300/cm³), but 15 minutes and 1 day, respectively, in polluted air (15 000/cm³).

Due to the short residence time of small particles, the number concentration is high close to sources and decreases rapidly with distance from the source. The number concentration near sources varies widely in time due to fluctuations in meteorology and source strength. Due to the short residence time, the number geometric mean diameters of the size distribution of aerosols increases from 10 nm in "freshly" polluted urban air to about 80 nm in "aged" air, found in clean background regions.

Summary and concluding remarks

Airborne PM is a very diverse material in terms of its physical and chemical properties, and many sources contribute to the atmospheric concentrations. Aerosol particles are typically very small, ranging in size from a few nanometers up to ≥ 100 μm . While all particles in this range can be found in the air, only particles in the range of 0.1–2 μm can remain airborne for long periods (≥ 10 days in clean air).

Particles less than about 10 μm (termed PM_{10}) are the most important from a health point of view, as larger particles do not reach the thoracic parts of the lung. In recent years, particles <2.5 μm (termed $PM_{2.5}$) have been suggested as more relevant for studies of the health effects of airborne particles.

Airborne particles may be of either primary or secondary origin. Primary particles, formed by mechanical processes or in combustion processes, are directly emitted to the air. Secondary particles are formed in the air by chemical reactions or the condensation of gases. Me-

chanically formed particles are normally larger than 2.5 μm exposure (termed coarse particles), while the particles formed from gas conversions are smaller than 2.5 μm (termed fine particles). Due to their different size and formation processes, fine and coarse particles have substantially different properties (chemical composition, atmospheric life-time, temporal and spatial variability).

The annual Swedish anthropogenic emission of primary particles is estimated to be 42 000–100 000 t. Residential wood burning for heating is probably the major source, but the emission estimate is based on limited data. Heavy-duty diesel vehicles, the combustion of heavy oil for energy production, machinery, and industrial processes are other important sources. The resuspension of road dust is probably another important source, but no reliable estimates of its contribution are available on the national level. Industrial emissions and the resuspended dust consist mainly of coarse particles; all other sources emit mainly fine particles. The formation of secondary particles due to emissions from various sources is not included in the emission estimates.

The rural background PM_{10} concentration in the Stockholm region (south central Sweden) is about 10 $\mu g/m^3$. The background concentration in the far north can be estimated to be 4–5 $\mu g/m^3$ based on data from northern Finland. PM_{10} concentrations in the far south can be estimated to be 13–14 $\mu g/m^3$, if the ratio between particulate sulfate concentrations in central and south Sweden is also assumed to be valid for PM_{10} .

Regular monitoring of PM_{10} in a few major cities in southern Sweden since the beginning of the 1990s shows that the average urban background concentrations are 12–20 $\mu g/m^3$. The narrow range is due to the strong influence of the long-range transport of particles on the concentrations in urban backgrounds. The 98th percentiles of the daily mean values range from 30 to 50 $\mu g/m^3$, the maximum daily mean concentrations are in the range of 50–100 $\mu g/m^3$. At street level, the mean concentrations range from 20 to 40 $\mu g/m^3$, the 98th percentiles of the daily means being 50–100 $\mu g/m^3$. The maximum daily concentrations range from 100 to 150 $\mu g/m^3$, and hourly mean concentrations can reach 300 $\mu g/m^3$. Data on PM_{10} in the towns and municipalities of northern Sweden are sparse. However, regular BS measurements at a number of sites in the north and short-term PM_{10} measurements in a typical inland municipality show that the concentrations in the cities and municipalities in northern Sweden may be about the same as in the southern part. The influence of long-range transport is strong in the south, but decreases with latitude, while the importance of low dispersion during inversions increases with latitude.

The seasonal variation (ie, the difference between the highest and lowest monthly means of PM_{10}) is 5–10 $\mu g/m^3$ in the urban background. PM_{10} concentra-

tions are highest in spring, possibly because of the high contribution of road dust resuspension due to the build up of particles on the road surface during sanding and salting, as well as road wear from studded tires in the winter season.

Urban background PM₁₀ concentrations in Sweden are generally lower than in other parts of Europe. In western Europe, the concentrations average 30% to 130% higher than the ones found in Swedish cities. In central and eastern Europe, the average concentration in major urban areas is 2.5 to 5 times the Swedish urban background. However, different sampling methods and sampling site criteria may introduce bias into the comparisons.

There was no time trend for PM₁₀ in Swedish cities in the 1990s. Very few data are available before 1990, making longer trend analyses very uncertain. However, the large reduction of particle precursors in Sweden, as well as elsewhere in Europe, justifies the assumption that the particle concentrations have decreased. The assumption is supported by the observation that the PM₁₀ concentrations in Göteborg have decreased from about 60 to about 15 µg/m³ since 1975. The magnitude of the observed trend should be treated with caution, as the sampling method and site have changed during this period. The assumption is also supported by the large decrease of BS, an indirect measurement of particles, from 45 to 5 µg/m³, since the beginning of the 1960s in Göteborg.

No major changes of the concentrations are anticipated during the next few decades. There are indications that reduced emissions due to better combustion technology for vehicles and wood boilers will be counteracted by an increased share of diesel cars and an increased use of wood for heating. Moreover, the contribution from long-range transported inorganic fine particles has been estimated to be about the same in 2010 as now.

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Deposition and clearance of particles in the human lung

by Lena Låstbom & Per Camner

The upper respiratory tract consists of the nose, mouth, pharynx, and larynx. For particles with diameters larger than around 1 μm , the nose is a much more efficient filter than the mouth. During physical exercise, breathing occurs to a great deal via the mouth. Also at low physical activity, quiet breathing via the mouth may occur to some extent, especially when people are talking (1). The PM_{10} concept is based on the assumption that mouth breathing occurs (2). During the determination of the PM_{10} (particulate matter <10 μm in diameter) fraction in air, the mass of particles which penetrate a preseparator is measured. The deposition characteristics of this preseparator are similar to those of the mouth and throat. Another important function of the respiratory tract, besides acting as a filter of inhaled particles, is to warm and humidify the air. Already in the subglottic space, the relative humidity during inspiration is 98–99% during nasal breathing and around 90% during oral breathing (3). Therefore particles of soluble materials will take up water and grow, a phenomenon called hygroscopic growth. The diameter of a particle can increase several times, and the growth is rapid as the relative humidity increases from around 95% to 100%, especially during the increase from 99% to 100%.

Traditionally, the lung has been divided into a tracheobronchial region of conducting airways with a ciliated epithelium and an alveolar region of respiratory bronchioles, alveolar ducts, and alveoli without a ciliated epithelium. Until some years ago, there was a consensus that only smaller fractions of particles are retained for more than 24 hours in the tracheobronchial region in healthy persons. In recent years, this idea has been questioned, and there are experimental data supporting the fact that particles, especially in small ciliated airways, are, to a great extent, retained after 24 hours. There are therefore reasons for discussing larger airways (trachea and bronchi) and small ciliated airways (bronchioles) separately. The deposition and clearance of particles in the human lung have recently been exhaustively reviewed by a task group of the International Commission on Radiological Protection (ICRP) (4) and also by the Institute of Environmental Medicine (5).

Deposition

The deposition of particles in the respiratory tract is a function of particle size, inhalation and exhalation flow patterns, and the anatomy of the respiratory tract. The most important mechanisms for the deposition of particles are impaction, sedimentation, and diffusion. Parti-

cles are deposited by impaction when the airstream changes direction and the particles continue in their original direction due to their momentum. Impaction is of importance for the upper airways and in larger airways of the lung. Its effect increases with air velocity and particle size, and it is important for particles down to 1 or 2 μm . Particles are deposited by sedimentation when they fall because of gravitational force. This mechanism is valid for the entire respiratory tract, but it is generally the most important for the alveolar region, where the dimensions are small and the transition time long. Deposition increases with particle size and with decreasing air velocity and is important for particles down to around 0.5 μm in size. Diffusion denotes the mechanism by which particles move randomly because they collide with gas molecules. Deposition by this mechanism is important only for particles less than 0.5 μm , and the effect increases with decreasing size. Therefore there is a minimum deposition in the respiratory tract around the size of 0.5 μm . The mechanism is important for deposition in the entire respiratory tract. Impaction and sedimentation are dependent on the aerodynamic diameter of the particles, which is determined by the density, geometric size, and shape of the particles. Diffusion is not dependent on the density of the particles and therefore depends on the true geometric rather than the aerodynamic diameter of particles.

Theoretical models for the deposition of particles generally agree fairly well with the results from experimental studies. Figure 1 shows the deposition in various regions of the respiratory tract as a function of particle size, calculated with the theoretical model that was developed for particle deposition in the lung in 1994 by the ICRP (4). It can be seen from the figure that deposition of submicron particles increases markedly with decreasing size due to the effect of diffusion. In real life, size distributions of aerosols are usually very broad and often lognormal. However, deposition in the respiratory tract can fairly well be described by the mass median aerodynamic diameter of aerosols, for which impaction and sedimentation are the major deposition mechanisms.

Tracheobronchial and bronchiolar clearance

Mucociliary clearance

The airways in human lung have ciliated epithelium down to and including the terminal bronchioles. There was previously a consensus that the large majority of particles deposited in the ciliated region cleared within 24 hours, although small fractions of particles were

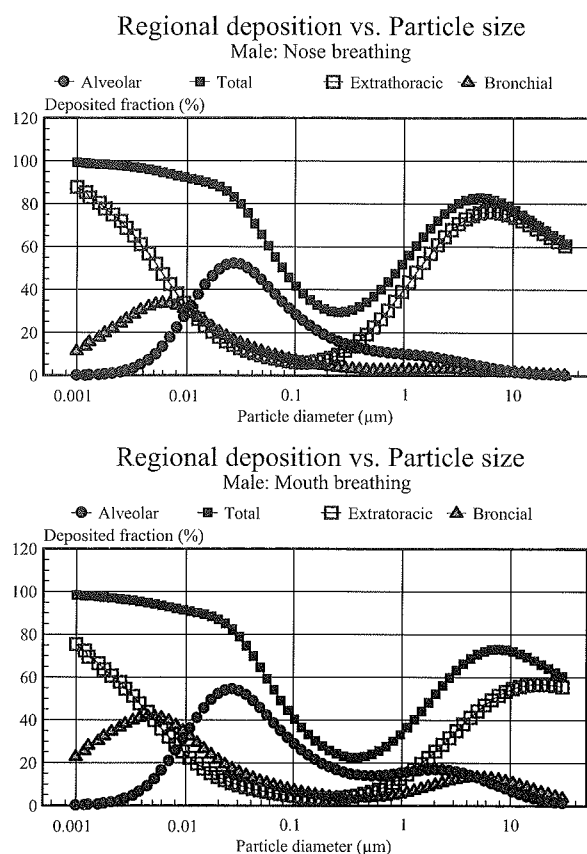


Figure 1. Deposition of particles during nose breathing (a) and during mouth breathing (b).

known to be retained for more than 24 hours (6–8). However, Stahlhofen and his co-workers (9–12) found that a large fraction of particles inhaled as a bolus with a penetration depth of less than the dead space was retained after 24 hours. The results of these bolus experiments have had a large impact on the ICRP Human Respiratory Tract Model for Radiological Protection (4). However, such a large retained fraction in large airways is contradictory to results from studies of the retention of particles inhaled in normal volumes in the human lung, because the 24-hour retention in these studies is often well below 50% (13–16). To handle these conflicting data, the ICRP model assumes that the slow clearing fraction of particles deposited in the tracheobronchial tree decreases with increasing geometric particle size, as proposed by Stahlhofen et al (17). However, the results of the bolus studies can also be interpreted in another way. The particles may in fact have penetrated deeper than the estimated penetration depth and deposited in the alveolar region or in the small ciliated airways with incomplete mucociliary transport. This latter explanation has some support from the results of Scheuch et al (12).

Recently, a method was developed for determining the clearance of particles in the bronchiolar region (18). Rather large particles, 6 μm, are inhaled at an extreme-

ly slow inhalation flow, 0.05 l/s. Deposition by impaction in large airways is reduced due to the slow inhalation flow, and the majority of the particles deposit by sedimentation before they reach the alveolar region. Calculations with several theoretical models for particle deposition in the lung, including the ICRP model, all show that the majority of the particles are deposited in the bronchiolar region and only relatively small fractions are found in the bronchial and alveolar regions (19). Particles 6 μm in size and inhaled at 0.5 l/s mainly deposit in the bronchial and alveolar regions and only to a small extent in the bronchiolar region. Camner et al (19) calculated that the large majority of particles deposited in the most peripheral part of ciliated airways is retained after 24 hours. This figure should be compared with the around 20% retained in generations 0–12, which include both large and small ciliated airways. The 24-hour retention of these extremely slowly inhaled particles was measured to be 50% in healthy subjects. In order to evaluate whether or not this high fraction of particles in fact could be due to deposition in the alveolar region, as has been suggested for particles inhaled in boli, Falk et al (20) followed the clearance of 6-μm particles inhaled by healthy subjects over a period of 1 month at both 0.5 l/s and 0.05 l/s. The particles inhaled with the extremely slow inhalation cleared with a half-time of 45 days, which was significantly faster than when particles were inhaled at 0.5 l/s, for which the half-time was 190 days, and much slower than the bronchial mucociliary transport, which is considered to be finished within 24 hours. The large retained fraction at 24 hours in the experiments with the 6-μm particles, inhaled extremely slowly, can thus not be explained by assuming that all these particles have been deposited in the alveolar region.

Roth et al (21) studied human clearance of inhaled ultrafine ^{111}In -labeled indium oxide particles. The count median diameter of the aerosol was 18 nm, and the mass median diameter was 27 nm. During the first few days, 7% of the particles deposited in the lungs were cleared. This is a considerably lower value when compared with the percentage that the ICRP model predicted would be deposited in the tracheobronchial region (figure 1). The study indicates that a considerable fraction of the ultrafine particles deposited in the tracheobronchial region is not cleared within a few days.

Cough

Coughing is also an important mechanism for the clearance of particles deposited in the tracheobronchial region, at least for the trachea and bronchi. There must be an increased amount of secretion in the airways for coughing to be effective. Patients with chronic bronchitis have a severely impaired mucociliary transport, and patients with immotile cilia syndrome have more or less absent mucociliary transport. However, both these

groups of patients have been shown to eliminate 6- μm particles inhaled at 0.5 l/s efficiently (22, 23). The fast tracheobronchial clearance phase was not completely finished until after 72 hours, which should be compared with the 24 hours determined for healthy subjects. As previously mentioned, 6- μm particles inhaled at 0.5 l/s mainly deposit in the large airways and in the alveolar region and only minimally in the bronchioles. The total cross areas of the airway generations in the bronchial part (generations 0–8) are rather small, and therefore the air velocity can be high during coughing, and the effect of coughing is important.

Groups of patients with chronic bronchitis and immotile cilia syndrome have also inhaled 6- μm particles with an extremely slow flow, 0.05 l/s (24, 25). Although, the retention measured at 24, 48, and 72 hours was significantly higher for the patient groups than for healthy subjects, the differences were rather moderate. One explanation for this rather efficient clearance also from the bronchiolar region in patients with impaired or absent mucociliary transport may be that coughing is an important elimination mechanism also in this region. On the other hand, the total cross-sectional area in this region is large, and therefore the air velocity during coughing should be low. A better explanation may be that mucociliary transport is of little importance for particles deposited in this region, at least the fraction of particles retained after 24 hours, and that clearance, both in healthy subjects and in patients with lung diseases, occurs by a mechanism other than mucociliary transport and cough. The idea that mucociliary transport is not important in the bronchiolar region is supported by the fact that exposures to cholinergic and adrenergic compounds, which are known to stimulate mucociliary clearance markedly in large airways, have no effect on bronchiolar clearance (26, 27).

Alveolar clearance

Studies of mechanical clearance (clearance of entire particles) from the human alveolar region require extremely insoluble particles firmly labeled with long-lived radionuclides, and it is not surprising that only a few such studies have been made. The retention of inhaled radiolabeled particles of polystyrene (28), fused clay (29), and Teflon™ (30) in the thoracic region has been studied for periods of about 1 year. In these studies, a minor fraction of the particles cleared with biological half-times of tens of days, while a major fraction cleared with a much longer half-time of one or several years. In the study by Bohning et al (28), no information about the leakage of radionuclides from the particles was given, but the leakage reported in the two other studies was not negligible considering the long half-time. In a more

recent study on healthy persons, Philipson et al (31) studied mechanical alveolar clearance of extremely firmly radiolabeled 5.3 μm Teflon particles for almost 3 years. For the first 250 days after the exposure, the half-time averaged 740 days. Between day 250 and day 900, the average half-time was 1750 days (almost 5 years) of the radioactivity over the thorax region. All the particles that cleared from the thoracic region left the body via the feces. This extremely slow clearance of highly insoluble material should have relevance to ambient air particles, which, to a considerable extent, consist of extremely insoluble carbon.

However, the particles are not only mechanically cleared from the alveolar region. Alveolar macrophages phagocytize particles deposited in this region. Several *in vitro* studies with alveolar macrophages, including human alveolar macrophages, have shown that these cells efficiently dissolve metal particles that are generally considered insoluble in water (32–36). One mechanism behind this ability of the macrophages is the acid milieu in the phagolysosomes in the cells (35). The pH in these phagolysosomes has been found to be around 5 in macrophages from several species (37–39).

There is also a slow transport of particles from the alveolar region to the regional lymph nodes. Such a clearance route has been seen in animal experiments, especially for highly toxic particles (eg, quartz and plutonium oxide particles) (40, 41). Also in animal experiments with very high lung burdens of rather innocuous particles such as titanium dioxide, the transport to the lymph nodes has been found to increase (42). In more recent experiments, in which rats have been exposed via inhalation to aggregates of ultrafine and fine titanium dioxide particles, the ultrafine particles have been found to be translocated to a much higher extent to the lymph nodes than the fine titanium dioxide particles are at similar lung burdens (43, 44). A possible explanation for the more efficient transport to the lymph nodes in all these cases may be that the particles are located to a relatively large extent outside the alveolar macrophages.

Summary and concluding remarks

Deposition of particles in the airways is dependent on their size, density, and shape. Particles of soluble material can take up water in the airways and grow considerably, hygroscopic growth. Deposition is also dependent on the respiration pattern, including mouth or nose breathing. In the alveolar region there is a maximum deposition, about 50%, for 20–30 nm particles (ie, ultrafine particles).

Particles deposited in large ciliated airways (bronchi) seem to clear within 24 hours. However, for small ciliated airways (bronchioli), there is a strong

indication of large retained fractions after 24 hours, and these fractions seem to clear with a half-time with a magnitude of tens of days.

Clearance by coughing is also an important mechanism in larger airways in the lung, but its importance in small ciliated airways is uncertain. An increased amount of secretion in the airways is necessary for coughing to be efficient.

Mechanical clearance (ie, clearance of whole particles) from the alveolar region in humans is extremely slow with a half-time of 5 years for the majority of particles. Mechanical clearance should be relevant for the carbon skeleton of ambient particles. However, particles of materials that are usually considered to be insoluble in water, for example, many metal oxides, can be cleared at a much faster rate because they are dissolved in the acid milieu (pH 5) in the phagolysosomes of the alveolar macrophages.

Particles deposited in the alveolar region can be transported to the regional lymph nodes. This is especially the case for highly toxic particles, for example, quartz particles, for ultrafine particles, and also for rather large inert particles when the inhaled amount is extremely high. A common explanation for all these three cases may be a considerable number of particles outside alveolar macrophages.

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Experimental studies on the effects of diesel exhaust emissions

by Anita Sydbom & Sven-Erik Dahlén

Patients with asthma and other airway diseases have been found to be more vulnerable than the normal population to the inhalation of air pollution components like sulfur dioxide (SO₂), nitrogen dioxide (NO₂), and ozone (O₃) (1–4). This review is focused on experimental studies of the health effects of the particulate component of air pollution, especially diesel emissions. However, interactions between particles and photochemical pollutants are likely to be important during natural exposures. The vast majority of published studies deal with the health effects of diesel exhaust particles, and this trend is natural in view of the major contribution of such particles to air pollution in the urban regions of Sweden and the rest of Europe. It would be of interest to compare the effects of diesel exhaust particles with those possibly induced by the inhalation of particles generated during the burning of wood, but the literature on the latter topic is very limited.

Diesel engines produce a mixture of nitrogen oxides (NO_x), formaldehyde, carbon monoxide, hydrocarbons, ash, transition metals, and carbon particles. Compared with gasoline engines, diesel engines produce far less carbon monoxide but give rise to greater concentrations of NO_x and aldehydes, which are particularly prone to cause irritation of the upper respiratory tract. Diesel engines also produce submicron soot or black smoke particles (BS) that are believed to mediate several of the observed adverse effects. The recent indications that such ultrafine particles may be particularly harmful are dealt with in the section of this report called "Experimental Studies on the Effects of Ultrafine Particles". In fact, it has been estimated that the particulate emission from diesel engines per mile (1.6 km) of traveled distance is over 100 times higher than that emitted from gasoline engines of equivalent power running on unleaded gasoline (5). The diesel exhaust particles are readily respirable, with a diameter of <0.05 µm, and they consist of a carbonaceous core similar to carbon black, with adsorbed hydrocarbons. In this review, the term diesel exhaust particles is used without further specification, although it is clear that different grades and sources of diesel will result in emissions with different characteristics with regard to both particulate matter (PM) and photochemical components. Variability in the relative composition of diesel exhaust may thus be one cause of variability in results between different investigations. From studies generally carried out on rats there are also reports on carcinogenic effects and, especially, the induction of lung cancer by diesel exhaust particles, but this association has been reviewed previously (6) and will not be discussed in this report.

Inflammation in lung and airways

As discussed in detail in another section of this report ("Human Experimental Studies on the Effects of Inhaled Particles"), Rudell and co-workers have conducted experiments with human healthy volunteers and described both symptoms and changes in inflammation markers following exposure to diesel exhaust. Therefore, this account is limited to experimental studies with animal models or in vitro systems.

In vivo studies

Rat

Long-term studies of animal exposure to diesel exhaust have shown an accumulation of particles in the lungs and an increased lung burden of soot. Aggregates of macrophages with particles are found in alveoli and peribronchial interstitial tissues and are associated with local inflammation, epithelial proliferation, fibrosis, and emphysematous lesions.

Rats (F344 strain) were exposed to diesel exhaust particles at 350, 3500, or 7000 µg/m³ for 7 hours a day, 5 days a week for 6, 12, 18, or 24 months (7). A progressive increase in the lung burden of particles was observed in the animals exposed to higher levels of diesel exhaust particles. Tracheal mucociliary clearance [using ⁶⁷gallium sesquioxide (⁶⁷Ga₂O₃) as the test substance] showed no changes, however. There was significant prolongation of the long-term pulmonary clearance half-times (using ¹³⁴cesium-fused aluminosilicate particles) in the two highest exposure groups, with increases from 79 to 264 and 240 days, respectively.

Another study, using the same strain of rats, investigated the effect of low-exposure doses for 52 weeks (diesel exhaust particles 50 µg/m³, 20 hours a day, 7 days a week) (8). At 1 year postexposure more than 80% of the particles had been eliminated. Acute high exposure was also tested, with 5700 µg/m³ for 3 days, and animals exposed to higher concentrations cleared more of the lung burden during the postexposure period. A brief high exposure resulted in a rapid increase and decline in macrophage burden. At the longer low concentration, however, the macrophage burden was intermediate, and it stimulated a steady development of lung maculae. This result may indicate that low continuous exposure may be more detrimental than acute exposure, to even high loads.

Yu & Yoon (9) constructed a mathematical model for the prediction of lung burden and alveolar clearance

from rats. At low lung burdens, the alveolar clearance rate of diesel soot was constant, whereas at a high lung burden the alveolar clearance was determined principally by the capacity for transport to the lymphatic system.

Diesel exhaust particles cause dust overloading and impair pulmonary clearance at high doses in both rats and humans. There appears to be a threshold above which particle retention and inflammation occurs. It has, with most evidence from animal studies, been calculated that the threshold is around a load of 500 µg per gram of lung tissue (10). It is, however, difficult to assess how this value correlates with levels in the inhaled air.

Rats (F344) exposed to diesel emission for 30 months were examined anatomically and pathologically by an electron microscope every 6 months (11). Morphological changes in the lung were seen after 6 months of exposure at concentrations of 1000 µg/m³. The main change was anthracosis by inhaled diesel soot. Foci of alveolar macrophages laden with diesel particles were found. Diesel exhaust particles were found in type 1 epithelial cells, and hypertrophy and proliferation were found for type 2 cells. An infiltration of particle-laden macrophages, neutrophils, mast cells, and plasma cells into the interstitium of alveolar septa was seen. However, the most prominent changes found in the airways were focal shortening of cilia and protrusion of nonciliated cells.

Three groups of female Wistar rats were exposed during a lifetime either to clean air or to filtered or unfiltered diesel exhaust particles (4000 µg/m³), and another group was exposed to coal oven flue gas mixed with pitch fumes pyrolyzed under nitrogen (12). Most of the animals exposed to diesel exhaust particles had deposits of large amounts of carbonaceous particles phagocytosed by alveolar macrophages, severe chronic inflammation, alveolar septal thickening, bronchiolo-alveolar hyperplasia, and alveolar lipoproteinosis. Rats exposed to coal oven flue gas had much fewer severe inflammatory changes.

Studies of developing lung in the rat. Human studies in different areas have raised the concern that children and elderly people are more susceptible to the harmful effects of air pollution. There have been some earlier studies implying that lung development in animals exposed to oxidant gases early in life could be impaired or that young animals would be more susceptible to inhaled toxicants. In one study, however, two groups of rats were exposed 7 hours a day, 5 days a week for 6 months to NO₂ (9.5 ppm), to diesel exhaust diluted to a soot concentration of 3500 µg/m³, or to control air (13). The younger group was exposed in utero, by exposing the mother from conception through gestation and then exposing the newborns from birth up to the age of 6 months. The other group was exposed between the ages

of 6 and 12 months and considered to be a model for grown-ups.

Diesel exhaust particles altered the airway fluid constituents and tissue collagen in both groups. There was a sixfold increase in neutrophils, an increase in the number of cells in lung-associated lymph nodes, delayed clearance of particles, and an increase in the lung weight of adult rats. However, none of these changes were found in the rats exposed during development. In adult rats there was a focal aggregation of soot-laden alveolar macrophages but only scattered individual macrophages were found in young rats.

The authors concluded that the effects were equal or less in the developing rats and that there was no evidence for developing rats being more susceptible to the toxic effects of NO₂ or diesel exhaust.

Studies in animals with experimental lung disease. Epidemiologic studies have indicated that subjects with pre-existing lung disease may be more susceptible to episodic high levels of airborne pollutants than normal subjects. In an effort to define the mechanisms, this possibility has been studied in detail in an animal model in which lung disease has been experimentally induced (14). In this model, pulmonary emphysema was induced in rats through the intratracheal installation of the proteolytic enzyme elastase and manifested as enlarged alveoli and alveolar ducts and ruptured alveolar septa. These structural changes were not, by themselves, associated with inflammation or alterations of bronchioles. Such emphysematous rats and control rats were then exposed for 24 months to diesel exhaust at 3500 µg/m³, 7 hours a day, 5 days a week or to NO₂ at a concentration of 9.5 ppm, or to clean air, as the control. Different parameters were measured, such as the lung burden of diesel soot particles, respiratory function, the composition of bronchoalveolar lavage fluid, the clearance of radiolabeled particles, pulmonary immune response, lung collagen, excised lung weight and volume, and histopathology. The hypothesis was that the effect of pre-existing emphysema and long-term diesel exhaust exposure on lung function and morphology were more than additive and therefore indicated increased susceptibility. The results, however, showed that rats with experimentally induced emphysema were no more susceptible to the inhalation of NO₂ or diesel exhaust than control rats were. In fact fewer soot particles accumulated in the emphysematous lungs (14, 15).

In another study, however, only published in abstract form, rats with pulmonary inflammation induced by monocrotaline (50 mg/kg, administered subcutaneously) or chronic bronchitis induced by SO₂ were reported to have an increase in mortality of 19% and 37%, respectively, after exposure to a particle load when compared with control rats with no lung disease (16).

Mouse

When the *in vivo* toxicity of diesel exhaust particles was studied in male mice (ICR) (17), the acute intratracheal instillation of diesel exhaust particles (400 to 1000 µg/mouse) caused severe lung injury and a high mortality rate. The cause of death was pulmonary edema mediated by endothelial cell damage. The toxicologic effect and the increased mortality were, to a great extent, prevented by pretreatment with the oxygen radical scavenger superoxide dismutase. This finding supports the hypothesis that the toxicity of diesel exhaust particles is connected to endothelial cell damage through the production of the radical superoxide.

The effect of diesel exhaust particles on allergen-induced bronchial hyperresponsiveness was studied in mice. Mice (C3H/HeN) were made allergic by intraperitoneal sensitization to ovalbumin and thereafter exposed to diesel exhaust (3000 µg/m³) by inhalation for 12 hours a day for 3 months (18). Three weeks after the onset of the exposure, there was a challenge with ovalbumin (1% for 6 minutes) every third week. Twenty-four hours after the last challenge the animals were sacrificed and airway responsiveness was measured, inflammatory cells in bronchoalveolar lavage were analyzed, and the lungs were examined histologically. Diesel exhaust exposure combined with antigen challenge induced airway hyperresponsiveness and airway inflammation, including increased eosinophils and mast cells in lung tissue. With only exposure to diesel exhaust particles there was also increased airway hyperresponsiveness but no eosinophil infiltration. In a similar setup, diesel exhaust inhalation (3000 µg/m³) in combination with ovalbumin sensitization increased the number of goblet cells in lung tissue, caused increased respiratory resistance, and increased the immune response measured as specific immunoglobulin (Ig)E, IgG₁, and interleukin-5 (IL-5) in lung tissue (19).

Guinea pig

A rhinitis model was used to study short-term effects of diesel exhaust (3 hours of exposure at 1000 and 3200 µg/m³) on guinea pigs (20). Following diesel exhaust exposure alone, there was no induction of sneezing, nasal secretion, or congestion. However, diesel exhaust particles augmented the sneezing and nasal secretion induced by histamine, but they had no significant effect on histamine-induced nasal congestion. The observations suggest that acute exposure to high levels of diesel exhaust may cause nasal mucosal hyperresponsiveness, but no overt symptoms of rhinitis.

Cat

Cats have also been exposed to diesel exhaust particles for more than 2 years (21). Cats were exposed for 8

hours a day, 7 days a week. During the initial 61 weeks the concentration of diesel exhaust particles was 6000 µg/m³, and during the following 62 weeks it was 12 000 µg/m³. During the first period no evident functional changes were seen, but after 2 years a pattern of restrictive lung disease developed.

In another study cats were exposed to diesel exhaust particles for 8 hours a day, 7 days a week for 27 months, and the exposure concentration was nearly doubled after 62 weeks, from 6340 to 11 700 µg/m³, and the NO₂ concentration rose from 2.68 to 4.37 ppm (22). The following morphologic findings were reported: lesions in proximal acinar regions of lungs, peribronchial fibrosis, an increase of lymphocytes, fibroblasts and interstitial macrophages containing diesel exhaust particles, and bronchiolar metaplasia. The study implied that chronic exposure to diesel exhaust particles has a persistent fibrogenic effect on the proximal acinar region of the lung.

Monkey

Male Cynomolgus monkeys were exposed 7 hours a day, 5 days a week for 24 months to ambient air, diesel exhaust particles (2000 µg/m³), coal dust (2000 µg/m³), or diesel exhaust particles and coal dust in combination (1000 µg/m³ + 1000 µg/m³) and, interestingly enough, compared with rats receiving the same exposures (23). The monkeys retained relatively more particulate material than the rats. The sites of particle retention were the same for the diesel exhaust particles, coal dust, or the combination. Rats retained more material in the lumen of alveolar ducts and alveoli, whereas monkeys retained more in the interstitium. Rats showed significant alveolar epithelial hyperplasia, inflammation, and septal fibrosis. In contrast, such morphological changes were not seen in the monkeys. The results indicate that particle retention patterns and tissue reactions in rats exposed to diesel exhaust particles may not be predictive of the reactions in primates (24), which may be less sensitive to diesel exhaust particles.

In vitro studies

The effect of diesel exhaust particles on isolated tissues and cultured cells from the respiratory tract of guinea pigs was studied (25). Diesel exhaust particles induced a dose-dependent relaxation of tracheal smooth muscle and time-dependent cytotoxicity of tracheal smooth muscle cells and lung fibroblasts. On the basis of pharmacological interventions, it was suggested that the cytotoxicity of diesel exhaust particles is mediated via the generation of oxygen radicals. Diesel exhaust particles have also been shown to produce aggressive oxygen radicals in a cell-free *in vitro* system in the presence of ap-

proprate electron donors (26), which in part may explain the potential toxicity and mutagenicity of diesel exhaust particles.

Allergy, immunology and related mechanisms

There are reports from Japan suggesting that children living close to roads with heavy traffic are more likely to develop allergies. A higher prevalence of allergy to cedar pollen was thus observed in a population living close to motorways, as compared with a reference group living close to a cedar forest and being exposed to the same number of cedar pollens (27). Therefore, some experimental studies with possible relevance to these epidemiologic observations are reviewed (5, 28–30).

In vivo studies

Humans

Studies have indicated that asthmatics are more sensitive to air pollutants and, in particular, acid aerosols (31). Hyperosmolar aerosols also induce bronchoconstriction in asthmatics, and this response is potentiated by acidity. Other studies show that young allergic asthmatics with exercise-induced bronchoconstriction are more sensitive than adult asthmatics to acid aerosols.

There is, however, a remarkable case report of diesel exhaust particles themselves causing asthma (32). Three railroad workers, nonsmokers and without any previous history of asthma, developed persistent asthma after acute exposure to excessive levels of diesel exhaust. This phenomenon occurred in situations where two locomotive units were coupled together and the crew riding in the second locomotive unit was exposed to significant diesel exposure. After 2–5 hours of exposure, there was an acute onset of shortness of breath, chest tightness, burning chest pain, and wheezing. All three subjects developed asthma, which still persisted 1 to 3 years postexposure. Although the actual levels were never assessed, it is likely that such excessive exposures rarely occur even in occupational situations.

Diesel exhaust particles potentiate IgE production in human respiratory mucosal membranes, as shown for example in a study by nasal challenge with varying doses of diesel exhaust particles (33). Four days after a challenge with 0.30 mg of diesel exhaust particles there was a significant increase in nasal IgE but not in the other Ig classes. There was also an increase in the number of IgE-secreting cells in lavage but no increase in IgA-secreting cells.

Diesel exhaust particles appear capable of acting as an adjuvant to allergens. Human nasal provocation studies were performed with challenges with diesel exhaust particles (0.3 mg) or the ragweed allergen *Amb a 1* or

both in a group of ragweed-sensitive subjects (34). When the challenge was with ragweed alone, there was an increase in IgE and IgG₄, and ragweed-specific IgE was also detectable in the lavage fluid. However, after challenge with the allergen and diesel exhaust particles, there was a 16-fold increase in ragweed-specific IgE. Diesel exhaust particles alone could increase total IgE, but in the presence of allergen there was an increase in antigen-specific IgE and in the expression of T_{H0}- and T_{H2}-type cytokines (IL-4, IL-5, IL-6, IL-10 and IL-13). It is currently believed that such deviations of the immune system may play a crucial role in the development of an atopic response. These studies suggest that diesel exhaust particles can enhance B-cell differentiation. By initiating and elevating IgE production, diesel exhaust particles may theoretically play a role in the increased prevalence of allergic disease.

The combination of nasal challenge with diesel exhaust particles and allergen has shown that, in comparison with the challenge with only diesel exhaust particles, diesel exhaust particles together with ragweed allergen induces higher ragweed-specific IgE and IgG₄ responses. However the total IgE levels were unchanged (35). Also in this study, there was a change in the cytokine pattern that would favor allergic sensitization. The authors suggested that the synergism between diesel exhaust particles and natural allergens is a key feature in increasing allergen-induced respiratory allergic disease.

Recently there has been evidence of diesel exhaust particles inducing what is called IgE isotype switching (3). Human volunteers were exposed by nasal challenge to diesel exhaust particles together with ragweed allergen. There was a local increase in IgE production, cytokine production, and an even greater increase in mucosa-specific ragweed IgE production. The isotype switching occurred only when diesel exhaust particles and allergen exposure was combined. The findings suggest that increasing environmental diesel exhaust particles with the same environmental load of allergen could be a factor behind the increasing sensitization and prevalence of allergic asthma.

Healthy, nonsmoking human volunteers have been exposed to diesel exhaust particles by intranasal instillation and cytokines in nasal lavage estimated after 18 hours by an indirect approach (mRNA) (36). Before the challenge, most of the subjects had detectable mRNA levels of only a few cytokines [interferon gamma (IFN- γ), IL-2 and IL-13], while after a challenge with 0.3 mg of diesel exhaust particles these three cytokines and a number of additional other cytokines (IL-4, IL-5, IL-6 and IL-10) were found in increasing levels. An increase in such nasal cytokine expression after exposure to diesel exhaust particles could again contribute to enhanced local IgE production.

Rat and mouse

Bice et al (37) studied the effect of exposure to diesel exhaust particles on the accumulation of particles in lung-associated lymph nodes and the possible effect on the antibody immune response after immunization in rats (F344) and mice (CD-1). Animals were exposed in chambers to diesel exhaust particles, 7000 µg/m³, 3500 µg/m³ or 350 µg/m³, 7 hours a day, 5 days a week for 24 months. Control and exposed animals were immunized by the intratracheal instillation of sheep red blood cells after exposure for 6, 12, 18, and 24 months. Maximal pathological changes were found after exposure for 18 to 24 months at 3500 or 7000 µg/m³, but there were also some effects in the low-dose group. Microscopic findings were an increase in the particle content of alveolar macrophages, a concentration of macrophages closer to terminal bronchioles, wall fibrosis, bronchial metaplasia, and, in some cases, squamous metaplasia. There were cholesterol clefts and increased interstitial neutrophils and intraalveolar granular eosinophilic material with entrapped free particles. Lung-associated lymph nodes were enlarged and black due to clusters of diesel exhaust particles. The number of lymphoid cells was elevated in rats exposed to the highest dose. However, the levels of specific antibodies were not significantly changed. The findings suggest that the lymph nodes accumulate diesel exhaust particles, and this accumulation leads to an increase in lymphoid cells in the tissue, but this change appears to have no consequence for antigen retention and immune functions.

Diesel exhaust particles show an adjuvant activity on IgE production in mice. Mice injected intraperitoneally with ovalbumin mixed with diesel exhaust particles showed higher IgE levels than mice immunized with ovalbumin alone. A production of Japanese-cedar-pollen-specific IgE was also found in mice immunized with Japanese cedar pollen mixed with diesel exhaust particles but not in animals immunized with Japanese cedar pollen alone (38).

The adjuvant effect on IgE production by different particles induced by carbon black and diesel exhaust particles were also studied in BDF₁ mice (39). Particles (25 µg) were instilled intranasally, and the animals were exposed to an aerosol of Japanese cedar pollen for 30 minutes a day at 1-week intervals for 8 weeks, followed by exposure for 30 minutes every 3 weeks for 9 weeks. There was a significant adjuvant effect of the particles on the production of Japanese-cedar-pollen-specific IgE and IgG. IgE production seemed to occur earlier in mice treated with particles than in mice immunized with allergens alone.

The adjuvant effect of diesel exhaust particles on systemic IgE production has also been studied in mice after intranasal challenge in order to elucidate which

part of the exhaust, the carbon core or the absorbed organic substance, is responsible for the effect (40). Balb/cA mice were immunized four times with ovalbumin alone or in combination with diesel exhaust particles or carbon black particles, and ovalbumin-specific IgE was analyzed. Both diesel exhaust particles and carbon black particles showed an adjuvant activity for specific IgE production after intranasal instillation, the implication being that both the organic matter absorbed on diesel exhaust particles and the nonextractable carbon core were responsible for the effect.

Using another mouse model, the popliteal lymph node assay, Lövik et al (41) showed that the nonextractable particle core contributed substantially to the adjuvant effect of diesel exhaust particles. Mice were immunized with ovalbumin together with diesel exhaust particles in the hind foot pad, and changes in popliteal lymph-node weight, cell numbers, cell proliferation, and specific IgE were measured. Ovalbumin inoculated together with diesel exhaust particles significantly augmented the response.

Combined intratracheal inoculations of diesel exhaust particles and antigen in mice increased airway inflammation induced by antigens and increased antigen-specific IgG₁ production but not antigen-specific IgE after 6 weeks (42). However, after a longer exposure (9 weeks), antigen-specific IgE was also increased. This may be another indication that there are differences between acute and chronic exposure.

Mice from five different strains were injected intratracheally with ovalbumin alone or together with diesel exhaust particles four times at 3-week intervals (43). Significant adjuvant activity of IgE production by diesel exhaust particles (50 µg) was not observed in any strain. However, the degree of eosinophilic inflammation in the airways corresponded with the specific IgG₁ production. There may be differences due to exposure route or dose, as higher doses of diesel exhaust particles (300 µg) showed an increase in specific IgE under similar conditions (44).

In another study, the effect of diesel exhaust particles was tested on two strains of mice, a high IgG responder strain (C3H/He) and a high IgE responder strain (BALB/c) (45). The mice were exposed through the intratracheal instillation of diesel exhaust particles (0.1 ml of 250 µg/ml) once a week for 5 weeks with ovalbumin sensitization intraperitoneally starting after 1 week. Twenty-four hours after diesel exhaust particles were administered, the mice were challenged with an aerosol of 1% ovalbumin. The diesel exhaust particles caused increased IgG₁ production and airway hyperresponsiveness in C3C/He mice and an increase in eosinophils and goblet cells in lung tissue and an increase in cytokines involved in eosinophilic function (IL-2 and IL-5). There was no effect on IgE production in any strain, and only

low effects on other parameters were found in the BALB/c mice. There are thus murine-strain differences, and the effect on mice appears to be related to IgG₁ production.

Takano et al (42) also studied the effect of diesel exhaust particles on ICR mice and found that the intratracheal instillation of diesel exhaust particles increased antigen-induced airway inflammation, as indicated by an increase in eosinophils, lymphocytes, and goblet cells in bronchial epithelium and an increase in IgG and IgE production. There was also an increase in the proallergic cytokines IL-2, IL-4, IL-5, and granulocyte macrophage-colony stimulating factor (GM-CSF) but not in the suppressive cytokine IFN- γ . They also found that a combination of diesel exhaust particles and ovalbumin increased the bronchoconstriction response to inhaled acetylcholine in this model (46). Furthermore, daily inhalations of diesel exhaust particles may enhance allergen response, possibly through an increased local expression of proinflammatory cytokines such as IL-5 and GM-CSF (47). In another study, increased IgE production was also found in mice after the intranasal administration of suspended particulate matter (SPM) together with ovalbumin at 3-week intervals until 21 weeks (48).

The role of nitric oxide in asthma-like symptoms induced by diesel exhaust particles has been studied in mice (49). The repeated intratracheal instillation of diesel exhaust particles in mice induced a fourfold increase in macrophages, neutrophils, eosinophils, and lymphocytes in bronchoalveolar lavage fluid. Diesel exhaust particles induced a twofold increase of nitric oxide in the exhaled air and an increase in staining of nitric oxide synthetase in the airway epithelium. The increase in respiratory resistance induced by the installation of diesel exhaust particles was suppressed by N^G-methyl-L-arginine, an inhibitor of nitric oxide synthetase.

In vitro studies

Human cells

Complement activation is a part of the host defense system, and the effect of diesel exhaust particles on the hemolytic activity of human serum complement has been studied (50). Pretreatment of human serum with extracts of diesel exhaust particles (500–2500 μ g/ml) showed a dose-dependent decrease in hemolytic activity to 20% of the total at the highest tested dose. These studies also indicate that diesel exhaust particles can activate the alternative pathway of the complement system and result in a decrease in the hemolytic activity of the complement.

Studies on isolated human B-lymphocytes have shown that exposure to diesel exhaust particles enhances the synthesis of IgE by these cells. Airway epithelial cells play a prominent role in the pathogenesis of air-

way disease. Various studies have shown that the exposure of nasal or bronchial epithelial cells to diesel exhaust particles results in increased synthesis and a release of proinflammatory mediators, cytokines such as IL-6, IL-8 or GM-CSF, and adhesion molecules (51).

The ability of diesel exhaust particles to induce IgE production has been mimicked by polycyclic aromatic hydrocarbons extracted from diesel exhaust particles and shown to enhance IgE production from purified human B-cells stimulated by IL-4 (52). However, the polycyclic aromatic hydrocarbons from diesel exhaust particles did not induce IgE production in unstimulated B-cells, the implication being that it only enhances ongoing IgE production. Phenanthrene, a major polycyclic aromatic hydrocarbon and an important component of diesel exhaust particles, has shown the same effect on IgE production in a human B-cell line (53).

Other studies were performed using cultured human bronchial epithelial cells exposed to diesel exhaust particles (54). Exposure of these cells to diesel exhaust particles at a concentration of 50 μ g/ml, a filtered solution of diesel exhaust particles, or diesel exhaust particles at a concentration of 100 μ g/ml attenuated the ciliary beat frequency dose dependently and increased the release of IL-8, GM-CSF, and soluble intracellular cell adhesion molecule (ICAM-1). The observations support the possibility that exposure to diesel exhaust particles may lead to functional changes and a release of proinflammatory mediators that have the potential to influence the development of airway disease. Specifically, infiltrations of neutrophils and other inflammatory cells would be promoted by the observed changes.

The effect of diesel exhaust particles was also studied in three different in vitro systems of human airway epithelial cells, in epithelial cells from nasal polyps, in human bronchial cells obtained during lung tumor resection or at autopsy, and in a human bronchial epithelial cell line (BEAS-2B) (55). Diesel exhaust particles (10–100 μ g/ml) induced a dose- and time-dependent stimulation of IL-8 and GM-CSF production by all three kinds of epithelial cells. With the use of double chamber plates, it was shown that the cells could only be stimulated from the apical side. As a control, neither coal nor graphite showed any stimulatory effect, whereas, benzpyrene, a constituent of diesel exhaust particles, did. It thus appears that the exposure of human epithelial cells to diesel exhaust particles may stimulate cytokine production, with possible relevance for allergic inflammation.

In another study the effect of diesel exhaust particles in doses between 40 to 330 μ g/ml was investigated using a human bronchial epithelial cell line (56). Diesel exhaust particles ranged between 25 to 35 nm and were phagocytized by these cells. There was an increase in IL-6 and IL-8 production (11-fold and 4-fold,

respectively). Exposure of these cells to tumor necrosis factor alpha (TNF- α) also stimulated a strong increase in IL-6 and IL-8 production. There was an additive effect on the production of IL-6 and IL-8 after TNF- α priming and subsequent exposure to diesel exhaust particles, seen only at low doses of diesel exhaust particles (10–70 $\mu\text{g/ml}$) and TNF- α (0.05–0.2 ng/ml).

Mechanisms involved in asthma development after exposure to diesel exhaust particles may include a better penetration of allergen across the respiratory mucosa or direct modulation of the immunologic response (57). Particulate air pollution includes particles from diesel and gasoline engine exhaust and biological materials such as plant debris and tire debris (eg, latex) that may be allergens (58). Some allergens, such as the major grass pollen *Lolium perenne*-1 (Lol p1) allergen, are also shown to bind specifically to diesel exhaust particles. This might be a possible mechanism for triggering asthma attacks and one theoretical explanation for the increase in asthma prevalence (59).

Ormstad et al (60) have also studied the allergen-carrying effect of diesel exhaust particles, in an *in vitro* study of allergen adsorption to particles such as indoor SPM and diesel exhaust particles. They found that a cat allergen (Fel d1), dog allergen (Can f1), and birch pollen allergen (Bet v1) were all found on the surface of SPM, whereas house-dust-mite allergen (Der p1) was not. However, all four allergens were found to be absorbed by diesel exhaust particles.

A chemical characterization has been studied of the coating of birch pollen grains collected during the pollen season in the north of Stockholm. The greatest portion (80%) consisted of n-alkanes and n-alkenes, but also methylketones, ethers, alcohols, and amino alcohol were identified (61).

Rat

Yang et al (62) studied the possible role of cytokines for the toxic effect of diesel exhaust particles. Rat alveolar macrophages were incubated with diesel exhaust particles in different concentrations, as well as with methanol, washed diesel exhaust particles, or methanol extracts of diesel exhaust particles. High concentrations of diesel exhaust particles and methanol extracts increased IL-1 secretion by alveolar macrophages, while there was no effect on TNF- α . Diesel exhaust particles inhibited the production of IL-1 and TNF- α stimulated by endotoxin (lipopolysaccharide). This inhibition suggests that the proinflammatory cytokine IL-1 may play a role in the pulmonary response to the inhalation of diesel exhaust particles. Furthermore, pretreatment of alveolar macrophages with diesel exhaust particles suppresses the response to lipopolysaccharide stimulation, which may be a factor contributing to the impairment

of the pulmonary defense system after prolonged exposure to diesel exhaust particles.

Rabbit

The effect of diesel exhaust particles on endogenous production or the action of nitric oxide has been studied by Muto et al (63), who worked with a model using rabbit bronchial or aortic rings. As nitric oxide is present in exhaled air, they studied whether diesel exhaust particles inhibit the synthesis of nitric oxide. It is well known that nitric oxide released from vascular endothelium after stimulation by acetylcholine accounts for the biological activity of endothelium-derived relaxing factor. They found that diesel exhaust particles, as well as N^G-methyl-L-arginine (an inhibitor of nitric oxide synthetase), alter the effect of acetylcholine, as it abolished the acetylcholine-induced relaxation of aortic rings pre-constricted with phenylephrine. Nitric oxide release by acetylcholine from aortic rings was inhibited by diesel exhaust particles (100 $\mu\text{g/ml}$, 60 minutes). Nitric oxide released by the bronchial epithelium in rabbit bronchial strips attenuated the bronchoconstriction induced by acetylcholine, and this attenuation was abolished by 60 minutes of preincubation with diesel exhaust particles (100 $\mu\text{g/ml}$) or N^G-methyl-L-arginine (5×10^{-4} M). Their conclusion was that the inhibition of nitric oxide availability by diesel exhaust particles may be a part of the observed respiratory effects of such particles, but further studies are required to establish the significance of their findings.

Cardiovascular effects

The direct toxic action of diesel exhaust particles has been examined in a model of isolated atria in guinea pigs (64). Diesel exhaust particles in lower doses (between 10 and 500 $\mu\text{g/ml}$) induced a transient but dose-dependent increase in contractile force (positive inotropic response). In doses higher than 500 $\mu\text{g/ml}$, diesel exhaust particles only decreased contractile force (negative inotropic response) and induced cardiac arrest. It was concluded that the cardiac toxicity contributes to the lung edema that is known to be a prominent cause of death of animals exposed to diesel exhaust particles. It appears unlikely, however, that the inhalation of diesel exhaust particles by humans may produce the concentrations employed in these particular experiments.

Epidemiologic studies have shown increased mortality in cardiovascular disease and respiratory disease during heavy air pollution (see the section "Epidemiologic studies on Health Effects of Ambient Particulate Air Pollution"). In a meta-analysis, Seaton et al (65) suggested that ultrafine particles induce inflammation

in the lung in susceptible persons, the release of mediators, and an increase in blood coagulability. There has been a hypothesis of a possible association between occupational exposure to dust and ischemic heart disease, and Sjögren has tried to test this idea in a literature survey (66–68). Coal miners showed manifestations of pneumoconiosis and an increased incidence of ischemic heart disease. Fibrinogen is a risk factor for ischemic heart disease, and there are increased levels of fibrinogen in coal miners with pneumoconiosis. The hypothesis is that long-term inhalation of particles retained in the lung induces inflammation, accompanied by an increase in plasma fibrinogen, which leads to an elevated risk for blood clotting and ischemic heart disease (68). There are, however, no experimental data at the moment which support the possibility that the inhalation of PM by humans has direct effects on fibrinogen levels or activity, and the hypothesis is built on circumstantial evidence.

Summary and concluding remarks

Diesel exhaust particles can have several effects on the lung and the cardiovascular system and may interfere with immunologic and allergic reactions.

The acute effects include irritation of the nose and eyes by an unpleasant odor, a transient decline in ventilatory capacity, cardiovascular symptoms, headache, fatigue, and nausea. These symptoms are usually reversible within a few days.

Chronic exposure to diesel exhaust induces cough, sputum production, and lung function decrements. It has been speculated that there are exacerbations of asthma and respiratory disease due to the inhalation of PM₁₀ particles from diesel exhaust particles, but there is no direct experimental support for this view. The relative role of diesel exhaust particles and other particles for the pulmonary effects of exposure to road tunnel air remains to be established (69).

Pathological and histological findings in lung after exposure to diesel exhaust particles have mostly been studied in rats and include increases in lung weight, increases in particles in lung, and an increased burden of BS, associated with alveolar infiltration of macrophages, macrophage aggregation, chronic inflammatory expression, proliferation and hyperplasia of alveolar epithelium and type 2 cells, thickening of alveolar septa, wall fibrosis, and emphysema.

Comparisons of diesel exhaust particles and carbon black in animal inhalation studies show that a reduction in lung function and an accumulation of macrophages appear in parallel, the result suggesting that the toxic effect of diesel exhaust particles is in part coupled to

the carbon core. The toxicity of diesel exhaust particles could in part also be mediated via the production of oxygen radicals.

Diesel exhaust particles introduced by different routes, intraperitoneally, intranasally or intratracheally, may act as an adjuvant to pollen and hence increase the sensitization response. Such a phenomenon has been observed in both human and animal studies, mostly in mice, in which the IgE production in response to allergen has been enhanced by diesel exhaust particles. Diesel exhaust particles can also activate the alternative pathway of complement activation. Diesel exhaust particles affect human B cells and may enhance IgE production through several mechanisms. In addition, diesel exhaust particles show effects on allergic responses that involve inflammatory cells in respiratory mucosa, like T cells, mast cells and epithelial cells, and also on the local production of different proinflammatory cytokines.

Another possible mechanism for diesel exhaust particles in allergic responses may also be to act as a carrier of pollen allergens, allowing enhanced deposition of pollen in the lower airways. Allergen binding to diesel exhaust particles may trigger asthma attacks and may facilitate the penetration of allergen through the airway mucosa.

Published data do not indicate that there is a unifying mechanism of action which can explain different alleged public health effects of particulate air pollution. One major shortcoming of many experimental studies relates to the inability to establish whether the exposures used for the studies are relevant to the background or peak exposures which may occur in real life, acutely or chronically. There is therefore a great need to assess such relations in humans or in animal models that are sufficiently predictive and sensitive.

The particle concentrations that include diesel emissions (ie, particles less than PM₁₀) are reported to be 30–100 µg/m³ in urban situations in Sweden and Europe. The highest exposures occur in occupational situations and have been reported to vary between 4 and 1740 µg/m³ (for railroad workers, miners, or truck drivers) (70). In experimental situations with animals, the doses have usually varied between 100 and 11 700 µg/m³ (71). Therefore the effects observed probably have the greatest relevance to situations of relatively high exposure (ie, occupational). Theoretically, acute exposure to high levels of diesel exhaust particles or chronic exposure to low levels may both impair respiratory functions, but the mechanisms may differ. It is, for example, known for a classical trigger of asthma such as allergen that acute exposure to high allergen doses produces effects which differ from those caused by repeated low-dose exposure (72). After the results of chronic-exposure studies on rats have been combined with

mathematical models for lung clearance, it has been proposed that the effects on lung function, especially lung clearance, occur at doses that are 10–50 times lower than those required to induce carcinogenic effects (73). A threshold dose (no observable adverse effect level) has been noted for the appearance of symptoms or effects on lung function, and it is reported to be 2000, 350 and 250 $\mu\text{g}/\text{m}^3$ for monkeys, rats, and guinea pigs, respectively. Such findings, and other data, give the impression that primates are less sensitive than rodents to diesel exhaust particles. Extrapolations from the dose-response relationships in animal studies and transformation to the human situation have been reported. Thus from the NOAEL level in animal studies there have been attempts to calculate a corresponding safe dose for humans, and the Environmental Protection Agency (EPA) in the United States has accordingly established a limit of 5 $\mu\text{g}/\text{m}^3$ for continuous lifetime exposure. It must however be recognized that such calculations have many limitations, as they are based on mathematical modeling and interspecies extrapolations.

Finally, during the compilation of this section, new epidemiologic data appeared in the literature that supported the assumption that atopic children constitute a group with particular risk of developing significant health effects as a result of exposure to airborne particles (74). The existence of such sensitive groups would seem to deserve particular attention in risk assessment.

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Experimental studies on the effects of ultrafine particles

by Lena Låstbom & Per Camner

Ultrafine particles are usually defined as particles smaller than 20 or 40 nm and sometimes less than 100 nm. Such particles have, for several reasons, been regarded as a tentative cause of the health effects associated with particles found in a large number of epidemiologic studies (see the section "Epidemiologic Studies on the Health Effects of Ambient Particulate Air Pollution"). Ultrafine particles are produced in combustion processes. They occur in large numbers in the ambient air (see the section "Particles in the Ambient Atmosphere"). The mass fraction of ultrafine particles is, however, small because ultrafine particles rapidly form aggregates. One crucial question concerning the role of ultrafine particles is whether the toxicity of inhaled particles is determined by the number, the surface area, or the mass of particles. If the first two alternatives are correct, it is obvious that ultrafine particles are of great importance. For example, one 2- μm particle has the same mass as 1×10^6 20 nm particles, and the same surface area as 1×10^4 20 nm particles. Furthermore, the deposition in the lungs, especially in the alveolar region, is high for ultrafine particles (see the section "Deposition and Clearance of Particles in the Human Lung"). There are also toxicologic data which can be considered evidence for the importance of ultrafine particles in causing toxic effects. One set of evidence comes from studies of the effect of heated perfluoropolymers such as polytetrafluoroethylene and tetrafluoroethylene-hexafluoropropylene copolymer, which have long been known to be extremely toxic to the lungs. Recent studies indicate that ultrafine particles play an important role in these effects. Another set of evidence comes from studies of exposure of the lung to aggregates of ultrafine particles. These aggregates have been found to be more toxic than solid particles of the same size as the aggregates and of the same material.

Heated perfluoropolymers

Already in 1955, Zapp et al (1) found that the inhalation of heated perfluoropolymers was highly toxic in animal experiments. Inhalation exposure of rodents to heated perfluoropolymer fumes induced massive acute lung injury with focal hemorrhage, pulmonary edema, and necrosis of tracheobronchial epithelium (2, 3). These severe effects on the lung could be avoided when rats were exposed via a filter or by letting the combustion products age (4, 5). The median particle diameter was estimated to be 30 nm by Warheit et al (5). The reduction of the toxic effects by aging was probably

caused by aggregation of the ultrafine particles. These results suggest that severe toxic effects are caused by ultrafine particles, either because of the effect of the particles themselves or because of toxic compounds on the surface of the particles. However, Seidel et al (6) found that 10-minute exposure with a particle concentration of 200 $\mu\text{g}/\text{m}^3$ of fumes from heated perfluoropolymers was mortal to rats, even when the heating temperature was so low (370°C) that no free radicals were present in the fumes.

Lee & Seidel (7) exposed rats to fresh fumes, aged fumes, filtered fumes, and reheated fumes from perfluoropolymers generated at a low temperature (370°C). The particle sizes in the fresh fumes were in the range of 20–70 nm. Exposure to 200 $\mu\text{g}/\text{m}^3$ for 30 minutes killed eight of eight rats. In the aged fumes, there was a small number of individual particles within the size range of 20–70 nm, but many particles formed aggregates ranging from 0.5 to 4 μm . Exposure to a 400 $\mu\text{g}/\text{m}^3$ concentration of the aged fumes for 30 minutes killed 4 of 24 rats. The 18 rats that were exposed for 30 minutes to the filtered fumes showed no abnormal clinical signs, and the four rats that were taken for pathological evaluation had normal lungs. The reheated fumes (240°C) consisted of numerous particles measuring 20–200 nm and aggregates up to 800 nm. Two of three rats died after exposure to 760 $\mu\text{g}/\text{m}^3$ of the reheated fumes for 30 minutes.

Oberdörster et al (8) exposed rats for up to 30 minutes to fumes of heated polytetrafluoroethylene, generated at 405–425°C. The particle concentration varied in the range of 0.74– 1.0×10^6 particles/ cm^3 . The number median diameter was 26.2 nm with a geometric standard deviation of 1.44. On the assumption of unit density (1 g/cm^3), 1×10^6 particles/ cm^3 was calculated to have a mass of 64 $\mu\text{g}/\text{m}^3$. Several rats were killed by exposure to these fumes. The lavage fluids of these rats were largely contaminated with red blood cells, which indicated severe injury to the capillary-epithelial barrier, and the pathological evaluation of the lungs showed acute hemorrhagic inflammatory edema. In the surviving rats, the polymorphonuclear leukocytes in the lavage fluid were markedly increased (by a factor of 100) 4 hours after the exposure.

In a later study by the same group (9), rats were exposed to fumes from heated polytetrafluoroethylene (450–460°C) for 15 minutes. The number median diameter was 18 μm , and the particle concentration was 0.5×10^6 particles/ cm^3 , which is equivalent to about 50 $\mu\text{g}/\text{m}^3$. Four hours after the exposure, the lungs were lavaged. Again, there was a massive increase in

Table 1. Total number of cells and neutrophils in lavage fluid after the tracheal instillation of aggregates of fine or ultrafine particles.

	Control	Fine particles	Ultrafine particles
Total number of cells in the lavage	1.15×10^7	1.48×10^7	4.68×10^7
Neutrophils in the lavage	1.6%	8.9%	50.5%

neutrophils. The exposure also initiated an antioxidant and cytokine response for compounds produced from inflammatory, epithelial, and endothelial cells.

Oberdörster et al (10) reported that fumes from polytetrafluoroethylene generated in heated argon gas consisted of ultrafine particles of the same size as in polytetrafluoroethylene fumes generated in air, but that the gas phase did not contain fluoride, which is a main gas component in air-generated polytetrafluoroethylene fumes. Rats exposed to polytetrafluoroethylene generated in argon gas did not show any inflammatory response. This finding suggests that the earlier reported effects from exposures to perfluoropolymer fumes were not a specific effect of ultrafine particles. One possibility for these effects may be that hydrogen fluoride produced during the pyrolysis was transported down to the alveolar region by the particles and that it damaged this part of the lung. Pure hydrogen fluoride, even at a concentration of more than 1000 ppm, only produced damage in the nasal region (11).

Aggregates of ultrafine particles

In an earlier review article (12), it was evident that aggregates of ultrafine particles of titanium dioxide and carbon black induced more lung tumors in rats than larger particles of the same material. Driscoll (13) compiled a large number of long-term inhalation experiments on rats with particles of different materials and sizes. For rats he found a better correlation between the surface area of the lung burden and lung tumors than between the mass of the lung burden and lung tumors.

Ferin et al (14) instilled aggregates (500 µg) of two types of ultrafine titanium dioxide particles, rutile and anatase, with primary particle diameters of 12 nm and 21 nm, respectively. They also instilled fine titanium dioxide particles of rutile and anatase with primary diameters of 230 nm and 250 nm. The fraction which could not be removed by lavage increased markedly with decreasing particle size, from 19% for 250 nm particles to 61% for 12 nm particles. The same group (15) studied the inflammatory response of aggregates of ultrafine (primary diameter 20 nm) and fine (primary di-

ameter 250 nm) titanium dioxide particles. Twenty-four hours after the instillation, the animals were killed and the lungs lavaged. The estimated dose to the interstitial part of the lung was 2.8 µg for the fine particles and 51.8 µg for the ultrafine particles. The total number of cells obtained in the lavage was markedly enhanced in the rats exposed to the ultrafine particles when compared with the lavages from control rats and rats exposed to fine particles (table 1). Especially the neutrophils were increased in the group exposed to the ultrafine particles. In an additional experiment, the authors instilled around 100 µg of aggregated ultrafine titanium dioxide particles in the form of either free particles, particles coated with rat serum, or phagocytized particles in combination with alveolar macrophages and neutrophils. The free and serum-coated particles both induced a marked and similar increase in neutrophils (neutrophils constituted about 15% of the total cell numbers), whereas the phagocytized particles did not induce any increase in the neutrophils.

Ferin et al (14) and Oberdörster et al (16) also exposed rats via inhalation to aggregates of ultrafine (21 nm) and fine (250 nm) titanium dioxide particles. The mass median diameter was 0.78 µm for the ultrafine aerosol and 0.71 µm for the fine aerosol. The concentration was 23.5 (SD 2.9) mg/m³ for the ultrafine particles and 22.3 (SD 4.2) mg/m³ for the fine particles. The exposure lasted for 12 weeks (6 hours a day, 5 days a week). The animals were followed up to 64 weeks. The lung burdens after 12 weeks were 6.62 (SD 1.22) mg for the fine particles and 5.22 (SD 0.75) mg for the ultrafine particles. The half-time of the retention in the lungs for the ultrafine particles was around 500 days, and for the fine particles it was about 170 days. After 8 weeks, the interstitial burden was markedly higher for the ultrafine than for the fine particles (eg, around 500 µg of the fine particles, and more than 2000 µg of the ultrafine particles was located in this region after 41 weeks). The content in the hilar lymph nodes was also much higher for the ultrafine than for the fine particles (eg, 807 µg of the ultrafine particles compared with 69 µg of the fine particles was located in this region after 41 weeks). With respect to the inflammatory response, the ultrafine particles induced a marked increase in the total number of cells in the lung lavage, especially in neutrophils, but also in alveolar macrophages. After 12 weeks, there was, for example, an increase of neutrophils with a factor of 100 and of macrophages with a factor of 3. The fine titanium dioxide particles induced no clear effect on the total number of cells and macrophages, but an increase in neutrophils occurred with almost a factor of 10 after 12 weeks.

When radiolabeled polystyrene particles were inhaled 12 weeks after the start of the exposure to titanium dioxide particles, the retention half-times were 66

days for the controls, 117 days for the group exposed to fine particles, and 541 days for the group exposed to ultrafine particles. When the dose was expressed as the surface area of retained particles per 1×10^6 alveolar macrophages, the relationship between the dose and the retention half-times for the two particle types was described by one curve (figure 1). When radiolabeled test particles were inhaled 7 months after the start of the exposure, clearance in the group exposed to the fine titanium dioxide particles was similar to that of the controls, whereas the group exposed to ultrafine particles still had a significantly slower clearance than the controls. A histological evaluation after 41 weeks showed early fibrotic reaction in the ultrafine particle group and, to a less degree, also in the fine particle group. This reaction was less prominent 1 year after the exposure.

Single ultrafine soluble particles

Chen et al (17) exposed guinea pigs to a $300 \mu\text{g}/\text{m}^3$ of fine (mass median diameter 300 nm) and ultrafine (mass median diameter 41 nm) sulfuric acid aerosols. Some animals were exposed for a single 3-hour period, and other animals were exposed for 3 hours a day for 3 days. The animals were killed immediately after the exposure or 24 hours later. The lungs were lavaged and cell viability, β -glucuronidase activity, lactate dehydrogenase activity, and total protein concentration was measured. Although there were statistically significant differences in these parameters, they were rather small, and there was no clear pattern of difference between the two aerosols. Changes in the tumor necrosis factor alpha (TNF- α) were also seen, but they did not differ between exposure to the fine and the ultrafine aerosol. Alveolar macrophage phagocytic function was tested and found to be depressed in the animals killed 24 hours after the exposure to the ultrafine aerosol and increased in animals killed 24 hours after the exposure to the fine aerosol.

Summary and concluding remarks

Ultrafine particles are usually defined as particles less than 20 or 40 nm in size and sometimes less than 100 nm. These particles occur in large numbers in the ambient air and are mainly deposited in the alveolar region.

Heated perfluoropolymers are lethal to animals in low concentrations, less than $100 \mu\text{g}/\text{m}^3$, and the fumes consist of ultrafine particles. Therefore, attention toward the evaluation of toxicity caused by ultrafine particles

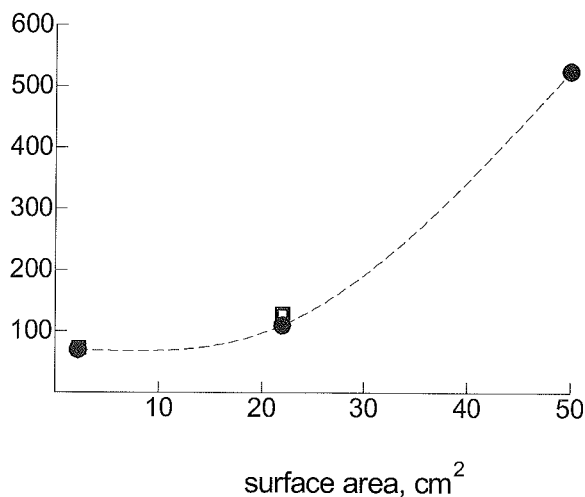


Figure 1. Half-time of inhaled polystyrene particles as the function of the surface area of titanium dioxide particles (fine and ultrafine). Rats had been exposed to the titanium dioxide particles before the study of the retention of the polystyrene particles. [From Oberdörster et al, 1994 (16)]

has increased. The fact that filtered and aged fumes of perfluoropolymers are considerably less toxic than fresh fumes has been taken as an indication that ultrafine particles in general are toxic. However, a recent study showed that, when perfluoropolymers are heated in argon gas, the concentration of ultrafine particles is similar, but the toxicity is lower. This finding indicates that the toxic effects of heated perfluoropolymers may not be a specific effect of ultrafine particles.

Animal experiments show that aggregates of ultrafine particles are more toxic than aggregates of fine particles. When aggregates of ultrafine and fine particles have been instilled via the trachea or inhaled, the ultrafine particles have induced much stronger inflammatory reactions, for example, more neutrophils in the lavage fluid. Furthermore, the ultrafine particles are, to a greater extent, located in the interstitium and in the regional lymph nodes. Interestingly, the relationship between dose and the alveolar retention half-time of test particles could be well described by one curve for both fine and ultrafine particles when the dose was expressed by the surface area of the particles. This finding suggests that the surface area is a better measure of dose than mass is. The difference between solid fine and ultrafine particles in effect contrasts with the difference in effect between fine and ultrafine liquid particles (sulfuric acid), which is small.

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Human experimental studies on the effects of inhaled particles

by Lena Låstbom & Per Camner

Human experimental studies on the effects of inhaled particles have mainly dealt with the effects of acid particles and, especially, their effects on lung function. Concerning the effects on lung function, it seems that the more acid the particles are the more severe the effects, and that asthmatic persons are more sensitive than healthy subjects (1, 2). It is therefore understandable that experiments with sulfuric acid aerosols in asthmatics have been given such a high priority.

Acid particles

Effects on lung function

There have been several short-term studies with rather similar designs. The exposure times have been one or several hours. Various groups of asthmatics have been studied using conventional lung function parameters such as forced expiratory volume in 1 second ($FEV_{1.0}$), maximum expiratory flow, and airway resistance (R_{aw}), and in some studies bronchial reactivity has also been measured. During the exposure, both periods with physical exercise and periods with rest have been used. This approach is important as physical exercise has been shown to increase the effect. In spite of the similarities in design, the studies have given markedly different results. Some studies have shown significant but small decreases in lung function for exposure at concentrations around or even below $100 \mu\text{g}/\text{m}^3$ of sulfuric acid. Koenig et al (3) found significant changes in young asthmatics already at $70 \mu\text{g}/\text{m}^3$. The decrease in $FEV_{1.0}$ was, for example, 6% after exposure to sulfuric acid but only 2% after exposure to air. However, the same group found no clear decrease in elderly asthmatics at this concentration (4). Similarly, Utell et al (1) found small effects on the lung function of asthmatic patients at a sulfuric acid concentration of $750 \mu\text{g}/\text{m}^3$. On the other hand, there are studies in which concentrations of $1000 \mu\text{g}/\text{m}^3$ or higher have been necessary to induce significant effects on lung function (5–7).

It seems difficult to explain these remarkably different results by differences in methodology. One important parameter in particle exposure is the size distribution. However, the mass median aerodynamic diameter was $0.6 \mu\text{m}$ in the study by Koenig et al (3), and this figure does not differ much from the mass median aerodynamic diameters in the studies by Avol et al (5) ($0.9 \mu\text{m}$) and Aris et al (7) ($0.4 \mu\text{m}$). As already mentioned, the designs and the method for lung function studies were rather similar. One possible explanation for the

different results may be that, although patients with asthma were used in all the studies, these patients might differ in bronchial reactivity. It is known that, when studied with clinical tests such as the methacholine or histamine test, bronchial reactivity differs markedly. Svarthengren et al (8) found that, in healthy subjects, the concentrations of methacholine needed to cause a 20% reduction in $FEV_{1.0}$ varied by a factor of 100.

Combined effect of acid aerosols and other pollutants

Ozone (O_3) is a common air pollutant that can damage the lungs. Linn et al (9) exposed both 30 asthmatic patients and 15 healthy subjects during a relatively long time, 6.5 hours, to either $100 \mu\text{g}/\text{m}^3$ of sulfuric acid aerosol (mass median aerodynamic diameter $0.5 \mu\text{m}$) or to 0.12 ppm of O_3 or a combination of the two pollutants. The exposure to O_3 with or without sulfuric acid aerosol affected lung function significantly (eg, decreased $FEV_{1.0}$ and increased bronchial reactivity). The exposure to the sulfuric acid aerosol did not induce any significant changes in lung function when compared with exposure to clean air. There were no substantial differences between the effects of O_3 alone and the combination of O_3 and sulfuric acid aerosol. A similar lack of joint effect was also observed by the same group for O_3 and nitric acid on healthy subjects (10).

However, Frampton et al (11) studied the interaction between a sulfuric acid aerosol and O_3 in both healthy subjects and asthmatics using another design. They first exposed 12 subjects during a 3-hour period with both exercise and rest to either a sulfuric acid aerosol (mass median diameter $0.6 \mu\text{m}$) concentration of $100 \mu\text{g}/\text{m}^3$ or a control aerosol of sodium chloride of a similar concentration and particle size distribution. Twenty-four hours later, they exposed the subjects to O_3 at three different concentrations, 80, 120 and 180 ppb, during a 3-hour period with both physical exercise and rest. For the healthy subjects, there was no clear evidence of any effect of the preexposure to the acid aerosol on the response to O_3 . However, for the asthmatic persons, preexposure to the sulfuric acid aerosol but not to the sodium chloride aerosol caused dose-related small decreases (up to about 6%) in forced vital capacity (FVC) and $FEV_{1.0}$ after O_3 exposure and also 4 hours later.

Anderson et al (12) exposed 15 healthy and 15 asthmatic volunteers to carbon black particles both alone and in combination with sulfuric acid particles. Both the carbon black particles and the sulfuric acid particles had a diameter of $0.5 \mu\text{m}$. In the exposure to carbon

particles alone, the mean concentration was $200 \mu\text{g}/\text{m}^3$ for the healthy subjects and $145 \mu\text{g}/\text{m}^3$ for the asthmatics. In the combined exposure, the concentration of carbon black was $230 \mu\text{g}/\text{m}^3$ for the healthy subjects and $205 \mu\text{g}/\text{m}^3$ for the asthmatics, and the concentration of sulfuric acid was around $100 \mu\text{g}/\text{m}^3$. All the exposures lasted 60 minutes with alternating 10-minute periods of physical exercise and rest. Specific airway resistance (SR_{aw}), FVC and $\text{FEV}_{1.0}$ were measured before, during, and at the end of the exposure. In addition, bronchial reactivity was assessed after the exposure. Neither the exposure to carbon particles alone nor to the combination of carbon black and sulfuric acid particles induced any clear effect on lung function.

Effects on mucociliary clearance

When the concentration of a pollutant increases until it produces an effect on mucociliary clearance, the effect is usually increased mucociliary transport. A further increase in the concentration or a longer exposure may cause impaired transport. An increased mucociliary clearance, caused by acute inhalation of a pollutant, can therefore be considered to be an undesirable effect for the same reason that bronchoconstriction is generally considered to be undesirable (bronchoconstriction can be considered a positive defense mechanism as it results in a more central deposition of the particles and thereby faster elimination). For example, short-term cigarette smoking results in increased mucociliary transport (13, 14), but it is well known that long-term cigarette smoking results in impaired mucociliary transport.

There have been several studies in which persons have been exposed to aerosols of sulfuric acid with a mass median aerodynamic diameter of around $0.5 \mu\text{m}$, and tracheobronchial clearance using radiolabeled test aerosols have been studied. Newhouse et al (15) exposed healthy subjects to $1 \text{ mg}/\text{m}^3$ of a sulfuric acid aerosol for 2 hours. Clearance was studied with a test aerosol of radiolabeled particles with a mass median aerodynamic diameter of $3 \mu\text{m}$, and it was significantly increased by the sulfuric acid exposure. Leikauf et al (16) exposed healthy subjects to sulfuric acid particles at concentrations of 0, 110, 330, and $980 \mu\text{g}/\text{m}^3$ for 1 hour. Clearance was studied using $7.5 \mu\text{m}$ particles. The lowest concentration of sulfuric acid caused a significant increase in tracheobronchial clearance, from a half-time of 80 minutes to one of 50 minutes, and the highest concentration caused a significant reduction in clearance. Leikauf et al (17) also exposed healthy subjects to the same concentrations of sulfuric acid and studied clearance using somewhat smaller particles, $4.2 \mu\text{m}$. In this investigation, clearance was significantly reduced at both 100 (from a half-time of 80 minutes to 110 minutes) and $1000 \mu\text{g}/\text{m}^3$ (half-time 142 minutes) and tend-

ed to be reduced at $300 \mu\text{g}/\text{m}^3$ (half-time 106 minutes). The same group also exposed asthmatics to the same concentrations of sulfuric acid particles and used radiolabeled $3.9 \mu\text{m}$ particles for clearance studies (18). Of the 10 asthmatics, six suffered from asymptomatic mild asthma and four from more severe asthma. The group with the mild asthma had a slower clearance in the exposures to all three concentrations (100, 300 and $1000 \mu\text{g}/\text{m}^3$) of sulfuric acid than in the control exposure without sulfuric acid, but only for the highest concentration was clearance significantly slower. The group with the severe asthma showed no effect on clearance after exposure to sulfuric acid particles. Spektor et al (19) also exposed a group of healthy subjects to $100 \mu\text{g}/\text{m}^3$ of sulfuric acid particles, once for 1 hour and a second time for 2 hours. Clearance was studied using $5.2 \mu\text{m}$ particles. Clearance was reduced in both sulfuric acid exposures, but more markedly after the 2-hour than after the 1-hour exposure.

Effects on the mucociliary clearance of larger particles containing sulfuric acid have also been studied. Laube et al (20) exposed healthy subjects during 1 hour (rest and physical exercise) to an acid or saline fog concentration of $500 \text{ mg}/\text{m}^3$. The acid fog contained sulfuric acid and had a pH of 2 and a mass median diameter of $10.3 \mu\text{m}$. The saline fog had a mass median aerodynamic diameter of $10.9 \mu\text{m}$. Mucociliary clearance was studied using $3.4 \mu\text{m}$ of a radiolabeled test aerosol. Clearance was significantly increased after the acid fog exposure when compared with that after the saline fog exposure. Ventilatory function and bronchial reactivity were also studied, but they were unaffected by both fogs.

Effects on bronchoalveolar lavage

Frampton et al (21) exposed healthy subjects to a $1000 \mu\text{g}/\text{m}^3$ concentration of sulfuric acid or sodium chloride (mass median aerodynamic diameter $0.9 \mu\text{m}$) and studied bronchoalveolar lavage, which was made 18 hours later. The volunteers performed intermittent physical exercise during the 2-hour exposure period. There were no significant changes between the two exposures in the distribution of alveolar macrophages, lymphocytes, mononuclear leukocytes, mast cells, or the total number of cells obtained by lavage.

Diesel and other vehicle exhaust

Rudell et al (22) exposed healthy nonsmokers to clean air and filtered and unfiltered diesel exhaust. The exposure time was 60 minutes with alternated 10-minute periods of rest and light exercise. The number of particles was $2.6 \times 10^6/\text{cm}^3$ (estimated to correspond with about $300 \mu\text{g}/\text{m}^3$) in the unfiltered diesel exhaust and

$1.4 \times 10^6/\text{cm}^3$ in the filtered exhaust. The concentrations of nitrogen oxide, nitrogen dioxide (NO_2), carbon monoxide (CO), total hydrocarbons, and formaldehyde were highly similar in the two diesel exhaust exposures. The NO_2 concentration was, for example, 1.9 ppm in the unfiltered exhaust and 1.7 ppm in the filtered exhaust. Both diesel exhausts caused similar and significant increases in R_{aw} and SR_{aw} (around 15%). In a later study with 10 healthy never smokers, the same group used the same exposure design with filtered and unfiltered diesel exhaust and studied the effects on the lung lavage fluid (23). In this study, the concentration of particles was 2.6×10^6 particles/ cm^3 for the unfiltered exhaust and 1.3×10^6 particles/ cm^3 for the filtered exhaust. The same gases were measured as in the former study, and also in this study the concentrations were similar in both exhausts, for example, the concentration of NO_2 was 1.3 ppm in the unfiltered exhaust and 1.2 ppm in the filtered exhaust. In the lavage investigation, the first recovered 20 ml of the first instilled 60 ml was analyzed separately and defined as the bronchial portion. The remaining recovered fluid of the totally instilled 4×60 ml was defined as the bronchoalveolar portion. The number geometric mean was $0.041 \mu\text{m}$ for the unfiltered exhaust and $0.044 \mu\text{m}$ for the filtered exhaust, and the volume mean diameters were 0.11 and $0.13 \mu\text{m}$, respectively. In the bronchial portion of the lavage fluid, the total number of cells and the number of macrophages were significantly increased only after the exposure to the unfiltered diesel exhaust, whereas neutrophils increased by a factor of 3–4 after exposure to both filtered and unfiltered exhaust. In the bronchoalveolar portion, which should mainly reflect the alveolar region, there were only significant effects on the numbers of lymphocyte subsets. The percentage of CD3+ lymphocytes was increased to about the same extent after filtered and unfiltered exhaust exposure. Phagocytic activity of alveolar macrophages was studied *in vitro* after diesel exposure and was found to be significantly reduced after both types of diesel exposures.

The same group also studied acute inflammatory responses in the airways and peripheral blood after unfiltered diesel exposure (24). Fifteen healthy nonsmokers were exposed for 1 hour to air or diesel exhaust on two occasions. The particle concentration was $300 \mu\text{g}/\text{m}^3$ (4.3×10^6 particles/ cm^3), and the concentration was 1.6 ppm for NO_2 , 4.5 ppm for nitrogen oxide, 7.5 ppm for CO, 4.3 ppm for total hydrocarbon, and $0.26 \text{ mg}/\text{m}^3$ for formaldehyde. Standard lung function parameters, such as peak expiratory flow rate (PEFR), FVC, $\text{FEV}_{1.0}$ and forced expiratory volume at 0.25–0.75 seconds ($\text{FEF}_{25-75}\%$), were measured, and no significant changes were seen immediately after the exposure. Six hours after the exposure, there was a threefold increase in the number of neutrophils but no significant change in the

number of macrophages in the bronchial portion of the lavage. In the bronchoalveolar lavage, there was an increase in B lymphocytes. Bronchial biopsies were taken after the diesel exhaust exposure, and immunostaining for inflammatory cells was performed. There was a substantial increase in the number of neutrophils in the epithelium and submucosa. Mast cells were significantly increased in the submucosa and also lymphocytes with differentiation clusters (CD) of specific surface molecules (CD3+, CD4+ and CD8+ cells) were increased. There was also an increased expression of endothelial and leucocyte adhesion molecules, for example, of intercellular adhesion molecule-1 (ICAM-1), in the bronchial tissue after the exposure to diesel exhaust. Six hours after the diesel exhaust exposure, there was a significant increase in neutrophils and platelets in the peripheral blood and a significant reduction in lymphocytes with human leucocytes antigen related to the D-region (HLA-DR +).

The group also studied the level of antioxidants after the diesel exhaust inhalation (25). These levels were studied in the bronchial portion of the lavage, the bronchoalveolar lavage, and the nasal lavage. There was a marked increase in the concentration of ascorbic acid in the nasal lavage after 60 minutes of exposure to the diesel exhaust, but no effects on antioxidants in the bronchial or bronchoalveolar lavage.

Svartengren et al (26) have studied the effects of 30 minutes of exposure to the atmosphere in a road tunnel in Stockholm on 20 volunteers. The volunteers had mild asthma (allergic to pollen) and were inside a car during the exposure. As a control, 30-minute exposure to fairly low levels of air pollutants in a hotel was studied. Both exposures took place during the winter and in random order. Inside the car in the tunnel, the median concentration of NO_2 was $313 \mu\text{g}/\text{m}^3$ and the PM_{10} and $\text{PM}_{2.5}$ (particulate matter with an aerodynamic diameter of $10 \mu\text{m}$ and $2.5 \mu\text{m}$, respectively) were $170 \mu\text{g}/\text{m}^3$ and $95 \mu\text{g}/\text{m}^3$, respectively. The median concentration of the hotel air during rush hour was $14 \mu\text{g}/\text{m}^3$ for NO_2 , $7 \mu\text{g}/\text{m}^3$ for PM_{10} and $5 \mu\text{g}/\text{m}^3$ for $\text{PM}_{2.5}$. The symptoms during the exposures were studied using a questionnaire. Symptoms such as cough, irritation, chest tightness, and breathing discomfort were significantly higher in the tunnel than in the control exposure, although the magnitude of these symptoms was rather small. There was no clear effect on lung function (eg, the $\text{FEV}_{1.0}$ or the SR_{aw} of the subjects exposed in the tunnel). Four hours after the end of the tunnel and control exposures, the volunteers inhaled pollen allergens. After the tunnel exposure, the SR_{aw} increased from 5.0 to $7.2 \text{ cm water} \times \text{l}^{-1} \times \text{s}^{-1}$ and the thoracic gas volume (TGV) increased from 3.5 to 3.7 l. After the control exposure, the SR_{aw} increased from 5.1 to $6.7 \text{ cm water} \times \text{l}^{-1} \times \text{s}^{-1}$, and the TGV decreased from 3.4 to 3.2 l. The increases in

SR_{aw} and TGV were significantly larger after the tunnel exposure than after the control exposure. In the evening, the volunteers had more asthma symptoms after the tunnel exposure than after the control exposure. The asthma symptoms in the evening, night, and morning after the allergen inhalation correlated both with the NO_2 exposure and the $PM_{2.5}$ exposure. The relationship between the asthmatic symptoms and the NO_2 concentration seemed to be clearer than the relationship between the asthmatic symptoms and the particle concentration.

Number or mass as a dose measure

It is clear that aerosol particles that have the same chemical composition with a different size distribution can give different toxic effects due to different deposition in the respiratory tract. Another and more difficult question to answer is whether or not the effects on a certain region in the respiratory tract are dependent on the size of particles deposited in this region, that is, if the effect is dependent on the number, the surface area, or the mass of the particles or a combination of these parameters. For the answers to these questions, both data on effects and dose in a certain region of the respiratory tract are needed.

Anderson et al (27) exposed healthy subjects to two aerosols of methacholine with mass median aerodynamic diameters of 3 and 7 μm . The concentrations of the two aerosols were chosen for each subject so that they induced a $FEV_{1.0}$ decrease of 20%, and they also induced the same increase in R_{aw} . The dose to the tracheobronchial region (ie, the region responsible for changes in the measured R_{aw}) was calculated from data from human experimental studies with well-defined test particles. Although the increase in R_{aw} was the same for the two aerosols, the calculated dose (mass) to the tracheobronchial tract was three to four times higher for the aerosol with the larger particles than for that with the smaller particles. It can therefore be concluded that, for cholinergic aerosols, a certain dose (mass) to the tracheobronchial tract apparently gives a markedly greater effect if the mass is spread over many small particles than over a few larger ones. This result may be relevant also for at least some ambient air particles, as Utell et al (28) found a significant relationship between the effect of a cholinergic aerosol and sulfuric acid aerosol on airway conductance in asthmatics.

Summary and concluding remarks

Most experimental studies have dealt with sulfuric acid aerosols and asthmatic persons who are more sensitive to these particles with respect to lung function than

healthy subjects are. The studies on ventilatory function, design, and methods for lung function measurements have been similar. Still, the results have differed remarkably. Significant changes in young asthmatics have, for example, been found already at 70 $\mu g/m^3$, whereas concentrations of 1000 $\mu g/m^3$ or higher have been necessary to induce significant changes in asthmatics in other studies. An explanation for the different results may be that the groups of asthmatics differed in bronchial reactivity. In combined exposures of sulfuric acid aerosol and O_3 , there was no indication of any effect larger than an additive one. Short-time exposure of healthy subjects and asthmatics to carbon black particles (0.5 μm , 200 $\mu g/m^3$) together with sulfuric acid particles (6.5 μm , 100 $\mu g/m^3$) gave no effect on lung function, nor did the carbon black or the sulfuric acid particles alone.

Despite the fact that the methods for studying bronchial clearance are more complicated and less standardized than those for lung function tests, the results of the clearance studies seem more consistent. Apparently, there is an effect of sulfuric acid particles on mucociliary clearance at least down to 100 $\mu g/m^3$ in short-term exposures. The effect seems to increase with increasing exposure time. In contrast to the results of the studies on ventilatory function, asthmatics do not seem more sensitive to exposure to sulfuric acid particles than healthy subjects are.

Healthy volunteers exposed to both filtered and unfiltered diesel exhaust showed only small differences in effects. The filtered exhaust had about half the number of particles as the unfiltered one (1.4×10^6 and 2.6×10^6 particles/cm³), but the NO_2 concentration was similar in the two exposures (1.7 and 1.9 ppm). In a later study 4.3×10^6 particles/cm³ was reported to correspond to 300 $\mu g/m^3$. There was an increase in R_{aw} (SR_{aw} and R_{aw}) (around 15%) for both exposures. In the bronchial proportion of the lavage fluid, the number of macrophages was significantly increased only after the exposure to the unfiltered diesel exhaust, whereas the neutrophils increased by a factor of 3–4 after both exposures. The phagocytic activity of alveolar macrophages was significantly reduced after both exposures. In these studies, it was difficult to evaluate whether the effects were caused by particles or by gases, for example, NO_2 , or a combination of particles and gases, because only half the number of particles was removed by the filter.

In another study with realistic but complex exposures, volunteers with mild asthma were exposed to the atmosphere in a road tunnel. Compared with subjects exposed in rather clean ambient air, they showed more symptoms, such as coughing, irritation, and chest tightness, but no clear effect on lung function. However, when the volunteers inhaled pollen antigens 4 hours after the end of the exposures, the SR_{aw} and TGV increased significantly more after the tunnel exposure than

after the control exposure, and later in the evening more asthma symptoms were noted after the tunnel exposure. The asthma symptoms correlated with both the NO₂ and PM_{2.5} levels, but the relationship seemed to be stronger for NO₂. The late-phase reaction tended to be higher for the group with PM_{2.5} exposure above 100 µg/m³ than for the control exposure.

There are very limited human data that can offer any answers on whether the number, the surface area, or the mass of the particles is the most appropriate for measuring dose. Healthy subjects who inhaled cholinergic aerosols with a mass median diameter of 3 or 7 µm required a three to four times higher mass of the large particles than of the small particles to induce the same effect on R_{aw} and FEV_{1.0} in the tracheobronchial tract. This result may be relevant also for at least some particles in ambient air, as another study has shown a strong correlation between the effects of cholinergic aerosols and the effects of sulfuric acid aerosols on asthmatic subjects.

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Epidemiologic studies on the health effects of ambient particulate air pollution

by Fredrik Nyberg & Göran Pershagen

This review primarily considers studies published until 31 December 1997; it also focuses on studies of the last decade which have tended to investigate lower air pollution levels and use more developed methods. Mainly studies with actual measurements of particles that are subsequently used in the analyses are reviewed. We also consider a few important later publications (eg, updated reports from previously published large multicenter studies). In some cases, studies using similar methodology have already been analyzed together. In the case of such meta-analyses, we have focused on the pooled results and have discussed the results of the individual studies only when they provide contrasts of particular interest. To facilitate an overview of the abundant evidence, all relevant references with original data are included in an appropriate table. Occasional reference is made to recent comprehensive reviews [such as the 1996 report from the United States (US) Environmental Protection Agency (EPA) (1)], to which the reader can turn for more-detailed descriptions of individual studies. For older studies, previous EPA reports provide extensive reviews (2–5).

A problem in common with all epidemiologic studies on the health effects of ambient air pollution is that particles are only one component in a complex mixture of potentially noxious substances with which they may correlate. In addition, particulate air pollution is an extremely heterogeneous entity, composed of particles of various sizes and origins, which can vary in chemical composition and acidity. Particulate air pollution can also correlate with meteorological variables such as temperature or air humidity. It is thus difficult to elucidate etiologic relationships. Mainly studies that have made adequate attempts to control for other variables are reviewed, and they form the basis for the risk assessment.

Epidemiologic studies of the acute health effects of particulates fall into several different categories. Time-series analyses evaluate health effects of time-varying exposures. Individual-level time-series studies ("panel studies") use repeated measurements on the same person over a period of time, in effect using the person as his or her own control, to examine short-term effects. The outcomes evaluated are generally either continuous data (eg, lung function), or binary data (eg, presence or absence of symptoms, especially respiratory symptoms) (6). Binary outcomes are however sometimes aggregated for analysis into grouped daily prevalence or incidence data (7). Primarily aggregate-level time-series studies evaluate exposure and short-term temporal var-

iations in outcomes such as mortality, hospital admissions, or outpatient visits in a population as a whole, and the effect measure is generally the number of outcomes in the population in successive time periods (ie, count data). In any time-series study, different averaging times and lag times may be used for the exposure variable, and an attempt can even be made to evaluate the lag structure within a study (6). Most commonly, however, daily average particulate levels on the same day, or with 1 or possibly 2 days of lag time, have been correlated with the daily health effects under study. For some study purposes, more simple analytical methods are used (eg, comparing the proportion of persons with symptoms on days with high particle concentrations versus low concentrations). Chronic effects are best elucidated in longitudinal studies (ie, with a cohort design using survival-type data). Incident case-referent studies can also be used, but they have been less common in the epidemiology of particulate air pollution. Cross-sectional (prevalence) studies are also used to evaluate chronic effects, but it is difficult to separate clearly the effects of short- and long-term exposure in this type of study. In all of these study designs, other risk factors for the outcome under study which correlate with the studied exposure can potentially confound the exposure-outcome relationship and may need to be addressed in the analysis (8). In time-series studies of short-term effects, many traditional confounders are less problematic. Instead, potential confounding by factors which covary with air pollution on a daily basis (eg, temperature, infectious epidemics) has to be controlled in the analysis (9).

In epidemiologic research, the relative risk (RR) (ie, the ratio of disease or symptom incidence among the exposed to that among the unexposed) is often the effect parameter of fundamental interest, although it may also be the variation in other effect measures such as symptom severity or lung function due to exposure. Multiple regression techniques are commonly used to estimate the effect and simultaneously control for other exposure factors of relevance. In time-series studies, different types of regression models are used depending on the type of data collected. For continuous time-series data, models based on linear (Gaussian) regression are commonly used; for binary data logistic regression models are generally appropriate (6). Special techniques must be used to handle autocorrelation in the data due to the fact that successive observations on the same person over time are not independent of each other (6, 7). Interindividual heterogeneity in the response usually also needs to be

addressed by various modeling techniques, although it is sometimes ignored, for example, when binary outcomes are analyzed (eg, by logistic regression) with the use of aggregated daily prevalence or incidence data (7). For time-series count data, linear (Gaussian) regression is sometimes used, in particular in earlier studies. However, small counts such as daily deaths in a limited area may not be normally distributed, but tend to follow a Poisson distribution, and therefore log-linear Poisson regression is commonly used (6, 8, 9). From cohort data ("survival" data), the RR can be directly estimated using, for example, Cox proportional hazards regression. The term odds ratio (OR) is often used to denote the estimates obtained from logistic regression analyses, which are used for various types of binary or binomial data. It may be equivalent to the RR in studies of case-referent type, given that referents are adequately sampled. However, in other case-referent designs, in time-series analyses of binary data, and in cross-sectional studies of point prevalence, the OR should in fact be interpreted as the ratio of the odds of a positive outcome among the exposed as compared with the outcome of the unexposed, and it is similar to the RR or prevalence ratio only if the outcome is rare (8).

In epidemiologic studies, confidence intervals (CI) rather than P-values are usually computed for point estimates. In the text and tables, 95% CI values are used throughout. A P-value of <0.05 (2-sided test) thus corresponds to a 95% CI that does not include the null value (usually 0 for change in a continuous outcome, or 1.0 for an OR or RR). This review has not placed particular emphasis on P-values or tests of statistical significance, which are highly dependent on the size of the data set considered (10). With large enough numbers, almost any deviation from the null becomes statistically significant, and vice versa. Of public health importance and of concern here, however, is not the statistical significance per se but the magnitude of a possible effect as it is estimated in individual studies and pooling efforts, evaluated in relation to the total body of research. It is also generally more important to consider design and systematic errors carefully than it is to consider random variation in the evaluation of study results. For example, statistically significant but small deviations from the null may be wholly explained by bias, such as confounding or systematic measurement error.

In this review, a common effect measure relating to particulate matter <10 µm in diameter (PM₁₀) has been calculated where possible. One necessary assumption for such calculations is for a conversion factor to PM₁₀ from other particulate measures. Obviously, such fac-

tors are not constant, and therefore the original particle measure has also been given in the tables of this report. For example, a recent European study found ratios of daily average PM₁₀ to black smoke (BS) ranging from 0.67 to 3.67 and slopes from the univariate regression from 0.52 to 2.49 (11). For more exact comparisons (ie, formal meta-analyses) other conversion factors might be preferable, chosen individually for each study, but for simplicity we have used the following previously suggested conversion factors: PM₁₀ ≈ PM₁₅ ≈ BS ≈ SO₄ × 4 ≈ PM_{2.5}/0.60 ≈ CoH (in units of 10³ linear feet, used in most studies) × 55^a ≈ TSP × 0.55 (12, 13) and PM₁₀ ≈ light scattering (measured by nephelometry, in units of 10⁻⁵/m) × 10 (14, 15), with the remaining particle measures in micrograms per cubic meter. Even when the same measure has been used, one should be aware that there may be substantial variation between samplers and laboratories (17), and therefore any between-study comparison would be approximate. Knowing the conversion factors used, the interested reader can easily recalculate to another conversion factor. For more details on the calculation of the summary measure from various types of regression estimates, see the appendix.

Another implicit assumption is that estimates for different lag times of the exposure variable used in different studies can be combined. Most commonly, daily averages with lag times of 0 (same day) and 1 (previous day) have been related to the health effect, but lag times of 2, 3, 4, and rarely others have also been used. In other studies, averages over several days have been used (eg, lag time of 0–2 (3-day average) or 0–4 (5-day average)). Although multiday averages generally have a smaller range, there appears to be no consistent relation between the lag time or averaging time and effect estimates of per 10 µg/m³ PM₁₀ for the various health effects. It is also impossible to recalculate to a common lag time based on published data. Therefore, the effect estimates are taken as presented in the original studies and mostly the lag time is not explicitly stated in our text, although lag times are discussed in some places. As most studies use daily average particulate levels, the reader is thus advised to think generally of the particulate exposure in terms of 24-hour averages. In most cases the lag time for a particular study can be found in the corresponding table; otherwise the reader must turn to the original publication.

Time-series studies of variations in mortality

The studies on daily mortality and particulate air pollution are presented in table 1 (14, 16, 18–80).

^a PM₁₀ ≈ CoH/0.55 in reference 13 appears to be a printing error. In this equation, the CoH values referred to are 10 × CoH units, as given by Fairley (16), which apparently correspond to units of 10¹ linear feet, and in these units, CoH ≈ TSP rather than < PM₁₀ [ie, PM₁₀ ≈ CoH × 0.55 (12, 16)].

Table 1. Time series studies of daily mortality and particulate air pollution. (For any abbreviation not found in the footnotes, see page 4.)

Study	Measurement data (particle measure, lag time and levels) ^a	Measured or calculated PM ₁₀ ^{b,c} (µg/m ³)	Increase in mortality per 10 µg/m ³ PM ₁₀ ^b or a short summary of the results			Comments ^d
			Cause	%	95% CI	
Schimmel & Murawski, 1976 (18); Schimmel, 1978 (19) - New York City 1963–1976	CoH, LT 0 days, M 1.96	M 108	All RD+CVD+ cancer	0.1 0.2	0.0–0.3 0.1–0.4	0.2 (95% CI 0.0–0.3) and 0.2 (95% CI 0.1–0.4) with SO ₂ in model. Stronger with LT 0–1 days: 0.3 (95% CI 0.1–0.5) and 0.4 (95% CI 0.2–0.6) with SO ₂ in model. No positive effect of SO ₂ .
Mazumdar & Sussman, 1983 (20) - Hazelwood/Bellevue/Logans Ferry, Pittsburgh (PA) 1972–1977	CoH, LT 0 days (?), M(R ₁) 1.0 (0–3.5)	M 54	All HD	0.1 0.3	-0.1–0.3 0.0–0.5	Very similar with SO ₂ in model. Estimates are here pooled over all 3 locations. Some inconsistency, however, with a clear effect seen mainly in Hazelwood.
Fairley, 1990 (16) - Santa Clara (CA) 1980–1982, 1984–1986 winters	CoH, LT 0 days, M 0.67	M 37	All All, ≥70years RD CVD	0.8 0.8 3.2 0.8	0.3–1.3 0.1–1.4 1.4–5.0 0.1–1.5	Linear regressions. With Poisson regression 0.7 (95% CI 0.3–1.1) for total mortality.
Schwartz, 1991 (21) - Detroit (MI) 1973–1982	TSP, LT 1 day, M(R ₂) 87 (46–137)	M 48	All	1.0	0.5–1.5	0.9 (95% CI 0.4–1.5) with SO ₂ in model. O ₃ in model did not alter estimates.
Schwartz & Dockery, 1992 (22) - Steubenville (OH) 1974–1984	TSP, LT 1 day, M(R ₃) 111 (36–209)	M 61	All	0.7	0.4–1.0	0.5 (95% CI 0.1–1.0) with SO ₂ in model.
Moolgavkar & Luebeck, 1995 (85) - Steubenville (OH) 1974–1984	TSP, LT 1 day, M(R ₃) 113 (38–212)	M 62	All	0.6	0.1–1.0	0.5 (95% CI 0.0–1.0) with SO ₂ in model.
Schwartz & Dockery, 1992 (23) - Philadelphia (PA) 1973–1980	TSP, LT 0–1 days, M(R ₂) 77 (37–132)	M 42	All All, >65 years COPD Pneumonia CVD	1.2 1.7 3.3 1.9 1.7	0.7–1.7 1.1–1.3 0.1–6.6 -0.6–4.4 1.0–2.4	0.9 (95% CI 0.3–1.6) with SO ₂ in model.
Moolgavkar et al, 1995 (24) - Philadelphia (PA) 1973–1988	TSP, LT 1 day, M(R ₁) 68 (14–338)	M 37	All, spring All, summer All, autumn All, winter	0.2 1.2 0.2 -0.2	-0.6–1.0 0.4–2.0 -0.6–1.0 -1.1–0.6	With SO ₂ in model. Analyses by season only. Slightly lower estimates with O ₃ also in model.
Li & Roth, 1995 (25) - Philadelphia (PA) 1973–1990	TSP, various LT, M(R ₂) 69 (32–120)	M 38	Results: estimates not available; most TSP results not significant			Article presents only t-values for various subgroup analyses, various models, etc.
Moolgavkar & Luebeck, 1996 (26) - Philadelphia (PA) 1973–1988	TSP, LT 1 day, M(R ₁) 68 (14–338)	M 37	All, summer All, winter	0.7 -0.2	-0.1–1.5 -1.0–0.6	With SO ₂ , O ₃ , and NO ₂ in model. Analyses by season only (data from figure).
Samet et al, 1997 (27); Kelsall et al, 1997 (28) - Philadelphia (PA) 1974–1988	TSP, LT 0–1 days, M(R ₁) 67 (14–222)	M 37	All All, 65–74 years All, ≥75 years RD ≥75 years CVD ≥75years	0.6 0.4 1.1 2.3 1.0	0.0–1.1 -0.4–1.2 0.4–1.8 -0.4–5.2 0.0–1.9	With SO ₂ , NO ₂ , O ₃ and lagged CO in model. As comparison – for total mortality: 0.6 (95% CI 0.2–1.0) with TSP singly in model and 0.4 (95% CI -0.1–0.9) for TSP with only SO ₂ added.
Pope et al, 1992 (29) - Utah County (UT) 1985–1989	PM ₁₀ , LT 0–4 days, M(R ₁) 47 (1–365)	M 47	All RD CVD	1.5 3.7 1.8	0.9–2.1 0.7–6.7 0.4–3.3	Very low levels of SO ₂ and low NO ₂ levels. Particles highest in winter
Pope & Kalkstein, 1996 (30) - Utah County (UT) 1985–1989	PM ₁₀ , LT 0–4 days, M(R ₁) 47 (1–365)	M 47	All RD CVD	1.3 3.1 1.9	0.4–2.2 0.4–5.9 0.6–3.2	With nonparametric smoothing and synoptic weather modeling. Results not sensitive to exact model specification.
Lyon et al, 1995 (31) - Utah County (UT) 1985–1992	PM ₁₀ , LT 0–4 days, M ~44	M ~44	All	1.2	0.4–2.0	For ≥50 versus <50 µg/m ³ : All + 4% (95% CI -2–+10) RD + 3% (95% CI -4–+25) CVD +13% (95% CI +4–+24)
Dockery et al, 1992 (32) - St Louis (MO) 1985–1986	PM ₁₀ , LT 1 day, M(R ₁) 28 (1–97)	M 28	All	1.5	0.1–2.9	For both locations, little change when SO ₂ was added to model. PM _{2.5} , SO ₄ and H ⁺ were not superior to PM ₁₀ as predictors.
- Kingston/Harriman (TN) 1985–1986	PM ₁₀ , LT 1 day, M(R ₁) 30 (4–67)	M 30	All	1.6	-1.3–4.6	
Schwartz, 1991 (33) - Minneapolis-St Paul (MN) 1973–1982	TSP, LT 0 days (?), M 78	M 43	All	1.0	0.4–1.5	.

(continued)

Table 1. Continued.

Study	Measurement data (particle measure, lag time and levels) ^a	Measured or calculated PM ₁₀ ^{b,c} (µg/m ³)	Increase in mortality per 10 µg/m ³ PM ₁₀ ^b or a short summary of the results			Comments ^d
			Cause	%	95% CI	
Schwartz, 1993 (34) - Birmingham (AL) 1985–1988	PM ₁₀ , LT 0–2 days, M(R ₃) 48 (21–80)	M 48	All RD HD	1.0 1.5 1.6	0.2–1.9 -2.6–5.7 0.4–2.8	.
Samet et al, 1995 (35) (extensive reanalysis of the following) - Philadelphia (PA) 1973–1980 & 1973–1988 - St Louis (MO) 1985–1986 - Kingston/Harriman (TN) 1985–1986 - Utah County (Provo) (UT) 1985–1989 - Birmingham (AL) 1985–1988 - Santa Clara (CA) 1980–1982, 1984–1986 winters	See the respective original study		All Pneumonia CVD All All All All	1.5 3.7 1.9 1.5 1.6 1.6 1.0 0.8	1.1–2.0 1.1–6.3 1.2–2.5 0.1–2.9 -1.1–4.4 0.6–2.6 0.2–1.8 0.3–1.4	Results similar to those of the original analyses. All estimates are with no other co-pollutants in the model (not available in most cases). Philadelphia estimates for all causes and CVD but not pneumonia were somewhat attenuated by including SO ₂ in the model. [For multipollutant models in the Philadelphia dataset, see Kelsall et al, 1997 (28).]
Schwartz, 1994 (36) - Cincinnati (OH) 1977–1982	TSP, LT 0 days, M(R ₁) 76 (~15–155)	M 42	All All, ≥65 years Pneumonia CVD	1.1 1.6 2.7 1.4	0.5–1.7 1.2–2.0 -1.0–6.6 0.5–2.3	.
Schwartz et al, 1996 (37) - Six US cities, 1979–1988	PM ₁₀ , LT 0–1 days, Md (R ₂) 25 (8–68); PM _{2.5} , LT 0–1 days, Md(R ₂) 15 (4–43)	Md 25	All All, ≥65 years COPD Pneumonia IHD	0.8 1.0 2.0 2.4 1.3	0.5–1.1 0.7–1.3 0.6–3.4 1.1–3.7 0.8–1.7	Also associations with TSP, PM _{2.5} , H ⁺ , slightly stronger with PM _{2.5} . Tabulated estimate for total mortality is from PM ₁₀ model and estimates for ≥65 years and cause-specific mortality calculated from PM _{2.5} models.
Kinney & Özkaynak, 1991 (38); Shumway et al, 1988 (39) - Los Angeles County, Los Angeles (CA) 1970–1979	KM, LT 0 days, 25 units	.	Results: mortality associated with motor-vehicle pollutants (CO or KM or NO ₂)			Mortality also associated with temperature, and O ₃ . [In reference 39, weekly mortality counts were used.]
Kinney et al, 1995 (40) - Los Angeles County, Los Angeles (CA) 1985–1990	PM ₁₀ , LT 0 days, M(R ₁) 58 (15–177)	M 58	All	0.5	0.0–1.0	Changes little when O ₃ or CO included in model.
Ostro, 1995 (41) - San Bernardino + Riverside, Los Angeles (CA) 1980–1986	PM _{2.5} , LT 0 days, M(R ₁) 32.5 (9–190)	M 54	All All, ≥65 years All, summer RD	0.1 0.2 0.4 0.5	-0.1–0.3 -0.1–0.4 0.0–0.9 -0.1–1.1	Stronger effect during summer months (due mainly to RD). PM _{2.5} estimated based on visibility.
Styer et al, 1995 (42) - Cook County, Chicago (IL) 1985–1990 - Salt Lake County (UT) 1985–1990	PM ₁₀ , LT 0–2 days, Md(R ₁) 38 (3–365) PM ₁₀ , LT 0–2 days, Md(R ₁) 48 (9–194)	Md 38 Md 48	All, ≥65 years All, autumn RD, autumn All, ≥65 years	0.5 0.8 2.2 -0.2	0.1–0.9 0.0–1.6 -0.2–4.8 -1.1–0.6	In Cook County mostly spring and autumn effect, and effect particularly for RD. In Salt Lake County no effect of PM ₁₀ seen.
Ito et al, 1995 (43); Ito et al, 1996 (44) - Cook County, Chicago (IL) 1985–1990	PM ₁₀ , LT 0 days, M(R ₂) 41 (20–65)	M 41	All RD CVD	0.5 1.3 0.3	0.3–0.7 0.4–2.3 -0.1–0.7	0.4 (95% CI 0.1–0.7) with O ₃ in model. Higher for women than for men.
Mazumdar et al, 1982 (45) - London (United Kingdom) 1958–1972 winters	BS, LT 0 days (?), M 174	M 174	All	0.3	0.3–0.3	0.3 (95% CI 0.2–0.3) with SO ₂ in model. No association with SO ₂ . Possible synergism between BS and SO ₂ at high levels.
Ostro, 1984 (46) - London (United Kingdom) 1958–1972 winters	BS, LT 0 days (?), M(R ₁) 174 (11–1971)	M 174	Results: stronger effect on mortality below 150 µg/m ³ than above			Threshold search. No threshold could be found.
Schwartz & Marcus, 1990 (47) - London (United Kingdom) 1958–1972 winters	BS, LT 0 days, M 174	M 174	All	0.3	0.3–0.4	.
Ito et al, 1993 (48) - London (United Kingdom) 1965–1972 winters	BS, LT 0 days, M ~80	M ~80	All	0.4	0.2–0.5	BS, SO ₂ or acidity all with effect in separate models.

(continued)

Table 1. Continued.

Study	Measurement data (particle measure, lag time and levels) ^a	Measured or calculated PM ₁₀ ^{b,c} (µg/m ³)	Increase in mortality per 10 µg/m ³ PM ₁₀ ^b or a short summary of the results			Comments ^d
			Cause	%	95% CI	
Derriennic et al, 1989 (49) - Lyon (France) 1974–1976 - Marseilles (France) 1974–1976	SP, LT varied, M 87 SP, LT varied, M 126	M 48 M 70	Results: SP not significant (various lag times). SO ₂ significant for different mortality at ages ≥65 years for RD in Lyon and Marseilles and for CVD in Marseilles.			SO ₂ and SP correlated 0.27–0.60 in subareas.
Hatzakis et al, 1986 (50); Katsouyanni et al, 1990 (51) - Athens (Greece) 1975–1982	Smoke, GM 57	GM 57	Results: smoke not significant for mortality but SO ₂ was significant for mortality.			Effect contributed mainly by RD. SO ₂ and smoke highly correlated (r=0.73).
Katsouyanni et al, 1993 (52) - Athens (Greece), July 1987 compared with July 1981–1986	Smoke, M(R ₁) ?? (50–250)	.	Results: Interaction between temperature and air pollution significant for SO ₂ but not for smoke.			Analysis of pollution effects during a heat-wave episode.
Touloumi et al, 1994 (53) - Athens (Greece) 1984–1988	Smoke, M(R ₂) 83 (~35–175)	M 83	All	0.9	0.6–1.1	0.5 (95% CI 0.1–0.8) for smoke with SO ₂ in model. Similar effect for SO ₂ .
Spix et al, 1993 (54) - Erfurt (Germany) 1980–1989	SP, LT 0 days, Md(R ₁) 106 (10–650)	Md 58	All	1.1	0.1–2.1	0.9 (95% CI -0.4–2.3) with SO ₂ in model. Weaker effect for SO ₂ .
Rahlenbeck & Kahl, 1996 (55) - East Berlin (Germany) 1981–1989	SP, LT 2 days, M(R ₁) 66 (10–150) (truncated at 150) ^e	M 36	All	1.1	0.3–1.9	0.8 (95% CI -0.1–1.7) with SO ₂ in model. Slightly weaker effect for SO ₂ . Weaker effect when SP values >150 µg/m ³ were also included in model. ^e
Verhoeff et al, 1996 (56) - Amsterdam (The Netherlands) 1986–1992	PM ₁₀ , LT 0 days, M(R ₃) 38 (17–67)	M 38	All	0.6	-0.1–1.4	Somewhat attenuated with SO ₂ and O ₃ but not CO in model. BS had stronger effect than PM ₁₀ . Both were partly based on predicted values, PM ₁₀ more so.
Wietlisbach et al, 1996 (57) - Zurich (Switzerland) 1984–1989	TSP, LT 0–2 days, M(R ₁) 46 (?–182)	M 25	All All, ≥65 years RD CVD	0.7 1.0 2.5 0.5	0.0–1.4 0.2–1.8 0.8–4.3 -0.5–1.6	Mortality was similarly associated with TSP, NO ₂ , and SO ₂ . For SO ₂ , the effect was highly nonlinear with declining marginal effects at higher SO ₂ levels.
- Basle (Switzerland) 1984–1989	TSP, LT 0–2 days, M(R ₁) 45 (?–216)	M 25	All All, ≥65 years RD CVD	2.6 2.5 1.8 3.1	1.6–3.6 1.4–3.6 -0.3–3.9 1.6–4.7	
Wordley et al, 1997 (58) - Birmingham (United Kingdom) 1992–1994	PM ₁₀ , LT 1 day, M(R ₁) 26 (3–131)	M 26	All RD COPD IHD	1.1 1.8 4.8 1.7	0.1–2.1 -1.3–4.9 0.5–9.2 0.1–3.2	NO ₂ , SO ₂ or O ₃ in model did not change results appreciably. No clear effect for pneumonia deaths.
Ballester et al, 1996 (59) - Valencia (Spain) 1991–1993	BS, LT 3,0,1,4 days, M(R ₁) 68 (5–226)	M 68	All All, >70 years RD CVD	0.9 0.8 -0.7 1.2	0.3–1.5 0.1–1.6 -2.5–1.0 0.3–2.2	
Hoek et al, 1997 (60) - Rotterdam (Holland) 1983–1991	TSP, LT 1 day, Md(R ₂) 42 (21–112)	Md 23	All	1.0	0.2–1.8	0.8 with CO, SO ₂ or O ₃ + Fe in model. O ₃ was also consistently associated with mortality.
APHEA project - Katsouyanni et al, 1997 (61) - Katsouyanni et al, 1997 (62) (some center results & meta-analysis) - Zmirou et al, 1998 (63) (cause-specific mortality meta-analysis) - Anderson et al, 1996 (64) - London (United Kingdom), 1987–1991–1992 - Dab et al, 1996 (65) - Paris (France) 1987–1992	PM ₁₀ range over centers based on BS (8 cities)	Md 13–73, 90%ile 23–247	All, west & east All, west All, east RD, west RD, east CVD, west CVD, east	0.3 0.6 0.1 0.8 -0.4 0.4 0.0	0.2–0.3 0.4–0.7 0.0–0.2 0.3–1.3 -1.4–0.6 0.1–0.7 -0.3–0.3	Stronger effect in summer. No evidence of interaction between particulate measures and SO ₂ in interaction analyses, except for CVD in western cities (with effect mainly when both pollutants were high). O ₃ also has an effect on mortality in these data, as does NO ₂ , although it is somewhat inconsistent and may be as a proxy for other vehicle-derived pollutants (eg, particles) [Touloumi et al 1997 (74)]. Results for 2- to 4-day mean (also chosen by each center) were very similar in most of the analyses. For center-specific results, see the corresponding center-specific paper (references 64–73).
	PM ₁₀ range over centers based on PM ₁₃ (Paris, Lyon), on 90%ile PM ₇ (Köln), or on TSP (Milan, Barcelona, Bratislava)	Md 33–85, 90%ile 64–137	All, west & east All, west All, east (Bratislava)	0.4 0.4 0.8	0.3–0.6 0.2–0.6 0.1–1.6	

(continued)

Table 1. Continued.

Study	Measurement data (particle measure, lag time and levels) ^a	Measured or calculated PM ₁₀ ^{b,c} (µg/m ³)	Increase in mortality per 10 µg/m ³ PM ₁₀ ^b or a short summary of the results			Comments ^d
			Cause	%	95% CI	
- Spix & Wichmann, 1996 (66) (center results) - Köln (Germany) 1975–1985 - Sunyer et al, 1996 (67) - Barcelona (Spain) 1985–1991 - Touloumi et al, 1996 (68) - Athens (Greece) 1987–1991 - Vigotti et al, 1996 (69) - Milano (Italy) 1980–1989 - Wojtyniak & Piekarski, 1996 (70); Wojtyniak et al, 1997 (71) - Cracow, Lodz, Poznan, Wroclaw (Poland) 1977–1990 - Zmirou et al, 1996 (72) - Lyon (France) 1985–1990 - Bacharova et al, 1996 (73) - Bratislava (Slovak Republic) 1987–1991	LT 0, 1, 2 or 3 chosen by each center for each pollutant					
Borja-Aburto et al, 1997 (75) - Mexico City (Mexico) 1990–1992	TSP, LT 0 days, Md(R ₁) 204 (66–456)	M 118	All All, >65 years RD CVD	1.0 1.0 1.7 0.9	0.6–1.5 0.5–1.6 0.2–3.1 0.1–1.7	With SO ₂ and O ₃ in model. SO ₂ also associated with mortality (particularly CVD), O ₃ not consistently.
Saldiva et al, 1994 (76) - São Paulo (Brazil) 1990–1991 (children <5 years)	PM ₁₀ , LT 0–2 days, M 82	M 82	RD, <5 years	-2.0	-6.3–2.6	NO _x showed positive effect, but there was no PM ₁₀ effect.
Saldiva et al, 1995 (77) - São Paulo (Brazil) 1990–1991 (elderly)	PM ₁₀ , LT 0–1 days, M 82	M 82	All, ≥65 years	1.3	0.7–1.9	1.3 (95% CI 0.3–2.4) with SO ₂ , NO _x , O ₃ , and CO in model. Stronger in summer, but effect for all seasons.
Salinas & Vega, 1995 (78) - Santiago (Chile) 1988–1991	PM _{2.5} , LT 0 days (?), M(R ₁) ? (?–150) (truncated)	M ?	All	0.3	0.2–0.6	Weaker effect when PM _{2.5} values >150 µg/m ³ were also included in model. Also effect for CO.
Ostro et al, 1996 (79) - Santiago (Chile) 1989–1991	PM ₁₀ , LT 0 days, M(R ₁) 115 (30–367)	M 115	All All, ≥65 years RD CVD	0.7 0.8 1.1 0.7	0.4–0.9 0.5–1.1 0.6–1.7 0.3–1.0	Similar results for total mortality with other model specifications, including other LT. Suggested stronger effect for 3-day mean (LT 0–2).
Simpson et al, 1997 (14) - Brisbane (Australia) 1987–1993	Light scattering (nephelometry), LT 0 days, M(R ₁) 2.6 (0.3–15.2)	M 26	All All, ≥65 years RD HD	0.9 1.0 0.1 1.0	0.3–1.5 0.2–1.8 -2.0–2.3 -0.2–2.2	Similar effect with other pollutants in model. Effect also of O ₃ . No evidence of threshold for particle effect.
Xu et al, 1994 (80) - Beijing (China) 1989	TSP, LT 0 days, M(R ₂) 375 (155–760)	M 206	All All, summer COPD	0.3 0.7 2.3	-0.2–0.7 0.1–1.3 0.5–4.1	0.0 (95% CI -4.5–4.7) with SO ₂ in model. SO ₂ stronger effect. Effect for TSP in summer only, SO ₂ both seasons.

^a Given are the type of particle; lag time (LT); mean and range [M(R_n)] of daily air pollution readings, the range being as follows: R₁ = true range, R₂ = 5th to 95th percentile, R₃ = 10th to 90th percentile, R₄ = 20th to 80th percentile. The median (Md) or geometric mean (GM) is given when the mean was not available. Mostly daily means are used (eg, with LT 0 or LT 1); see page 49 for a discussion.

^b Conversion factors: PM₁₀ ≈ PM₁₅ ≈ BS ≈ SO₄ × 4 ≈ PM_{2.5}/0.60 ≈ CoH [in units of 10³ linear feet, used in most studies] × 55 ≈ TSP × 0.55 (12,13) and PM₁₀ ≈ light scattering (by nephelometry, in units of 10³/m) × 10 (14,15), with remaining particle measures in micrograms per cubic meter.

^c Values given are the mean (M), median (Md) or geometric mean (GM).

^d No co-pollutant in the main model unless indicated in this column.

^e In complete dataset – SP mean 97, range 10–566 — the estimate for total mortality was 0.4 (95% CI 0.1–0.7) per 10 µg/m³ PM₁₀.

Studies in the United States

A 1990 study in St Clara (16), a location with low levels of sulfur dioxide (SO₂), found a clear effect of same-day particulate levels measured as the coefficient of haze (CoH), equivalent to an 0.8% (95% CI 0.3–1.3) increase in daily mortality per a 10 µg/m³ increase in

daily PM₁₀, a finding which stimulated further research on this issue in the United States. Consequently, large contributions to our knowledge about the association between particulate air pollution and mortality have come from the United States in later years (21–23, 29, 30, 32–34, 36, 37). These studies have been carried

out using consistent methodology, with successive refinement. Initially the studies focused on total suspended particles (TSP), but, as the measurement of PM_{10} and smaller particle sizes has become more common in the United States, the focus has shifted accordingly. In a recent study of six US cities (37), $PM_{2.5}$ (particulate matter $<2.5 \mu m$ in diameter) was associated with a stronger effect than the coarse mass (the larger particles in PM_{10}) and overall with a slightly stronger effect than PM_{10} . A meta-analysis of eight locations in these US studies (21–23, 29, 32–34) estimated an increase of 1.06 (95% CI 1.04–1.06) per 100 $\mu g/m^3$ of TSP, corresponding to an increase in daily mortality of 1.1% (95% CI 0.9–1.2) per 10 $\mu g/m^3$ increase in PM_{10} (33). Two later studies also had similar results, with point estimates of 1.1% and 0.8% (36, 37).

Slightly smaller increases in mortality, around 0.5%, have been observed in Chicago (42–44), as well as Los Angeles (40, 41). An analysis of early Los Angeles data (1970–1979) (38) also showed associations with vehicle pollutants including KM (a particulate measure of optical reflectance), as well as ozone (O_3). A prior analysis of the same data (39) found that carbon monoxide (CO), hydrocarbons, and KM, all vehicle-derived pollutants, were the most highly correlated with low-frequency (ie, long-period) fluctuations in mortality, a result that may be of some relevance to health effects in relation to medium or long-term exposure.

Studies in Europe

The famous 1952 London air pollution episode with a very dramatic and acute peak of increased mortality provided a spectacular starting point for air pollution epidemiology. Subsequently, several analyses and reanalyses of mortality and air pollution data from London during more normal years have been performed; they confirmed an effect that appears to be associated with smoke levels more than with SO_2 , independently of episodic peaks (45–48). Early studies in France and in Athens, Greece, also observed increased mortality, although it appeared to be associated more with SO_2 than with smoke (49–52).

Since 1993, a large number of separate European studies has been performed in locations with varying pollution mixes (53–60), generally observing an increase of about 1% in daily mortality per a 10 $\mu g/m^3$ increase in PM_{10} , and often a similar or slightly weaker effect from SO_2 . Several of these studies have used the methodology developed within the APHEA study (short-term effects of Air Pollution and Health: a European Approach), a large multinational project aiming to quantify air pollution health effects in Europe using standardized methodology in multiple locations (9, 81, 82). In this collaborative effort, an effect of particles,

measured as TSP, PM_7 , PM_{10} , PM_{15} or BS was consistently observed, and an independent effect of SO_2 of similar magnitude appeared to be present in most study locations (61–73). The effect of an increase of 10 $\mu g/m^3$ in PM_{10} , based on conversion from gravimetric measures of particulates in six locations (see table 1), was a 0.4% (95% CI 0.2–0.6) increase in total mortality in five western European cities, but higher in Bratislava, the only eastern European city with such measurements [0.8% (95% CI 0.1–1.6)]. For BS, the west-east pattern was reversed, with 0.6% (95% CI 0.4–0.7) and 0.1% (95% CI 0.0–0.2) increases in mortality, respectively, based on results from four cities in each area (not including Bratislava). For SO_2 the pattern was similar to that for BS, and Bratislava did not differ from other eastern European sites. The reason for the heterogeneity of the observed effect is unclear. A positive correlation between average winter temperature and the size of the effect estimate exists for the cities participating in the APHEA study, although other factors, such as age-standardized mortality or proportion of older people, are similarly or even more strongly correlated (83, 84).

Other studies

From other parts of the world, high levels of TSP showed a strong relationship with mortality in Mexico City, whereas O_3 did not when analyzed together with particles, despite the high levels of photochemical pollution observed in this location (75). In Santiago, Chile, mortality was associated with $PM_{2.5}$ and PM_{10} (78, 79), and in Sao Paulo, Brazil, an effect on mortality among elderly people was shown, whereas child mortality was not affected by particles, but it was affected by nitrogen dioxide (NO_2) (76, 77). In Brisbane, effects were found for both particles and O_3 , but, whereas a threshold was suggested for the O_3 effect, no threshold was indicated for particles (14). In Beijing, where pollution levels were very high, SO_2 had a more consistent effect all year around, but there was an effect for TSP on total mortality during the summer (80).

Methodological issues

Research on the health effects of particles has become a field of great controversy, partly because of a revision of air pollution standards in the United States and Europe in the 1990s. A major discussion has focused on the appropriate statistical modeling for this type of data. One result has been multiple reanalyses of data — for example, in London (45, 47, 48), Steubenville, Ohio (85), Philadelphia, Pennsylvania (24–28, 35) (table 1), and, for hospital admissions, in Birmingham, Alabama, and Minneapolis-St Paul, Minnesota (86) (table 2),

Table 2. Time series studies of hospital admissions and particulate air pollution. (For any abbreviations not found in the footnotes, see page 4.)

Study	Measurement data (particle measure, lag time and levels) ^a	Measured or calculated PM ₁₀ ^{b,c} (µg/m ³)	Increase in admissions per 10 µg/m ³ PM ₁₀ ^b or a short summary of the results			Comments
			Cause	%	95% CI	
Mazumdar & Sussman, 1983 (20) - Hazelwood/Bellevue/Logans Ferry, Pittsburgh (PA), 1972–1977	CoH, LT 0 days (?), M(R ₁) 1.0 (0–3.5)	M 54	All RD HD VD	0.3 0.3 0.5 0.4	0.2–0.3 0.1–0.5 0.4–0.7 0.2–0.6	Very similar with SO ₂ in model. Estimates are here pooled over all 3 locations, all of which gave relatively consistent results.
Thurston et al, 1992 (99) - Buffalo, Albany (NY) 1988–1989 - New York City (NY) 1988–1989	SO ₄ , LT 0 days, M(R ₁) 9 (?–37.4) SO ₄ , LT 0 days, M(R ₁) 9.3 (?–33.6)	M 36 M 37.2	RD Asthma RD Asthma	2.3 2.2 1.0 1.9	0.6–3.9 -0.7–5.1 0.2–1.8 0.4–3.4	Estimates from SO ₄ regressions using 1988 data. 1989 data gave similar results. O ₃ and H ⁺ showed as strong or stronger effects.
Schwartz, 1994 (95) - Philadelphia (PA) 1986–1989 (≥65 years)	TSP, LT 0 days (?), M ? ¹	M ?	Pneumonia	3.7	1.7–5.7	3.2 (95% CI 1.2–5.3) with O ₃ in model. Also associations with O ₃ and SO ₂ , although strongest with TSP.
Schwartz, 1994 (100) - Birmingham (AL) 1986–1989 (≥65 years)	PM ₁₀ , LT 0 days, M(R ₃) 45 (19–77)	M 45	COPD Pneumonia	2.4 1.8	0.8–4.1 0.7–2.8	O ₃ also associated, more weakly, with COPD and pneumonia.
Schwartz, 1994 (101) - Minneapolis-St Paul (MN) 1986–1989 (≥65 years)	PM ₁₀ , LT 0–1 days or 0 days, M(R ₃) 36 (18–58)	M 36	COPD Pneumonia	4.6 1.6	1.8–7.5 0.2–2.9	O ₃ also associated with pneumonia.
Moolgavkar et al, 1997 (86) - Birmingham (AL) 1986–1991 (≥65 years) - Minneapolis - St Paul (MN) 1986–1991 (≥65 years)	PM ₁₀ , LT 0 days, M(R ₃) 43 (18–74) PM ₁₀ , LT 0–1 days, M(R ₃) 34 (17–55)	M 43 M 34	COPD & Pneumonia COPD Pneumonia	0.3 0.9 0.5	-0.3–0.9 -0.6–2.4 -0.5–1.5	For both weaker effects than in 1986–1989 analyses by Schwartz. For Birmingham no clear O ₃ effect. For Minneapolis-St Paul the estimates given are with O ₃ , SO ₂ and NO ₂ in models; PM ₁₀ estimates stronger in single pollutant models; strongest and most consistent effect for O ₃ , however.
Schwartz, 1994 (102); Schwartz & Morris, 1995 (103) - Detroit (MI) 1986–1989 (≥65 years)	PM ₁₀ , LT 0–1 days, M(R ₃) 48 (22–82)	M 48	COPD Pneumonia IHD HF CDR	2.0 1.2 0.6 0.7 0.6	0.9–3.2 0.4–1.9 0.1–1.0 0.1–1.4 -0.1–1.3	No association seen for asthma admissions. O ₃ also associated with COPD and pneumonia. CO also associated with HF, but O ₃ and SO ₂ with neither IHD nor HF.
Schwartz, 1995 (104) - New Haven (CT) 1988–1990 (≥65 years) - Tacoma (WA) 1988–1990 (≥65 years)	PM ₁₀ , LT 0 days, M(R ₃) 41 (19–67) PM ₁₀ , LT 0 days, M(R ₃) 37 (14–67)	M 41 M 37	RD RD	1.2 1.9	0.0–2.5 0.6–3.2	Slightly higher estimates with O ₃ and SO ₂ in model. Independent effect also for O ₃ and more weakly for SO ₂ .
Schwartz, 1996 (105) - Spokane, WA 1988–1990 (≥65 years)	PM ₁₀ , LT 0 days, M(R ₃) 46 (16–83)	M 46	RD COPD Pneumonia	1.6 3.2 1.0	0.7–2.6 1.5–4.9 -0.3–2.4	Very low SO ₂ levels. O ₃ also associated with RD admissions.
Schwartz et al, 1996 (9) - Cleveland, OH 1988–1990 (≥65 years)	PM ₁₀ , LT 1–2 days, M(R ₃) 43 (19–72)	M 43	RD	1.1	0.1–2.2	O ₃ also significant, weaker evidence for SO ₂ .
Schwartz, 1997 (106) - Tucson, AZ 1988–1990 (≥65 years)	PM ₁₀ , LT 0 days, M(R ₃) 42 (21–63)	M 42	HD	1.2	0.2–2.2	1.0 (95% CI 0.0–2.0) with CO in model. Similar effect for CO. No effect for SO ₂ , O ₃ or NO ₂ . Low SO ₂ levels.
Bates & Sizto, 1983 (107), 1986 (108), 1987 (109), 1989 (110) - Ontario (Canada) 1974 and 1976–1978, –1982 or –1983, summer - Ontario (Canada) 1974 and 1976–1978, –1982 or –1983, winter	SO ₄ , LT 0,1,2 days, M 9.5 SO ₄ , LT 0,1,2 days, M 10.3	M 38 M 41	RD RD	Effect for SO ₄ No effect		Summer effect also for O ₃ for RD admissions. No effect for O ₃ or SO ₄ for a group of nonrespiratory admissions.

(continued)

Table 2. Continued.

Study	Measurement data (particle measure, lag time and levels) ^a	Measured or calculated PM ₁₀ ^{b,c} (µg/m ³)	Increase in admissions per 10 µg/m ³ PM ₁₀ ^b or a short summary of the results			Comments
			Cause	%	95% CI	
Lipfert & Hammerstrom, 1992 (111) - Ontario (Canada) 1979–1985, summer/winter	TSP, LT 0–2 days, M 62	M 34	RD	No significant effect for TSP in stepwise regression		Some effects for O ₃ , SO ₂ and SO ₄ were found, particularly in summer.
Burnett et al, 1994 (112) - Ontario (Canada) 1983–1988	SO ₄ , LT 1 day, M 5.3	M 21	RD	0.8	0.5–1.1	.
Burnett et al, 1995 (113) - Ontario (Canada) 1983–1988	SO ₄ , LT 1 day, M(R ₂) 4.4 (?–13)	M 17	RD, all ages RD, ≥65 years COPD Pneumonia Asthma HD, all ages HD, ≥65 years IHD CDR HF	0.7 0.7 0.9 0.6 0.6 0.5 0.7 0.4 0.2 0.6	0.5–0.9 0.3–1.1 0.5–1.4 0.3–0.9 0.2–1.0 0.3–0.7 0.4–1.0 0.1–0.7 -0.4–0.9 0.1–1.0	0.7 (95% CI 0.4–0.9) with O ₃ in model. No clear seasonal difference. Note: HD here is only IHD+CDR+HF (ICD-9 codes 410+413, 427, 428).
Delfino et al, 1994 (114) - Montreal (Canada) 1984–1988 May–October	PM ₁₀ , LT 3 days, M(R ₂) 30 (?–46)	M 30	Asthma	2.3	0.6–4.0	Effect of high versus low SO ₄ days on non-asthma admissions July–August also seen.
Thurston et al, 1994 (115) - Toronto (Ontario) 1986–1988 summer	PM ₁₀ , LT 0 days, M 33	M 33	RD	4.5	0.4–8.7	2.5 (95% CI -2.4–7.4) with O ₃ in model. Effect for H ⁺ >SO ₄ >PM _{2.5} >PM ₁₀ >TSP.
Burnett et al, 1997 (116) - Toronto (Ontario) 1992–1994 summer	PM ₁₀ , LT 0–3 days, M(R ₁) 28 (4–102)	M 28	RD CD	2.1 2.3	0.9–3.3 0.3–4.4	Effect sensitive to other pollutants (particularly NO ₂) in model. Associations with O ₃ , and also NO ₂ , SO ₂ and CoH, more consistent.
Burnett et al, 1997 (117) - 10 Canadian cities 1981–1991 (>65 years)	CoH, LT 0 days, M(R ₂) 0.3 (0–0.9)	M 17	HF	2.2	0.8–3.6	No effect with O ₃ , NO ₂ , SO ₂ and CO in model. CO strongest effect in multipollutant models.
Burnett et al, 1997 (118) - 16 Canadian cities 1981–1991	CoH, LT 0 days, M(R ₂) 0.64 (?–1.5)	M 35	RD	1.1	0.6–1.6	With O ₃ and CO in model. Similar effects of these 2 pollutants.
Díaz-Caneja & Gutiérrez, 1991 (119) - Santander (Spain) 1979–1982	SPM, LT 0 days, M 66	M 36	COPD HF	8.7 6.3		Stepwise linear regression. Association with square and quadratic root of SPM.
Pantazopoulou et al, 1995 (120) - Athens (Greece) 1988 (winter & summer separately)	BS, LT 0 days (?), M(R ₂) 135 (46–281)	M 135	RD, winter HD, winter	0.9 0.7	0.2–1.7 0.3–1.1	Less effect in summer for both RD and HD.
Walters et al, 1994 (121) - Birmingham (United Kingdom) 1988–1990	BS, LT 2 days, M(R ₃) 13 (4–29)	M 13	RD, winter Asthma, winter	13.1 9.7	6.0–20.6 1.0–19.2	Less effect in summer, little observed in spring and autumn. SO ₂ similar but weaker effects.
Wordley et al, 1997 (58) - Birmingham (United Kingdom) 1992–1994	PM ₁₀ , LT 1 day, M(R ₁) 26 (3–131)	M 26	RD Asthma Bronchitis Pneumonia COPD IHD CerebroVD	2.9 4.0 5.8 6.2 1.8 0.3 2.1	1.2–4.5 0.8–7.6 1.7–11.9 2.5–10.1 -1.7–5.4 -0.9–1.5 0.0–4.2	.
Poloniecki et al, 1997 (122) - London (United Kingdom) 1987–1994	BS, LT 1 day, Md(R ₁) 12 (1–62)	Md 12	CVD AMI AP CDR HF	0.5 2.0 2.0 1.7 0.5	-1.0–2.1 0.6–3.5 0.2–3.9 -0.3–3.7 -1.0–2.1	No effect on cerebroVD. For AMI mainly effect in cool season, and similar effects for NO ₂ , SO ₂ , CO (SO ₂ most consistent) but not O ₃ .

(continued)

Table 2. Continued.

Study	Measurement data (particle measure, lag time and levels) ^a	Measured or calculated PM ₁₀ ^{b,e} (µg/m ³)	Increase in admissions per 10 µg/m ³ PM ₁₀ ^b or a short summary of the results			Comments
			Cause	%	95% CI	
APHEA project						
- Katsouyanni et al, 1997 (61) [center results for RD (≥65 years) and COPD (all ages) admissions]	BS (5 cities), range over centers Md 6–41	Md 6–41	RD, 15–64 years	0.6	0.1–1.0	<i>RD admissions:</i> Most consistent effect for O ₃ . No consistent effect for SO ₂ . Particle effect somewhat unstable. Effect of BS significantly stronger at high NO ₂ levels, but no clear overall NO ₂ effect.
- Amsterdam, Rotterdam, London, Paris, Milan			RD, ≥65 years	0.4	-0.1–0.9	
- Spix et al, 1998 (123) (meta-analysis for RD admissions)			COPD	0.7	0.2–1.2	
- Amsterdam, Rotterdam, London 1987–1991, Paris, Milan			COPD, cool season	0.6	0.0–1.2	
- Anderson et al, 1997 (124) (some center results & meta-analysis for COPD admissions)	TSP (4 cities), range over centers Md 41–155	Md 23–85	COPD, warm season	1.0	-0.4–2.3	<i>COPD admissions:</i> Most consistent effect for O ₃ . Some effect also observed for NO ₂ and SO ₂ . Seasonal variation inconsistent between BS and TSP.
- Amsterdam, Rotterdam, London Paris, Milan, Barcelona 1986–1992			Asthma, ≤14 years	0.6	-0.4–1.6	
- Sunyer et al, 1997 (125) (some center results & meta-analysis for asthma admissions)			Asthma, 15–64 years	0.4	-0.3–1.2	
- London, Paris, Barcelona, Helsinki ^d						
- Dab et al, 1996 (65)	LT 0, 1, or 3 chosen by each center for each pollutant		RD, 15–64 years	0.4	-0.4–1.1	<i>Asthma admissions:</i> Significant effects of NO ₂ in adults and SO ₂ in children were also seen, independent of particle effects. While the particle effect was weakened in 2-pollutant models, NO ₂ and SO ₂ , respectively, were strengthened. For O ₃ , no effect was seen in children and inconsistent results in adults. Seasonally, the particle effect was stronger in winter.
- Paris 1987–1992 (all ages)			RD, ≥65 years	0.6	-0.2–1.4	
- Schouten et al, 1996 (127)			COPD	0.8	-0.1–1.7	
- Amsterdam/Rotterdam 1977–1989			COPD, cool season	1.4	-0.3–3.2	
- Ponce de Leon et al, 1996 (126)			COPD, warm season	0.4	-0.9–1.6	
- London 1987–1988, 1991–1992;						
- Vigotti et al, 1996 (69)						
- Milano 1980–1989						
- Sunyer et al, 1991 (128);						
- Sunyer et al, 1993 (129)						
- Barcelona 1985–1989						
- Pönkä & Virtanen, 1996 (130)						
- Helsinki 1987–1989 ^d						

^a Given are the type of particle; lag time (LT); the mean and range [M(R_n)], the range being as follows: R₁ = true range, R₂ = 5th to 95th percentile, R₃ = 10th to 90th percentile. The median (Md) is given when the mean was not available. Mostly daily means are used (eg, with LT 0 or LT 1); see page 49 for a discussion.

^b Conversion factors: PM₁₀ ≈ PM₁₅ ≈ BS ≈ SO₄ × 4 ≈ PM_{2.5}/0.60 ≈ CoH [in units of 10³ linear feet, used in most studies] × 55 ≈ TSP × 0.55 (12,13) and PM₁₀ ≈ light scattering (by nephelometry, in units of 10⁻⁵/m) × 10 (14,15), with remaining particle measures in micrograms per cubic meter.

^c Values given are the mean (M) or median (Md).

^d No particle data for Helsinki.

in some cases with different conclusions. The US Health Effects Institute sponsored an extensive project to re-analyze six previous studies of mortality and particulate air pollution (35). With partly new methods, the original analyses were generally confirmed. In the case of Philadelphia, separate effects of SO₂ and TSP were found, and earlier observations of stronger relative increases associated with TSP in summer and autumn, but with SO₂ in winter and spring (24), were initially replicated, but not confirmed in detailed analyses by the new analysts (27, 28). Others have also investigated the sensitivity to modeling assumptions. For example, assumptions regarding the distribution of residual variability in mortality were investigated in a Los Angeles 1985–1990 dataset (average 153 deaths per day), and small differences were found between linear (Gaussian) and log-linear Poisson regressions (40). However, it is now generally recognized that some type of Poisson regression is the method of choice for data of this kind be-

cause it accommodates nonnormally distributed, small daily outcome counts and generally because the variance of the outcome may not be constant over the range of exposure, as assumed in a linear regression.

Seasonal differences have been observed in several studies, in some locations with higher effects of particles in the summer (24, 40, 41, 77) or spring or autumn (42), while others have found little variation (27, 28). The divergent findings are difficult to interpret, but could be due to, for example, a varying influence of photochemical or other pollutants, differing weather conditions, or industrial or other human activity that could lead to a variation in the composition of particles and hence to a variation in their biological effect by season. Uncontrolled confounding by unidentified or known risk factors (eg, temperature) could also vary by season. Other possible explanations include varying exposure misclassification (eg, due to indoor-outdoor activity patterns) or a true season or temperature

interaction with air pollution. This question deserves further study.

Several aspects of the mortality observed to be related to daily air pollution levels are important. First, the pattern of increased deaths on days with high versus low particulate pollution was shown in Philadelphia, Pennsylvania, to be similar to the pattern observed in the London air pollution episode in 1952. A disproportionate increase in chronic obstructive pulmonary disease (COPD) and pneumonia deaths was observed, as were increases in heart disease and stroke deaths, particularly with respiratory factors as contributing causes and a disproportionate increase in dead-on-arrival deaths and deaths outside of hospitals and clinics (87). Second, an important question to consider is how much the life of those dying from air pollution is shortened. According to one hypothesis, the effect seen in the daily time-series studies is largely a "harvesting effect", whereby death occurs for sensitive persons who would have died in the immediate future from preexisting disease. This hypothesis is biologically plausible and has some epidemiologic support (54). There is however also evidence of more long-term effects (88, 89). A third, related question, is whether the increased mortality is limited to sensitive subgroups or whether it affects even the previously "healthy" population. No data directly answering this question currently exist. The biological mechanisms underlying an effect on mortality are not clear. According to one hypothesis (90), low-grade inflammation caused by alveolar deposition of ultrafine particles may lead to increased blood coagulability. Indeed, a cross-sectional study observed an increased OR of approximately 3 for plasma viscosity above a 95th percentile cut point ($1.38 \text{ mPa} \times \text{s}$) for subjects of either gender sampled during an air pollution episode when they were compared with those sampled at other times (91). However, since ultrafine particles are not routinely measured, no time-series studies have yet investigated this pollutant measure in relation to mortality or hospital admissions, although initial contradictory results are available in relation to pulmonary function and symptoms of asthmatics (92, 93).

Exposure measurement is mainly of an ecological (aggregated) nature — generally one fixed air pollution monitor or an average from several monitors is used to estimate daily exposure for all persons in a study. Such exposure assignment has been shown to have a reasonably high correlation with personal exposure measurements (eg, for PM_{10}) (94). Some measurement error is inevitable but can generally be expected to be nonsystematic, and therefore there would generally be some attenuation of estimates for continuous exposure variables (8).

The analytical methods used attempt to control for confounding by season and long-term trends and there-

by eliminate the need to consider other traditional confounders that lack day-to-day variation. Weather variables, including temperature, are important potential confounders with short-term variation to consider, as well as day of week, holidays, and epidemics (eg, influenza). Several different methods may be appropriate to model such covariates in the regression analysis, ranging from dummy variables over parametric approaches to nonparametric smoothing, which may be incorporated into a generalized additive model (9, 95). In most instances, there is no general answer as to which approach is the most correct, and reanalyses of existing datasets have illustrated that alternative model specifications often make surprisingly little difference. Consequently, each study is best judged individually on the subject of confounding control.

Obviously, another set of vital potential confounders is other air pollutants. Most studies have not performed analyses including co-pollutants or including only one co-pollutant, often because of lacking data. It is also difficult to model meaningfully many co-pollutants when they are highly correlated, especially in small datasets. This problem is important in respect to future analyses, as particle measures can be sensitive to the inclusion of other pollutants in the statistical model (27, 28). In many instances, however, the estimated effects of particles have not been very sensitive to the inclusion of co-pollutants (96). Studies have also found significant associations with O_3 (38, 74, 97), generally a daily 1-hour or 8-hour maximum with 0, 1 or 2 days of lag time, although for O_3 , the evidence is stronger for other types of health effects than for mortality (98). In several locations, significant associations have also been observed for SO_2 and NO_2 (38, 47, 62, 74). Meta-analyses from the APHEA study indicate that all of the mentioned air pollutants show significant associations with mortality (62, 74). On the other hand, some studies were designed to take advantage of low levels of other air pollutants in specific locations, and effects of particles have been observed also in such locations (16, 29, 30).

Previous studies have examined various lag times and averaging times for the exposure variable. These are almost always less than 5 days, and generally particulate levels on the same or previous day are associated with increased daily mortality, even when another lag time or averaging time has been chosen in the final model. It is not clear whether the datasets have been extensive enough and the methods rigorous enough to draw any conclusions from the various lag times and averaging times used, as day-to-day particulate levels are highly correlated and these variable constructs may be measuring essentially the same thing with different amounts of measurement error, which may vary between studies. Recently, new methods have appeared to evaluate appropriate lag times more formally using the Akaike

information criterion within the framework of analyses employing generalized additive models (27, 28).

Evaluation

A large number of studies has consistently observed increased mortality in association with levels of particulate air pollution on the previous day or days. Different gravimetric measures such as TSP and PM_{10} and reflectance or visibility measures such as BS or CoH have been used with similar results. It has lately been suggested that the smaller particulate fractions (eg, $PM_{2.5}$ or even smaller) are primarily responsible for the health effects observed (37). The possibility that particles are a surrogate for other pollutants cannot be completely dismissed. However, the association has been consistently observed even in locations with low levels of other pollutants — for example, SO_2 in Utah Valley or St Clara — or high levels — for example, O_3 in Mexico City. The size of the effect is around a 0.5–1% increase in daily mortality for a $10 \mu g/m^3$ increase in PM_{10} , and it appears generally to be stronger for respiratory deaths and cardiovascular deaths than for total death counts. The effect appears to follow within one to a few days after high particle levels; depending on the study, the health effects have been related to daily mean particulate levels with a lag time of 0 to 4 (same day or closest preceding days) or an average over 2–5 days previously. Associations have been observed at particulate levels well below $100 \mu g/m^3$, and some studies indicate weaker relationships at higher levels. Similarly, several studies have reported stronger effects in the summer (when PM_{10} levels are usually lower), and a positive correlation between the average winter temperature and the size of the effect estimate exists for the cities that participated in the APHEA study.

Time-series studies of hospital admissions and outpatient visits

Hospital admissions

A large number of studies has also appeared relating particulate air pollution for one or a few days to morbidity, measured as daily hospital admissions for all causes, all or specified respiratory causes, or cardiovascular causes (9, 20, 58, 61, 65, 69, 86, 95, 99–130). For ease of reference, the studies are listed in table 2 with brief relevant information.

Studies in the United States. After a few early studies reporting an effect of particles on admissions for respiratory disease, including asthma, as well as cardiovascular disease (20, 99, 131–133), some of which used longer averaging times (see table 5 under “Miscellaneous

Health Effects in Relation to Medium-term Exposure”) (131–133), a large number of studies of this type has been conducted in the United States (9, 95, 100–106). These studies used a relatively consistent methodology, employing variants of Poisson regression and all focusing on PM_{10} as the exposure measure, and therefore the intercomparison is relatively straightforward. They all investigated admissions among elderly people and have reported consistent associations for all respiratory, COPD and pneumonia hospital admissions, as well as for heart disease admissions, with PM_{10} levels. Most of the studies have considered O_3 , and in some cases SO_2 , but otherwise multipollutant models were not investigated in the original reports. A reanalysis of data from two of the sites, which considered several pollutants, reported weaker effects than originally found and further weakening of the PM_{10} effect in multipollutant models (86). In some of the other studies, however, the study site was selected to have low levels of another pollutant or low correlations between pollutants.

Studies in Canada. A well-organized hospital system has provided substantial amounts of data for these kinds of analyses in Canada. Bates & Sizto (107–110) were the first to relate Ontario hospital admissions to air pollution data; they found consistent relationships during the summer with sulfates and O_3 , but not with CoH. They hypothesized that oxidant air pollution and irritating gases or acid aerosols, which tend to appear in summer, were responsible for the effects. Subsequent studies in Canada also tended to see O_3 effects, and thus analyses were focused on oxidants, acid aerosols, and sulfate ions (SO_4), as well as on seasonal differences or the summer season exclusively (115, 116). The study of effects of particulates was also hampered by the fact that, apart from SO_4 , the CoH was the only measure of particulate air pollution available on a large scale. Since it is a measure of sample filter staining, it is not particularly well characterized and is not ideally suited for studying particles. Until very recently, these studies used techniques based on linear regressions, and this approach may have been a reasonable analytic strategy considering the large number of daily admissions in most studies, even in subgroup analyses. As a group, the studies suggest that there may be an effect of particles on hospital admissions for respiratory disease, asthma, and some cardiac disease, but more extensive monitoring by gravimetric measuring methods would be helpful to determine which particulate components may be responsible.

Studies in Europe. The studies in Europe have used BS, a similar measure of sample filter staining, and only lately have gravimetric methods become more common. Similarly, before the coordinated APHEA study, which

employed Poisson regression methods, linear regression was generally used. In general, an effect of BS or other particulate measures has been observed for total respiratory admissions, bronchitis, and asthma, as well as for some cardiovascular conditions. The particulate effect has often been stronger in the cool season (58, 120–122), in contrast to the findings of mortality studies. In the large APHEA study a seasonal difference was consistently found for asthma admissions but not for total respiratory admissions or COPD (123–125). One explanation for finding a weaker effect for asthma in summer could be that the strong effect of elevated pollen levels makes it difficult to discern a particle effect when pollen data are lacking. The European results are generally consistent with other data in suggesting effects of air pollution including particles on respiratory and possibly cardiovascular admissions. The increased risks observed, especially in the APHEA study, are however generally somewhat lower than in studies from the American continent (in the range of a 0.4–0.9% increase per 10 $\mu\text{g}/\text{m}^3$ of PM_{10} for different end points in different subgroups of the APHEA study), and there is also clear heterogeneity between locations. Possible reasons for this heterogeneity include differences in population composition, baseline morbidity, meteorological conditions (including temperature), and a particulate air pollution mix due to different emission sources (heating, traffic, industry).

Outpatient visits

Fewer studies have investigated outpatient visits, partly because such data are more rarely routinely available. The studies are listed in table 3 (15, 120, 134–149).

In the United States, an overall increase in daily asthma visits by $\geq 2.0\%$ has been related to a 10 $\mu\text{g}/\text{m}^3$ increase in PM_{10} (135, 137–140). One of these studies reported a higher effect of PM_{10} at temperatures above 0°C than below 0°C (138), whereas in another the increase in asthma visits was 1.8% at the study mean temperature (5°C) but 6.1% at low temperatures (140). In addition, visits for respiratory disease in general (134), bronchitis (136, 139), and upper respiratory infections (139) have shown increases, although of a smaller magnitude. Another US study, as well as two Canadian studies, found relationships between asthma visits and other pollutants to be stronger (141–143), and a Canadian study of visits for respiratory disease found an effect of particles only in the age group of >64 years, although this effect was marked, 7.3% (95% CI 2.0–12.6) (144).

In Europe, a pronounced increase in croup cases in relation to TSP exposure was reported from Germany, corresponding to approximately 8% per 10 $\mu\text{g}/\text{m}^3$ (145).

Other studies have observed a possible limited effect of particles on all-cause visits (120), as well as a stronger effect on asthma visits specifically (146, 147), although NO_2 and sometimes also other pollutants (147) have been as strongly implicated. One study of asthma visits noted a seasonal interaction indicating a stronger effect on asthma at higher temperatures (146), whereas no seasonal variation in effect was seen for all-cause visits (120). A particularly strong effect on asthma in children was seen in a study on physician house calls in Paris, where an effect of O_3 only at 10°C or higher was also noted (147). No clear effect on cardiovascular visits could be observed. In Beijing, with very high pollution levels, only weak effects of particles and SO_2 on total all-cause emergency visits were found (148, 149). The effect size was similar to that of the European study of all visits (120) and may at least partly reflect that the outcome measure was nonspecific. In Australia, high particulate levels after extensive bush fires could not be related to asthma visits (15).

Evaluation

Several methodological aspects of relevance have already been discussed in the section on mortality. One difference is that, in relation to the underlying outcome of interest, in this case health deterioration, hospital admissions or outpatient visits are potentially more affected by the behavior of study subjects (eg, decision on whether to seek care or not at equivalent disease states) or societal factors (variations in access to care, etc). This difference may paradoxically result in greater misclassification for these morbidity outcomes than for mortality outcomes, although the morbidity outcomes are in a sense more specific. The possible impact of “harvesting” (ie, short-term advancement of the outcome) may also have a different implication than for mortality, as a proportion of admissions or visits due to air pollution is likely to represent cases which would not otherwise have occurred at all. Overall the studies on hospital admissions and emergency room visits provide additional evidence for adverse health effects due to short-term exposure to particles. Increases in daily admissions range from 0.5% to 3% per 10 $\mu\text{g}/\text{m}^3$ PM_{10} in most studies. The lag time between exposure and effect appears to be similar to that found for mortality end points — from one to a few days. An effect on many respiratory end points has been found, and in some studies there has also been an effect on certain cardiovascular conditions. Generally the estimated effect is stronger on respiratory disease such as COPD and pneumonia (ranging up to over 6% per 10 $\mu\text{g}/\text{m}^3$ of PM_{10}) and lower for cardiovascular disease or specific cardiac disease end points (up to 2.3% per 10 $\mu\text{g}/\text{m}^3$ of PM_{10} reported). The results regarding daily asthma admissions

Table 3. Time series studies of emergency visits and particulate air pollution. (For any abbreviations not found in the footnotes, see page 4.)

Study	Measurement data (particle measure, lag time and levels) ^a	Measured or calculated PM ₁₀ ^{b,c} (µg/m ³)	Increase in visits per 10 µg/m ³ PM ₁₀ ^b or a short summary of the results			Comments
			Cause	%	95% CI	
Samet et al, 1981 (134) - Steubenville (OH) 1974–1977	TSP, LT 0 days, M(R ₁) 156 (14–696)	M 86	All visits RD	0.2 0.5	0.0–0.4 0.0–1.0	RD: effect also of SO ₂ .
Schwartz et al, 1993 (135) - Seattle (WA) 1989–1990, <65 years	PM ₁₀ , LT 0–3 days, M(R ₁) 30 (6–103)	M 30	Asthma, <65 years	3.7	1.2–6.3	No association was seen for persons ≥65 years of age.
Hefflin et al, 1994 (136) - Washington State (US) 1991	PM ₁₀ , LT 0 days, M(R ₁) 40 (3–1689)	M 40	Bronchitis Sinusitis	0.4 0.5 ^d	0.3–0.4 0.3–0.6	URI or asthma: no significant association. Two days of dust storms during study.
White et al, 1994 (137) - Atlanta (GA) summer 1990	PM ₁₀ , LT 1 day, M(R ₁) 39 (19–87)	M 39	Asthma	2.0	-6.0–10.7	With O ₃ in model. High O ₃ days were also associated with asthma visits.
Choudhury et al, 1997 (138) - Anchorage (AK) 1990–1992	PM ₁₀ , LT 0 days, M(R ₁) 41 (1–565)	M 41	Asthma	4.2	2.4–6.2	Simple linear regression. Suggested lower PM ₁₀ effect at low temperature.
Gordian et al, 1996 (139) - Anchorage (AK) 1992–1994	PM ₁₀ , LT 0 days, M(R ₁) 46 (5–565)	M 46	Asthma Bronchitis UR illness	2.5 0.9 1.2	0.0–5.1 NS 0.0–2.4	Effects similar by season. UR illness: effect especially for ages <11 years and >45 years.
Lipsett et al, 1997 (140) - Santa Clara County (CA) 1988–1992, winter	PM ₁₀ , LT 0–2 or 2 days, M(R ₁) 61 (9–165)	M 61	Asthma	9.6 (overall estimate for LT 0–2)	0.1–20.0	Temperature interaction model, lag 2: 6.1 (95% CI 2.8–9.1) at -7°C (minimum temperature), 1.8 (95% CI 0.5–2.9) at 5°C (mean temperature).
Yang et al, 1997 (141) - Reno (NV) 1992–1994	PM ₁₀ , LT 0 day(?), M(R ₁) 34 (2–157)	M 34	Asthma	No significant PM ₁₀ effect		Effect of O ₃ , but not significant for PM ₁₀ or CO.
Bates et al, 1990 (142) - Vancouver (Canada) 1984–1986 (0–14, 15–60 & >60 years)	SO ₄ , LT 0, 1 & 2 days, M(R ₁) 3.4 ?–14.5	M 13	RD & asthma	Some correlations noted for SO ₂ , SO ₄ and NO ₂		Correlation analysis. Unclear, season-specific results.
Stieb et al, 1996 (143) - Saint John (Canada) 1984–1992	TSP, LT 3 days, M(R ₁) 37 (5–108)	M 20	Asthma	2.0	-11.4–17.3	With O ₃ and SO ₄ (!) in model. Primarily O ₃ effect (>95th versus <95th percentile). Limited sample size for TSP however.
Delfino et al, 1997 (144) - Montreal (Canada) 1993 summer	PM ₁₀ , LT 1 day, M(R ₁) 22 (?–51)	M 22	RD, all ages RD, ≥65 years RD, <2 years	3.5 7.6 4.8 ^e	0.7–6.4 2.0–13.5 0.1–9.8	RD: no effect among 2- to 64-year-olds. For ≥65 years also effects for PM _{2.5} , SO ₄ and O ₃ .
Schwartz et al, 1991 (145) - Five German cities, 1983–1987	TSP, LT 0 days, Md 17–56 across cities	Md 9–31 across cities	Croup	~4.1	..	Based on a 27 % increase in croup cases for TSP increase from 10 to 70 µg/m ³ (log TSP model). No seasonal difference. No evidence of effect for obstructive bronchitis visits.
Pantazopoulou et al, 1995 (120) - Athens (Greece) 1988, winter	BS, LT 0 days (?), M(R ₂) 135 (46–281)	M 135	All visits	0.3	-0.1–0.6	Only NO ₂ had significant effect. CO similar to BS. No multipollutant analyses.
- Athens (Greece) 1988, summer	BS, LT 0 days (?), M(R ₂) 106 (50–184)	M 106	All visits	0.2	-0.1–0.6	
Castellsague et al, 1995 (146) - Barcelona (Spain) 1985–1989, winter	BS, LT 0 days, M 68	M 68	Asthma	0.9	-0.8–2.6	Similar association with NO ₂ , but not with SO ₂ and O ₃ .
- Barcelona (Spain) 1985–1989, summer	BS, LT 0 days, M 48	M 48	Asthma	3.2	0.5–6.0	

(continued)

Table 3. Continued.

Study	Measurement data (particle measure, lag time and levels) ^a	Measured or calculated PM ₁₀ ^{b,c} (µg/m ³)	Increase in visits per 10 µg/m ³ PM ₁₀ ^b or a short summary of the results			Comments
			Cause	%	95% CI	
Medina et al, 1997 (147) - Paris (France) 1991–1995	PM ₁₀ , LT 0,1,2 & 0–3 days in different models, M(R ₁) 25 (6–96)	M 25	Asthma, all ages	2.4	1.0–3.8	Asthma: very similar risks for BS, NO ₂ and SO ₂ , as well as O ₃ at 10°C or higher and only BS and O ₃ were stable in multipollutant models for 0–14 years. AP/AMI: BS effect was +3.8% (95% CI 0.3–7.5), however, but the strongest effects for CVD visits overall and AP/AMI visits were for O ₃ , followed by SO ₂ and NO ₂ .
			Asthma, 0–14 years	7.2	3.7–10.8	
			Asthma, 15–64 years	1.2	-0.6–3.0	
			CVD visits	0.7	0.0–1.5	
			AP/AMI visits	-2.1	-7.3–3.5	
			Headache	3.1	2.3–3.9	
Xu et al, 1995 (148); Xu et al, 1995 (149) - Beijing (China) 1990	TSP, LT 0 days (?), M(R ₁) 387 (106–1255)	M 213	All visits	0.2	0.1–0.4	Similar effect for SO ₂ . Little seasonal difference for TSP.
			Internal medicine	0.2	0.0–0.4	
			Pediatrics	0.4	0.1–0.6	
Smith et al, 1996 (15) - Sydney (Australia) January 1994	Light scattering (nephelometry), Md 0.19	Md 18 (some PM ₁₀ data also)	Asthma, obstructive respiratory disease, not associated with maximum nephelometry readings			Visits were not significantly more frequent during a bushfire period.

^a Given are the type of particle; lag time (LT); mean and range [M(R_n)], the range being as follows: R₁ = true range, R₂ = 5th to 95th percentile. The median (Md) is given when the mean was not available. Mostly daily means are used (eg, with LT 0 or LT 1); see page 49 for a discussion.

^b Conversion factors: PM₁₀ ≈ PM₁₅ ≈ BS ≈ SO₄ × 4 ≈ PM_{2.5}/0.60 ≈ CoH [in units of 10³ linear feet, used in most studies] × 55 ≈ TSP × 0.55 (12,13) and PM₁₀ ≈ light scattering (by nephelometry, in units of 10⁻⁵/m) × 10 (14,15), with remaining particle measures in micrograms per cubic meter.

^c Values given are the mean (M) or median (Md).

^d Analysis only including high particle days (>150 µg/m³), with LT 2 days.

^e Estimate based on SO₄ measurement data.

show a larger variability that may be partly due to a smaller sample size, but asthma visits, particularly of children, appear to be rather consistently associated with particulate air pollution levels, with increases of roughly 1% to 4% reported per 10 µg/m³ of PM₁₀. The effects estimated in recent European studies of hospital admissions (0.4–0.9% increase per 10 µg/m³ of PM₁₀ for different end points in different subgroups) appear to be weaker than previous findings from the United States and elsewhere.

Lung function changes and respiratory symptoms

Temporal variations in symptoms such as cough, phlegm, chest discomfort and the like are examined in this section, as well as symptom exacerbation among asthmatics (wheeze, medication use) and patients with other respiratory conditions. Many studies measure both symptoms and lung function and are listed for ease of reference with their principal characteristics and results in table 4 (92, 93, 150–187). Because these studies show greater variation in design, they have been described in more detail than the studies in the previous sections.

Lung function changes and symptoms in healthy children

Lung function. In the ambitiously designed Harvard study of air pollution and health effects in six US cit-

ies, 330 children in Steubenville performed repeated pulmonary function tests. Only a small effect of TSP on forced vital capacity (FVC) and forced expiratory volume in 0.75 seconds (FEV_{0.75}) was observed, corresponding to less than 1% of the mean outcome level over the range of pollutant exposure studied (150). A sensitivity reanalysis confirmed this finding (151). In another of the six cities, 154 children in normal daily activity performed spirometry weekly during February to April (152). Significant negative regression coefficients for lung function parameters were obtained for 1-hour maximal O₃ concentrations (range 7–156 µg/m³), whereas no negative effect was seen for PM_{2.5}.

For 144 Pennsylvanian schoolchildren who daily measured peak expiratory flow rate (PEFR), neither SO₂ nor particle pollution measured as CoH nor O₃ were associated with a substantially decreased morning PEFR (153). Another study in an Ontario summer camp focused on acid aerosols and showed substantial variations in O₃, acid aerosols, and SO₄ levels. Among the 112 nonasthmatic girls studied, a methacholine test was positive (MCh⁺) for 40.6% and therefore indicated increased lung reactivity (154). Comparisons were made between afternoon lung function on days of a major pollution episode and the mean lung function on several preceding reference days. Maximum decrements of 3.5% for forced expiratory volume in 1 second (FEV_{1.0}) and 7% for PEFR were observed in the positive methacholine test group (corresponding to -0.63 ml per µg/m³ and -3.0 ml/s per µg/m³), whereas the results of the pulmonary function tests in the negative methacholine

Table 4. Studies of lung function changes and symptoms in relation to particulate air pollution. (For any abbreviations not found in the footnotes, see page 4.)

Study	Size of study data set for the analyses ^a			Measurement data (particle measure and levels) ^{d,e}	Outcome estimates or short summary of results						Comments
	Study subjects	Data points per subject ^a			Symptoms studied and effect per 50 µg/m ³ PM ₁₀			Lung function change in ml (PEFR: ml/s) per 50 µg/m ³ PM ₁₀			
		Diary days ^b	Pulmonary test days ^c		Symp- tom	OR ^f	95% CI ^f	Test	Change ^g & 95% CI		
Dockery et al, 1982 (150); Brunekreef et al, 1991 (151) (sensitivity reanalysis) - Steubenville (OH) 1978-1980	330 children, ~8-10 years (3rd-5th grade)	-	3-20 (mean 11)	TSP, R 11-292	-	-	-	FVC FEV _{0.75} FVC FEV _{0.75}	-7.4* (Md slope) -1.6* (Md slope) -9.0 (M slope) -7.8 (M slope)	Mean slope estimates from reanalysis of 165 children (74% of data) (Brunekreef et al)	
Kinney et al, 1989 (152) - Kingston (TN) 1981	154 schoolchildren, 10-12 years, 61% male	-	6	PM _{2.5} , R 15-35	-	-	-	FVC FEV _{1.0} MMEF	+47 +126 +357*	Significant negative effects of O ₃ .	
Vedal et al, 1987 (153) - Chestnut Ridge (PA) 1980-1981	128 (diary) & 144 (PEFR) elementary school children, mean age 10 years, 62% male	240	45	CoH, M(R) 0.4 (0.1-1.3)	LRI URI, wheeze	1.6 No effect	0.9-3.0	PEFR	No substantial effect of any pollutant or lag time.	-	
Raizenne et al, 1989 (154) - Ontario (Canada), summer 1986	112 girl guide camp (Lake Eire) participants, 8-14 years	-	5	SO ₄ , R 7-83	-	-	-	FEV _{1.0} PEFR	Decrease Decrease	FEV _{1.0} -3.5% and PEFR -7% on episode versus control days.	
Pope & Dockery, 1992 (155) - Utah Valley (UT), winter 1990/1991	40 healthy school-children, 10-12 years, 32% male	~82	~82	PM ₁₀ , M(R) 76 (7-251)	URS LRS Cough	1 1.2 1.4	0.8-1.4 0.9-1.6 1.1-1.7	PEFR	-21 (-37--6)	Results are for 5-day mean PM ₁₀ . Relationships to same-day PM ₁₀ were slightly weaker for both symptoms and PEFR	
	39 children with "asthma symptoms", 10-12 years, 54% male	~82	~82	PM ₁₀ , M(R) 76 (7-251)	URS LRS Cough	1.3 1.4 1.4	1.1-1.6 1.1-1.7 1.2-1.7	PEFR	-30 (-49--11)		
Koenig et al, 1993 (156) - Seattle (WA), winters 1988-1990	298 schoolchildren, ~8-11 years (3rd-6th grade), ~50% male	-	~2	PM _{2.5} , M-15 ? (in 1991)	-	-	-	FVC FEV _{1.0}	+10 (-1-+22) +5 (-7-+16)	PM _{2.5} was estimated indirectly from light scattering data (nephelometry).	
	30 asthmatics, ~8-11 years (3rd-6th grade), ~50% male	-	~6	-	-	-	-	FVC FEV _{1.0}	-55 (-83-28) -51 (-83-19)	Mean PM _{2.5} level estimated from figure	
Schwartz et al, 1994 (157) - Six US cities, 1985-1988	1844 schoolchildren, ~7-10 years (2nd-5th grade)	153	-	PM ₁₀ , Md(R) 30 (?-117)	URS LRS Cough	1.4 2.0 1.4	1.0-2.0 1.4-3.0 1.1-1.9	-	-	-	
Neas et al, 1995 (158) - Uniontown (PA), summer 1990	83 schoolchildren, ~9-10 years (4th-5th grade), 57% male, (no asthma)	-	43	PM _{2.5} , M(R) 24 (?-88)	Cough Wheeze, cold	1.6 Similar effects	1.1-2.3	PEFR	-28 (-55-+0.3)	Effect possibly attributable to particle strong acidity.	
Linn et al, 1996 (159) - Los Angeles area (CA), autumn-spring 1993-1994	269 schoolchildren, ~9-10 years (4th-5th grade), 51% male	~16	~16	PM ₅ , M(R) 24 (1-145)	Respiratory symptom score not related to pollutants	-	-	FVC FEV _{1.0}	-13 (-22-4) -6 (-15-+4)	-	

(continued)

Table 4. Continued.

Study	Size of study data set for the analyses ^a			Measurement data (particle measure and levels) ^{d,e}	Outcome estimates or short summary of results					Comments
	Study subjects	Data points per subject ^a			Symptoms studied and effect per 50 µg/m ³ PM ₁₀			Lung function change in ml (PEFR: ml/s) per 50 µg/m ³ PM ₁₀		
		Diary days ^b	Pulmonary test days ^c		Symp-tom	OR ^f	95% CI ^f	Test	Change ^g & 95% CI	
Dassen et al, 1986 (160) - IJmond area (The Netherlands), winter 1984–1985	163 schoolchildren, 7–11 years	2		TSP, R ?– ~220				FVC FEV _{1.0} PEFR	Significantly lower Significantly lower Significantly lower	Episode-post-episode test compared with baseline test. Other lung parameters also negatively affected.
Braun-Fahrländer et al, 1992 (161) - Basel & Zurich (Switzerland), 1985–1986	Random sample of 625 Swiss children, 0–5 years, 48% male	42		TSP Md(R) 43 (33–117)	URI Cough, dyspnea (daily incidence): no significant effect	1.5	1.1–2.1			6-week mean TSP also associated with incidence and duration of URI and cough.
Hoek & Brunekreef, 1994 (162) - 4 towns (The Netherlands), winters 1987–1990	695 (diary) & 782 (lung function) children, 7–11 years, ~50% male	~90	5–10 (mean 8)	PM ₁₀ , M(R) 45 (14–126)	URS, LRS, cough (both, prevalence and incidence): no clear effect of air pollutants			FVC FEV _{1.0} MMEF PEFR	+1 (-5–+6) -5 (-11–+1) -26 (-43–-9) -41 (-69–-13)	Four nonindustrial towns.
Hoek & Brunnekreef, 1993 (163) - Wageningen (Holland) winter 1990/1991	59 (diary) & 90 (lung function) children, 7–12 years, 57% male	98	5–7 (mean 6.5)	PM ₁₀ , R 30–144	URS, LRS, cough: no clear effect on prevalence for air pollutants despite air pollution episode			FVC FEV _{1.0} MMEF PEFR	-30 (-41–-19) -28 (-37–-18) -32 (-55–-9) -41 (-90–+8)	Lung function parameters similarly associated also with BS and SO ₂ .
Hoek et al, 1993 (164) - Deurne (The Netherlands), spring/summer 1989	314 children, 7–11 years, ~50% male		8	PM ₁₀ , only 1 day >100				PEFR	-109 (-180–-37)	Clear O ₃ effects also.
Hoek & Brunekreef, 1995 (165) - Deurne (The Netherlands), spring/summer 1989	241 children, 7–11 years, 49% male	~94		PM ₁₀ , M(R) 48 (13–124)	URS, LRS, cough, any. respiratory symptom: no association to PM ₁₀					Also no association with O ₃ , SO ₂ , NO ₂ , SO ₄ , or NO ₃ .
von Mutius et al, 1995 (166) - Leipzig (Germany), 1991–1992	1492 schoolchildren 9–11 years, 47% male	1 physician's examination per child (Md 15 subjects/day)		PM/TSP, Md(R) ~105 (~30–270)	URS (daily prevalence): OR significantly increased for daily mean NO _x , SO ₂ , and daily maximum PM					Confounders assessed by parent questionnaire.
Studnicka et al, 1995 (167) - Summer camp (Austria), 1991	133 children in rural summer camps, ≥7 (mean 10) years, 51% male		Up to 19	PM ₁₀ , M(R) 9 (5–58)	URS (daily prevalence): OR significantly increased for daily mean NO _x , SO ₂ , and daily maximum PM			FVC FEV _{1.0} PEFR	-18 (-99– +64) -67 (-143–+10) -99 (-294–+96)	Similar effects for H ⁺ (mean level ~20 nmol/m ³).
Scarlett et al, 1996 (168) - Surrey (England), summer 1994	154 schoolchildren, 7–11 years, 41% male		~27	PM ₁₀ , M(R) 71 (20–150)				FVC, FEV _{0.75}	-9 (-14–-3) -3 (-8–+1)	No relation to O ₃ or NO ₂ .
Awasthi et al, 1996 (169) - Lucknow (India), 1993–1994	664 slum children, 1 month-4.5 years, 56% male	~13		SPM, M(R) 370 (187–547)	“Respi-ratory symptom complex”	1.1	1.0–1.2			Very high SPM levels. Six months of interview data (biweekly) per child.

(continued)

Table 4. Continued.

Study	Size of study data set for the analyses ^a			Measure- ment data (particle measure and levels) ^{d,e}	Outcome estimates or short summary of results						Comments
	Study subjects	Data points per subject ^a			Symptoms studied and effect per 50 µg/m ³ PM ₁₀			Lung function change in ml (PEFR: ml/s) per 50 µg/m ³ PM ₁₀			
		Diary days ^b	Pulmo- nary test days ^c		Symp- tom	OR ^f	95% CI ^f	Test	Change ^g & 95% CI		
Krzyzanowski et al, 1992 (170); Lebowitz et al, 1992 (171) - Tucson (AZ), 1986–1988	287 children 6–15 years, 53% male, 13% asthmatic 523 adults, ≥16 years, 54% male 9% asthmatic, all non-smokers	~17	~10	.	.	Allergic or irritant symptoms related to the interaction between high PM and high O ₃ for both groups	.	PEFR	Negative PM effect overall for both groups	.	
Ostro et al, 1993 (172) -South California, 1978–1979	321 nonsmoking adults, ≥18 years, 48% male	181	.	CoH, M(R) 1.2 (0.4–2.6)	LRS, URS: no effect of CoH for either symptom, but LRS affected by SO ₄	.	.	.	.	SO ₄ was 2–37 (mean 8) µg/m ³ . LRS related also to O ₃ .	
Whittemore & Korn, 1980 (173) - Los Angeles area (CA) 1972–1975	259 child & 184 adult asthmatics in several different communities, ≤16 years, 64% male; >16 years, 35% male	.	.	TSP, R of daily Md 51–121 across com- munities	Asthma attacks	1.07 1.02– 1.13	.	.	.	Effect similar for adults and children.	
Ostro et al, 1991 (174) - Denver (CO), winter 1987–1988	207 asthmatics, 18–70 years, 34% male	90	.	PM _{2.5} , M(R) 22 (1–73)	Asthma rating: associ- ated with PM _{2.5} and H ⁺ Cough, dyspnea: More effect with H ⁺ (mean 10, range 2–41 neq/m ³)	.	.	.	.	Some symptom associations with SO ₄ , but not with NO _x or nitric acid.	
Quackenboss et al, 1991 (175) - Tucson (AZ) 1986–1988	30 asthmatic children, 6–15 years, 58% male	.	Up to 12	Indoor PM _{2.5} (& others)	Increased allergic symptoms: related to PM ₁₀	.	PEFR (morn- ing)	-450 (-58–842)	PEFR change per 50 µg/m ³ PM ₁₀ estimated based on measured indoor PM _{2.5} .		
Pope et al, 1991 (176) - Utah Valley (UT), winter 1990–1991	34 schoolchildren with “asthma symptoms”, 9–11 years, 62% male	~90	~90	PM ₁₀ , M(R) 46 (11–195)	URS LRS RM use XM use	1.2 1.3 1.6 1.7	1.0–1.4 1.1–1.6 1.1–2.2 1.1–2.6	PEFR	-53 (-84–22)	Stronger total effects on PEFR in both groups with multiple-day polynomial- distributed lag models.	
	21 asthma patients, 8–72 years, 48% male	~90	~90	PM ₁₀ , M(R) 46 (11–195)	URS LRS RM use XM use	1.0 1.0 1.2 1.8	0.8–1.2 0.8–1.3 0.9–1.6 1.3–2.5	PEFR	-13 (-60–+35)		
Pope & Kanner, 1993 (177) - Salt Lake City (UT) 1987–1989	251 current smokers with mild COPD, 35–60 years, 69% male	.	2	ΔPM ₁₀ M(R) 30 (0–133)	.	.	.	ΔFVC ΔFEV _{1.0}	-15 (-44–+14) -29 (-51–+7)	Effect of ΔPM ₁₀ between 2 test sessions on ΔFVC or ΔFEV _{1.0} .	
Silverman et al, 1992 (178) -Toronto (Canada) summer & winter	17+19 asthmatics, mean age 48 years, 25% male	.	PM ₂₅ & PM ₁₀ (personal)	Up to 20	.	.	.	FVC & FEV _{1.0}	Negative effect in summer, overall positive in winter	Interaction between negative PM effect & positive effect of medication use in winter. Personal exposure sampling used.	

(continued)

Table 4. Continued.

Study	Size of study data set for the analyses ^a			Measurement data (particle measure and levels) ^{d,e}	Outcome estimates or short summary of results					Comments
	Study subjects	Data points per subject ^a			Symptoms studied and effect per 50 µg/m ³ PM ₁₀			Lung function change in ml (PEFR: ml/s) per 50 µg/m ³ PM ₁₀		
		Diary days ^b	Pulmonary test days ^c		Symp- tom	OR ^f	95% CI ^f	Test	Change ^g & 95% CI	
Forsberg et al, 1993 (179) - Piteå (Sweden), March-April	31 asthmatics, 9–71 years, 42% male	49		BS, M(R) 7.1 (1–21)	Dyspnea Cough, phlegm	2.3 No effect	0.1–52 per 10 µg/m ³ BS ^h			Very low BS levels. However, nearby 12-hour TSP was a mean of 35 and a maximum of 101.
Roemer et al, 1993 (180) - Wageningen & Bennekorn (The Netherlands), winter 1990–1991	69 (diary) & 67 (PEFR) children with chronic respiratory symptoms, 6–12 years, ~55% male	50–83	~71	PM ₁₀ , R 10–174	Wheeze, BD use: prevalence related to daily PM ₁₀ , BS and SO ₂ Asthma attacks, dyspnea, cough, phlegm, runny nose: less clear relation between prevalence and daily PM ₁₀ , BS and SO ₂		PEFR (evening) PEFR (morning)	-23 (-49–+3) -34 (-59–10)		Prevalence effects generally stronger for weekly means of air pollutants. Symptom <i>incidence</i> showed few clear associations.
Dusseldorp et al, 1995 (181) - Wijk aan Zee (The Netherlands) 11 October–22 December 1993	32 patients with obstructive airway disease, 26–79 years, 34% male	17–67	66	PM ₁₀ , M(R) 54 (4–137)	Cough Wheeze Phlegm Dyspnea BD use RM use	1.1 1.2 1.1 1.2 1.1 1.1	1.0–1.3 1.0–1.5 0.9–1.3 1.1–1.4 1.0–1.2 1.0–1.2	PEFR (evening) PEFR (morning)	-45 (-81–9) -77 (-119–34)	Results given for a lag time of 0, except wheeze, dyspnea and RM use (lag time 2 days).
Romieu et al, 1996 (182) - Mexico City (Mexico) 1991–1992	71 children with light asthma, 5–13 years, 70% male	Up to 60	50	PM ₁₀ , M(R) 167 (29–363)	LRI Cough Wheeze Phlegm Dyspnea BD use	1.2 1.3 1.1 1.2 1.2 1.0	1.1–1.4 1.2–1.4 0.9–1.3 1.0–1.5 1.0–1.3 0.9–1.0	PEFR (evening) PEFR (morning)	-80 (-133–28) -78 (-128–28)	
Peters et al, 1996 (183) - Erfurt & Weimar (Germany) & Sokolov (Czech Republic) 1990–1992	102 (for PM ₁₀ only 72) asthmatic adults, 32–80 years, ~46% male 155 (for PM ₁₀ only 110) children, 7–15 years, ~63% male	~179 (~145)	~179 (~145)	PM ₁₀ , M(R) ~60 (?–247) PM ₁₀ , M(R) ~60 (?–247)	Symptom score: increase with PM ₁₀ , stronger for 5-day mean for both groups and also increase with SO ₂ , SO ₄ , and particle strong acidity			PEFR PEFR	-19 (-42–+4) -19 (-35–2)	SO ₂ and SO ₄ best predictors overall, especially for 5-day mean. PM ₁₀ only available for Erfurt & Sokolov 1991–1992 (most data; number of subjects, diary days and test days in parentheses)
Peters et al, 1997 (184) - Sokolov (Czech Republic), winter 1 September 1991 – 31 March 1992	89 asthmatic children, 6–14 years, 63% male	~151	~151	PM ₁₀ , M(R) 55 (3–171)	Cough Phlegm Dyspnea Runny nose Fever BD use	1.1 1.1 1.2 1.1 1.2 1.3	1.0–1.2 1.0–1.2 1.1–1.3 1.0–1.1 0.9–1.5 1.1–1.6	PEFR (evening) PEFR (morning)	-29 (-61–16) -15 (-46–+15)	Estimates are for 5-day mean. Largest effect was for SO ₄ .
Peters et al, 1997 (185) - Sokolov (Czech Republic) 15 November 1991–4 February 1992	82 asthmatic children, 6–14 years, 61% male, both medicated and nonmedicated	77	77	SO ₄ , M(R) 8.8 (?–24)	Nonmedicated: similar to above. Medicated: effect for cough and BD use, little else.			PEFR	Little effect among nonmedicated, strong among medicated	Analysis stratified for asthma medication and based on SO ₄ as particulate air pollution indicator.
Thurston et al, 1997 (186) - “Asthma camp” (CT) 1 week in June 1991–1993	52+58+56 children with asthma, 7–13 years	5	5	SO ₄ , M(R) 7 (1–27), also H ⁺	BD use: effect for SO ₄ and H ⁺ . LRS: mainly effect for O ₃			PEFR	Suggested effect for SO ₄	O ₃ most consistently associated with health effects.
Gielen et al, 1997 (187) - Amsterdam (The Netherlands), summer 1995	61 chronically ill schoolchildren, 77% on asthma medication, 7–13 years	35–46	35–46	PM ₁₀ , M(R) 30 (16–60), also BS	Cough, LRS, URS, BD use: positive effect of BS and PM ₁₀ but not of O ₃ .			PEFR (evening) PEFR (morning)	Most strongly associated with BS Most strongly associated with BS	Strongest associations with 5-day mean.

(continued)

Table 4. Continued.

Study	Size of study data set for the analyses ^a			Measure- ment data (particle measure and levels) ^{d,e}	Outcome estimates or short summary of results					Comments
	Study subjects	Data points per subject ^a			Symptoms studied and effect per 50 µg/m ³ PM ₁₀			Lung function change in ml (PEFR: ml/s) per 50 µg/m ³ PM ₁₀		
		Diary days ^b	Pulmo- nary test		Symp- tom	OR ^f	95% CI ^f	Test	Change ^g & 95% CI	
Peters et al, 1997 (93) - Erfurt (Germany) 1 October 1991– 31 March 1992	27 nonsmoking asthmatic adults, 44–80 years, 37% male	~100	~100	PM ₁₀ , Md(R) 59 (12–247)	Cough Phlegm, dyspnea, asthma attacks: no effect	1.3	1.2–1.5	PEFR (even- ing) PEFR (morn- ing)	-6 (-30–+18) -21 (-39–+4)	Stronger association with number of ultrafine particles.
Pekkanen et al, 1997 (92) - Kuopio (Finland) February–April 1994	39 asthmatic children, · 7–12 years, 54% male		34– 57	PM ₁₀ , M(R) 18 ?–60	·	·		PEFR (even- ing) PEFR (morn- ing)	-18 (-77–+40) -72 (-132–+12)	Estimates for daily mean PM ₁₀ , lag time 2 days. Stronger effect for 4-day mean. Not stronger effect for number of ultrafine particles.

^a Note that the number of days *do not* represent the entire study period. The approximate number of subjects and days of data or days of tests per subject for the analyses included in the table were extracted as possible from the publications to suggest the amount of data providing the results cited. Approximate person-days for the corresponding analyses are thus obtained by multiplying subjects x days or subjects x tests.

^b Number of days of diary data per subject.

^c Number of days with PEFR or full pulmonary test data per subject.

^d Conversion factors: PM₁₀ ≈ PM₁₅ ≈ BS ≈ SO₄ × 4 ≈ PM_{2.5}/0.60 ≈ CoH [in units of 10³ linear feet, used in most studies] × 55 ≈ TSP × 0.55 (12,13) and PM₁₀ ≈ light scattering (by nephelometry, in units of 10⁻⁵/m) × 10 (14,15), with remaining particle measures in milligrams per cubic meter.

^e Median (Md) is used when the mean (M) was not available (R=range). Mostly daily mean levels are used.

^f OR and 95% CI (in parentheses) per 50 µg/m³ PM₁₀ (measured or calculated), unless otherwise indicated.

^g Milliliters (PEFR: ml/s) per 50 µg/m³ PM₁₀ (measured or calculated), unless otherwise indicated. 95% CI values in parentheses. (* = significant, Md = median, M = mean).

^h Ratio of PM₁₀ to BS may be as high as 3 (value for Umeå, also in northern Sweden) (11).

group were less consistent across episodes. Effects of the acid haze and O₃ were difficult to separate.

In two studies comparing healthy children with asthmatics, slightly stronger effects of particulate pollution on PEFR among the children with asthma symptoms were found in Utah (155). Similarly, in Seattle, with heavy particulate pollution from wood burning in winter, decrements in the lung function parameters FVC and FEV_{1.0} in association with particle levels were seen in asthmatics, but this time not at all in healthy children (156). However, two subsequent US studies again found discrete but observable effects in healthy children. In Uniontown, Pennsylvania, 83 nonasthmatic children who recorded PEFR values in summer exhibited moderate decrements associated mainly with PM_{2.5} and particle strong acidity (158), and in another study on healthy schoolchildren in Los Angeles, FVC and FEV_{1.0} were weakly associated with particulate air pollution (159).

For Dutch children, significant decrements in several lung function parameters were observed up to 16 but not 25 days after an air pollution episode with TSP in the range of 200–250 µg/m³ when the figures were compared with pre-episode baseline data (160). Later, more ambitious Dutch studies on large numbers of children repeated the observation of decrements in lung

function parameters most consistently related to PM₁₀, especially for PEFR and MMEF, both for healthy children (162, 163) and children with chronic respiratory symptoms (180) (summarized in reference 188). In the largest study, slightly stronger effects were again observed in a subgroup of children with physician-diagnosed asthma, but the numbers were small (N=27) (162). In a spring-summer study in The Netherlands that focused on photochemical air pollution, independent effects of both O₃ and PM₁₀ on PEFR were also noted (164). Similarly, lung function decrements related to particulate air pollution have been reported in Austria (167) and southern England (168).

Symptoms. For Pennsylvania elementary-school children who recorded symptoms daily during 8 months, only low temperature was significantly related to lower respiratory symptoms (eg, wheeze, dyspnea, chest tightness, phlegm) and upper respiratory symptoms (eg, cough, sore throat, runny or stuffy nose, sneezing) in multivariate analyses (153). An increased OR for lower respiratory symptoms was, however, suggested in relation to the CoH. In the Utah study already mentioned, which compared healthy children with asthmatics, 5-day PM₁₀ averages were related to cough and lower respiratory symptoms among both healthy and asthmatic

children, but to upper respiratory symptoms only among asthmatics (155). In children from the Harvard Six Cities Study, cough was associated with both the O_3 and PM_{10} levels. For lower respiratory symptoms, the OR was higher, with a monotonic concentration-response relationship, and a similar effect was suggested for upper respiratory symptoms (157). For schoolchildren in Uniontown, Pennsylvania, studied in the summer with PEFR and symptom diaries, cough was associated with particulate measures, including $PM_{2.5}$ and particle strong acidity but also with O_3 and SO_2 (158). Similar associations were seen for wheeze and cold, and the associations were stronger when weighted by the proportion of hours spent outdoors during the previous 12 hours. Another study on schoolchildren in Los Angeles found no association between air pollution and a respiratory symptom score (159).

In a Swiss study, the incidence and duration of symptoms were reported daily in diaries from May to October. TSP was related to daily incidence rates of fever with earache and sore throat (upper respiratory infection). Another set of analyses examined 6-week averages of air pollutant levels and found that the TSP averages were related to both the incidence and duration of coughing and upper respiratory infection, but not to episodes of breathing difficulty. Some relationships were also found for NO_2 , but not for O_3 (161). Two later large Dutch studies on healthy children in winter found no consistent relationships between air pollutants and the daily prevalence or incidence of respiratory symptoms as reported in diaries (162, 163), nor did yet another spring-summer study in The Netherlands, which focused on photochemical air pollution (165). Among Dutch children with chronic respiratory symptoms, however, the daily prevalence but not the incidence of various symptoms, in particular wheeze, was related to PM_{10} , SO_2 , and BS but not to NO_2 , and the relationships appeared to be stronger for the weekly average air pollution variables than for the same-day or lagged variables (180).

In Leipzig, former East Germany, a large number of children was examined by a physician for upper respiratory symptoms. In a logistic regression analysis, statistically elevated OR values for such symptoms were observed in relation to the daily mean nitrogen oxides (NO_x), SO_2 , and daily maximum particulate matter (PM) levels (166). A study in India with even higher levels of suspended particulate matter (SPM) observed a statistically significantly elevated OR for a respiratory symptom complex ascertained in home interviews (169).

Lung function changes and symptoms in healthy adults

The only study available on PM and lung function in healthy adults focused on indoor-outdoor exposures and

respiratory effects in Tucson, Arizona, with basic screening data on 2322 persons (189). A subsample of primarily families with children was studied with detailed health questionnaires, skin prick tests, blood analyses, and pulmonary function tests. The exposure evaluation included household inventory questionnaires, personal or household samplers for NO_2 , particulates, and formaldehyde and ambient air monitoring data. Both outdoor PM and O_3 were associated with a decrease in PEFR in the whole study population (adults and children, mostly nonasthmatics) (171). Further analysis specifically addressed O_3 and found evening PEFR to be decreased by O_3 exposure, especially among asthmatics who spent much time outdoors (170). The effects of both O_3 and PM_{10} were stronger when the level of the other pollutant was high and at high temperatures. An increase in allergic or irritant symptoms related to the interaction between outdoor PM_{10} and the 8-hour maximum O_3 concentration was also suggested (170, 171). In another study of symptoms in nonsmoking adults during winter in greater Los Angeles, an increased OR of lower respiratory symptoms but not upper respiratory symptoms was related to both SO_4 and O_3 , but not significantly to CoH as a measure of particulate air pollution (172). Further data on healthy adults are not available.

Lung function changes, symptoms and symptom exacerbation in subjects with a respiratory disease

Lung function. For 30 asthmatic children in the Tucson study already described, the indoor $PM_{2.5}$ levels were associated with a decreased morning PEFR, and a similar effect was found in relation to PM_{10} measured by personal monitoring (175). A study in Utah found stronger effects on the PEFR (and symptoms) of children with light "asthma symptoms" than in a group of clinic-recruited asthmatics of all ages (176). Extra medication use among the diagnosed asthmatics was, however, strongly related to PM_{10} . The authors concluded that symptoms and pulmonary function among these asthmatics were possibly being managed by medication and life-style changes. Evidence for cumulative effects over several days was found using cumulative lag-time models. Another, previously mentioned, Utah study observed a similar effect on PEFR among children with "asthma symptoms" (155). A third Utah study on adults who were current smokers with moderate COPD measured FEV_{1.0} and FVC on two occasions and found an association with the difference in the PM_{10} levels between the test sessions (177). For more severely ill asthmatics in a Canadian study, negative effects on the same parameters were observed in summer but not in winter. In winter, however, an interaction between medication use and particulate levels was noted, the finding suggesting again that a main negative effect may be modified by

medication use (178). Among children, too, effects on these parameters in asthmatics have been noted (156). A large number of recent studies has found moderate negative effects on PEFr with the use of various particulate measures, both for children (180, 182–187) and adults (181, 183). In some studies, especially focusing on more severely ill asthmatics, bronchodilator use may have modified the effect observed (186, 187). Most studies, except one from Mexico City (182), found bronchodilator use to be associated with particles. In a study from the Czech Republic, medication was mainly with theophylline, and the effect of particulate air pollution measured as SO_4 was stronger among the medicated subjects (185). Several studies noted stronger effects for multiple-day average particulate concentrations (92, 180, 184, 187) or multiple lag times (155) or particulate levels more than 1 day previously (181). These findings may reflect the true time course and cumulative effects of particulate exposure on PEFr. It is also possible that extra medication use may modify the effect observed for recent exposure more than for exposure several days ago.

Recently it has been hypothesized that the large number of ultrafine particles in urban air may be the explanation for the observed health effects related to low levels of PM_{10} or other particulate measures (90). A study in Erfurt, in eastern Germany, with particulate emissions from the burning of brown coal included 27 adult asthmatic nonsmokers and focused on fine and ultrafine particles (93). Morning and evening PEFr values were related to daily PM_{10} , but the relationship appeared to be stronger for longer averaging times and for smaller particle fractions. Most of the particles (73%) were in the ultrafine fraction (<0.1 per μm), whereas most of the mass (82%) was attributable to particles in the size range 0.1 to 0.5 per μm . The two fractions were only moderately correlated, and the effect was stronger for the number of ultrafine particles than for measures of particle mass. A Finnish study attempting to replicate these results in children with asthmatic symptoms did not, however, find that the number of ultrafine particles was more strongly associated with PEFr than PM_{10} and BS concentrations were (92). The main emission source in this study was road traffic.

Symptoms. An early large study on asthmatics, both adults and children, in the United States found a small but significant increase in asthma attacks in relation to TSP exposure (173), and in another study of only adult asthmatics, asthma ratings were associated with $\text{PM}_{2.5}$ and acid particles (H^+), cough mainly with H^+ (174). For 30 asthmatic children in the Tucson study already described, increased allergic symptoms were related to PM_{10} exposure (175). As noted previously, the study in Utah found generally stronger effects of PM_{10} on vari-

ous symptoms in children with light “asthma symptoms” than in a group of clinic-recruited asthmatics of all ages, whereas the opposite was true for extra medication use (176). A Swedish study with very low levels of BS found no effect of air pollution levels on cough or phlegm in asthmatics of all ages, but dyspnea appeared to be related to BS levels (179). Other later studies have often observed associations between particulate air pollution and shortness of breath and dyspnea, wheeze and bronchodilator use, as well as cough and phlegm, for both children (180, 182–187) and adults (181, 183). Modification of the effect observed by medication use is a clear possibility in this case too, especially among adults who are better able to modulate their medication. The longer optimal lag time for dyspnea and wheeze than for cough and phlegm in one study (181) and the association only for cough in another (93) suggest that medication may modify primarily the immediate effect on asthma-type symptoms.

In the Erfurt study focused on ultrafine particles, PM_{10} and various number and mass particle fractions were related to feeling ill during the day and to cough among 27 asthmatic nonsmokers (93). The OR values were similar across an interquartile range for different particulate measures. Asthma attacks, dyspnea, and phlegm showed no association.

Evaluation

Particulate air pollution has been related to both the respiratory symptoms and lung function of healthy persons. Mostly children have been studied, often in the age span 5–15 years. The lung function decrements are of a relatively limited magnitude (ie, only about 0.5–1.5% per 50 $\mu\text{g}/\text{m}^3$ increase in PM_{10} levels). The largest database and most consistent effects concern PEFr, for which an effect was usually found and the absolute decrements centered around 30–60 ml/s. The decrements were often more strongly related to longer averaging or lag times than to previous-day levels, and therefore they raise the possibility of persistent, chronic effects. A comparison with O_3 suggests that different etiologic mechanisms may be operating. Short-term peaks of O_3 show a clear association to lung function decrements and some association to symptoms, but chiefly at high concentrations or high exposure levels due to increased physical activity (98). In contrast, the particle effect appears to be related to longer averaging or lag times, and the effect on symptoms is clearer and seems to exist even at relatively low exposure levels. The results for symptoms are, however, not fully consistent. Several studies observed no significant relationships for various end points. Many others reported increased OR values. Results appeared more consistent for lower respiratory

symptoms and cough than for upper respiratory symptoms, with generally a 10–40% excess RR associated with a 50 $\mu\text{g}/\text{m}^3$ increase in the PM_{10} level when an effect was observed. Among asthmatics, a somewhat stronger effect on pulmonary function has often been observed, while no stronger effect on symptoms has been found. Extra asthma medication, generally bronchodilator use, has mostly been associated with particulate exposure and may modify the observed effect on symptoms and lung function.

Miscellaneous health effects in relation to medium-term exposure

Table 5 lists studies of some additional health outcomes in relation to particulate pollution levels during the last weeks to months (131–133, 190–204).

Ostro & Rothschild (190–192) studied adults from the US National Health Interview Survey from 1976 to 1981, in which over 100 000 persons responded nationwide to questions on acute illnesses during the previous fortnight. $\text{PM}_{2.5}$ and O_3 were studied as air pollutant exposures. The number of “restricted activity days” (particularly respiratory-related) for each person was related to the particulate levels but not to the O_3 concentrations. For minor restrictions in activity (minor restricted activity days, excluding more serious work loss or bed disability conditions), O_3 showed a weak association. In a subset analysis controlling for active and passive smoking exposure, a 1–3% increase in respiratory-related restricted activity days among adults, as well as a 1% increase in bed disability days among children, was estimated per microgram-per-cubic-meter increase in the 2-week average $\text{PM}_{2.5}$ levels (193). When alternative particulate measures were investigated in the whole adult sample in 1979–1981, it was suggested that SO_4 was more strongly related to health effects than TSP, PM_{10} , or $\text{PM}_{2.5}$ (194). School absenteeism as a marker of illness was investigated in Utah Valley and found in two separate analyses to increase from approximately 4% to 6% with an increase of 100 $\mu\text{g}/\text{m}^3$ in the average PM_{10} level during the previous month (195). Hospital admissions for respiratory disease adjusted for temporal trend and meteorological variables (131–133), as well as pulmonary function decrements in children (196), have also been found to be associated with 4-week average PM_{10} levels, with a magnitude similar to that reported for the association with shorter averaging times (see tables 2 and 4). In a study from Hong Kong, quarter-yearly hospital discharge rates in the age group 1–4 years were also related to TSP levels (197), but long-term temporal trend and meteorological variables were not adjusted for. Because of the few data

points this analysis was inconclusive, and the result may largely reflect coincidentally correlated secular trends for TSP and asthma discharges among 1- to 4-year-olds over the 27 quarters. A similar relationship was not found in other age groups.

In Beijing, with high levels of TSP and SO_2 , pregnancy outcomes were studied. Preterm delivery was associated with the average TSP level during the week before delivery (198) and low birthweight (<2500 g) was associated with the average TSP levels during the third trimester of pregnancy (199). This relation held also on average, with an estimated average reduction in birthweight of 6.9 grams for each 100 $\mu\text{g}/\text{m}^3$ increase. For all outcomes, similar results were obtained with SO_2 as the air pollution indicator.

Sudden infant death syndrome is defined as the sudden death of an infant who was previously well, without any explanation found after examination and autopsy. It has been shown to be associated with passive smoking (205) and a prone sleeping position (206). Air pollution has also been implicated in its causation. The available studies are described in this section as the designs vary and the hypotheses tested include effects from both shorter and longer exposures. Three early studies that did not include particulate measures as such are mentioned briefly. A study in Chicago found no association between SO_2 exposure and sudden infant death syndrome, the only consistent finding being an inverse relationship between the syndrome and temperature (207). Pursuing a possible link, Hoppenbrouwers et al (208) found that deaths from sudden infant death syndrome peaked in Los Angeles a few weeks after air pollution peaked in midwinter, the finding suggesting an effect of air pollution. However, confounding by winter infections, which also peaked at that time, could not be excluded. Finally, a cross-sectional study in Germany found an increased incidence of sudden infant death syndrome in districts with a poor air quality index (209). Particulate air pollution in a subtropical climate (Brisbane, Australia) tended, on the average, to decrease from a slightly elevated level on the days prior to a death from the syndrome, and visibility increased during the days around the death (table 5) (200). The analyses were not multivariate, and the authors hypothesized an effect by light or increasing outdoor exposure on successively clearer days. More recently an association between sudden infant death syndrome and low visibility was reported from Taiwan (201). A longer averaging time gave a stronger result than daily visibility, the OR being 5.1 (95% CI 3.2–8.1) for the lowest category of average visibility 1 to 9 days before death when compared with the highest, in a multivariate analysis controlling for socioeconomic, weather, and disease confounders. Another study with more individual-level data and PM_{10} measurements from the United States found an OR of 1.26

Table 5. Studies of miscellaneous health effects in relation to short-to-medium-term exposure to particulate air pollution. (For abbreviations, see page 4.)

Study	Characteristics of study population	Exposure measure and levels ^a	Outcome	Results
Ostro, 1983 (190); Ostro, 1987 (191); Ostro & Rothschild, 1989 (192); Ostro, 1989 (193); Ostro, 1990 (194) - US (Health Interview Survey) 1976–1981, 1979–1981	~70 000 adults, 18–65 years, in total; ~5300 adults, 18–65 years, with smoking data; 1575 children, ≤6 years with parental smoking data; during 2 weeks	2-week means, SO ₄ ~8, PM _{2.5} ~23, TSP ~69	Restricted activity days (ie, work loss, bed confinement or minor restrictions); minor restricted activity days; work loss days; respiratory-related restricted activity days; bed disability days (children)	Restricted activity days: ~+0.5% per µg/m ³ PM _{2.5} . Work loss days: less consistent, up to +1.5%. Minor restricted activity days: +0–+1%, but more consistent association with O ₃ . Respiratory-related restricted activity days: +1–+3% per µg/m ³ PM _{2.5} . Bed disability days (children): +1%. Stronger results with 2-week lag time.
Ransom & Pope, 1992 (195) - Utah Valley (UT) 1985–1990	~1000 children, kindergarten–6th grade, during 1065 days; ~6800 children, 1st–6th grade, during 169 weeks	4-week mean PM ₁₀ 50	Daily or weekly school absence rates	Approximately 40% increase in absences per 100 µg/m ³ of PM ₁₀ (4-week mean). Similar results for kindergarten children.
Pope, 1989 (131); Pope, 1991 (132) - Utah Valley (UT) 1985–1988 Utah, Salt Lake & Cache Valleys (UT) 1985–1989	4742 pneumonia, 1635 bronchitis, 1914 asthma admissions; 48 months of data	Monthly mean PM ₁₀ 22–120	Monthly admissions for pneumonia, chronic bronchitis and asthma; all ages and preschool children	Approximately 3–7% increase in respiratory admissions (all ages) for 10 µg/m ³ increase in PM ₁₀ over a month or more (133). Slightly stronger among preschool children.
Spektor et al, 1991 (196) - Cubatao (Brazil) 1988	456 children, 55% male; 6–8 monthly lung function tests per subject	4-week mean PM ₁₀ (levels not given)	Lung function (annual mean PM ₁₀ was 59–110 in different school locations)	FVC -6 ml per 50 µg/m ³ PM ₁₀ . FEV _{0.1} -22 ml per 50 µg/m ³ (significant), PEFR -99 ml/s per 50 µg/m ³ (significant), MMEF -92 ml/s per 50 µg/m ³ (significant) (mean regression slopes, weighted by number of children in each school)
Tseng et al, 1992 (197) - Hong Kong, 1983–1989	Mean quarterly asthmatic hospital discharge rates: 15.4/10 ⁵ (0–1 years), 122.1/10 ⁵ (1–4 years), 106.1/10 ⁵ (4–15 years), 24.6/10 ⁵ (>15 years)	TSP quarter-yearly mean 54–136	Age-category-specific quarterly asthmatic hospital discharge rates – 27 quarters available for analysis	Discharge rates among 1- to 4-year-olds related to TSP. No significant association to air pollutants for 0–1 years. For 4–15 and >15 years only negative association with SO ₂ and NO _x .
Xu et al, 1995 (198) - Beijing (China) 1988	25 370 women, ≥20 years	1-week mean TSP 375	Preterm delivery	OR 1.10 (95% CI 1.01–1.20) per 100 µg/m ³ . Similar effect for SO ₂
Wang et al, 1997 (199) - Beijing (China) 1988–1991	74 671 live first-parity births	3 rd trimester median TSP 399	Low birthweight	OR 1.10 (95% CI 1.05–1.14) per 100 µg/m ³ . Reduction in birthweight 6.9 g (95% CI 4.2–9.6) per 100 µg/m ³ . Somewhat weaker effect for SO ₂ .
Aulicciems et al, 1987 (200) - Brisbane (Australia) 1967–1981	369 SIDS cases	Visibility index, lag times up to 30 days before or after tested	SIDS	On average, decreasing visibility index in week before SIDS death, from slightly elevated levels.
Knöbel et al, 1995 (201) - Taiwan, 1981–1991	3816 SIDS cases	Visibility, lag times up to 0 days or 1–9 days	SIDS	OR 3.8 (95% CI 2.8–5.1) for lowest versus highest visibility category. Slightly stronger using 9-day mean visibility.
Penna & Duchade, 1991 (202) - Rio de Janeiro (Brazil) 1985	27 study areas in Rio de Janeiro, mortality ~40/1000 (about ½ of which neonatal)	Annual mean TSP 74–227	Total mortality 0–1 years; pneumonia mortality 0–1 years; diarrheal mortality 0–1 years	Roughly 3–4% increase in pneumonia mortality per 10 µg/m ³ TSP. No significant effect on total or diarrheal mortality.
Bobak & Leon, 1992 (203) - Czech Republic, 1986–1988	~222 000 births; mortality 12.1/1000 (neonatal 8.2, postneonatal 3.9)	Annual mean PM ₁₀ 69	Total neonatal mortality, total postneonatal mortality, respiratory postneonatal mortality	Total neonatal mortality: OR 1.2 (95% CI 1.0–1.4). Total postneonatal mortality: OR 1.4 (95% CI 1.1–1.8). Respiratory postneonatal mortality: OR 2.4 (95% CI 1.1–5.3) – for highest to lowest quintile of PM ₁₀ exposure (>84.7 versus <53.6 µg/m ³). Similar results for SO ₂ .

(continued)

Table 5. Continued.

Study	Characteristics of study population	Exposure measure and levels ^a	Outcome	Results
Woodruff et al, 1997 (204) -US, 1989–1991	3 788 079 births; total postneonatal mortality 3.39/1000 (SIDS 1.10/1000, ie, ~4200 SIDS cases)	Individual 2-month mean PM ₁₀ 31, range 12–69	Total postneonatal mortality; respiratory postneonatal mortality (among normal birthweight and low birthweight babies separately); SIDS	Total postneonatal mortality: OR 1.4 (95% CI 1.05–1.85); SIDS: OR 1.26 (95% CI 1.14–1.39) for high to low PM ₁₀ exposure (3 categories) (PM ₁₀ mean 44.5 versus 23.6 mg/m ³). Total postneonatal mortality: +4% (95% CI +2–+7), respiratory postneonatal mortality (normal birthweight): +20% (95% CI +6–+36), respiratory postneonatal mortality (low birthweight): +5% (95% CI -9–+22), SIDS: +12% (95% CI +7–+17) per 10 mg/m ³ PM ₁₀ in a continuous analysis.

^a Short-to-medium-term air pollution levels [averaged over day(s), week(s), month(s), year or other period] with mean or range of values across study period, if available.

Table 6. Cross-sectional and cohort studies focusing on long-term health effects in relation to particulate air pollution. (For any abbreviations not found in the footnotes, see page 4.)

Study	Characteristics of study population	Exposure measure and levels ^a	Outcome ^b	Results
Cross-sectional studies				
<i>Mortality</i>				
Lave & Seskin, 1977 (210) Lave & Seskin, 1979 (212) - >100 SMSA 1960–1961 & 1969 Mendelsohn & Orcutt, 1979 (213) - Entire US in 404 county groups 1970 Lipfert, 1978 (211) Lipfert, 1980 (214) - 189 central cities 1969–1971 & 89 central cities 1959 Chapple & Lave, 1982 (215) - 104 SMSA 1975 Lipfert, 1984 (216) - 111 SMSAs 1970 Evans et al, 1984 (217) - Summarizes many cross-sectional studies on >100 US cities or SMSA 1960s–1970s Özkaynak & Thurston, 1987 (218) - 1980 US mortality rates (100 SMSAs)	Up to entire US population in ages relevant to analysis (up to ~150 million). Analysis units were cities, counties or SMSA.	Various particulate measures. Levels moderately high to high, declining over time.	Total mortality. Some studies also examined age-specific and cause-specific mortality.	Mean mortality effect of particles estimated at 3–8% of total mortality. Effect estimates often sensitive to choice of study area and model, including choice of demographic, social and other variables in the model. Some evidence for a stronger effect at ages >65 years, more inconsistent results for different causes of death. Suggested positive association for infant mortality [Lave & Seskin (210), Lipfert (211)]. See also 1996 US EPA report for further discussion (1).
Archer, 1990 (219) - Utah Valley (UT) 1950–1987	Three counties with low smoking rates.	TSP 40–93 (multiyear means), declining over time.	Cross-sectional and longitudinal differences in respiratory mortality, and the effect of a steel mill opening in 1 county.	In the most polluted county, 30–40% of respiratory disease deaths were associated with air pollution. Lung cancer death rates increased in the steel mill county in the decade after the mill opened.
<i>Respiratory symptoms or disease</i>				
Euler et al, 1987 (220) Euler et al, 1988 (221) - California 1966–1976	≥25 years, 7445 nonsmoking Seventh-Day Adventists	TSP; 25% of subjects had >750 hours per year at >200 mg/m ³	COPD	COPD associated with TSP, but also with oxidants and SO ₂ . Individual cumulative air pollution exposure estimated in this study.
Ware et al, 1986 (222) - Six US cities, 1976–1980	7–10 years, 8327 subjects	TSP R ₁ 39–114	Cough, bronchitis, LRI chest illness, wheeze.	Cough, bronchitis, LRI associated with TSP across cities.

(continued)

Table 6. Continued.

Study	Characteristics of study population	Exposure measure and levels ^a	Outcome ^b	Results
Dockery et al, 1989 (223) - Six US cities, 1980–1981	10–12 years, 5422 white children	TSP R ₁ 34–80, PM ₁₅ R ₁ 20–59	Cough, bronchitis, chest illness, asthma, wheeze, hay fever, earache.	Cough, bronchitis, chest illness associated with various particulate measures. Of these, PM ₁₅ provided significant estimates.
Portney & Mullahy, 1990 (224) - US (Health Interview Survey 1979)	17–93 years, 1318 subjects, 42% male	TSP, 6-year mean (1974–1979) R ₁ 35–140	Chronic bronchitis/asthma/emphysema, sinusitis, hay fever	Individual-level data on air pollution. Chronic bronchitis/asthma/emphysema associated with TSP.
Schwartz, 1993 (225) - 53 US urban areas (NHANES I)	30–74 years, 3874 subjects	TSP R ₂ 48–131	Diagnosed respiratory illness, reported bronchitis, reported asthma, reported dyspnea	Diagnosed respiratory illness and reported bronchitis, but not asthma or dyspnea, associated with TSP.
Walters et al, 1995 (249) - 24 UK electoral wards, 1988–1990	All ages & <5 years, 24 electoral wards	BS, levels not given	Respiratory admission rates, asthma admission rates	Weak nonsignificant association between BS and respiratory admissions. Only significant association was all respiratory admissions <5 years with NO ₂ .
Scarlett et al, 1995 (226) - 53 UK counties, 1981	23 years, 11 552 subjects	BS R ₁ 2–55	Phlegm, cough, wheeze	Only phlegm significantly associated with BS but not with SO ₂ .
Dockery et al, 1996 (227) - 24 communities in US & Canada, 1988–1991	8–12 years, 13 369 subjects, 50% male	PM ₁₀ R ₁ 15–33, H ⁺ R ₁ 0–52	Bronchitis, asthma, wheeze, cough, phlegm	Bronchitis related to particles, most strongly to H ⁺ (OR 1.7, 95% CI 1.1–2.5), and similarly to O ₃ and SO ₂ (neither significant). No other associations.
Braun-Fahrlander et al, 1997 (228) - Switzerland, 1992–1993	6–15 years, 4470 subjects, 50% male	PM ₁₀ R ₁ 10–33	Bronchitis, asthma, allergy, cough	Bronchitis, cough associated with PM ₁₀ , but not asthma or allergy.
Xu & Wang, 1993 (229) - Beijing, China 1986	40–69 years, 1576 never-smokers, 25% male	TSP 5-year mean R ₁ 261–449	Bronchitis, asthma, wheeze, cough, phlegm, dyspnea	OR for any symptom: 2.5 (95% CI 1.3–4.8) per ln(TSP) unit (ie. OR ~1.6 across range 261–449). Clearest effects for bronchitis, wheeze and cough.
<i>Lung function</i>				
Ware et al, 1986 (222) - Six US cities, 1974–1980	7–10 years, 8327 subjects	TSP R ₁ 39–114	FVC, FEV _{1.0}	No particle effect on FVC, FEV _{1.0} .
Dockery et al, 1989 (223) - Six US cities, 1980–1981	10–12 years, 5422 white children	TSP R ₁ 34–80, PM ₁₅ R ₁ 20–59	FVC, FEV _{1.0} , MMEF, PEFR	No effect on FVC, FEV _{1.0} , MMEF, PEFR.
Raizenne et al, 1996 (230) - 22 communities in US & Canada, 1988–1991	8–12 years, 10 251 subjects, 51% male	PM ₁₀ R ₁ 15–33	FVC, FEV _{1.0} , MMEF, PEFR	2–3% decrements of FVC, FEV _{1.0} , MMEF, PEFR for 1 standard deviation increase in PM ₁₀ .
Schwartz, 1989 (231) - 44 US locations (NHANES II) 1976–1980	6–24 years, 1849 subjects	TSP R ₃ 43–95	FVC, FEV _{1.0} , PEFR	Small significant particle effect on FVC, FEV _{1.0} , PEFR (but O ₃ effect stronger).
Chestnut et al, 1991 (232) - 49 US urban areas (NHANES I)	25–75 years, 963 subjects	TSP R ₁ 40–155	FVC, FEV _{1.0} , FEV _{1.0} /FVC, MMEF	Effect on FVC, FEV _{1.0} , but not FEV _{1.0} /FVC, MMEF.
Xu et al, 1991 (233) - 3 Beijing areas, China, 1986	40–69 years, 1440 subjects, ~25% male	TSP 5-year mean R ₁ 261–449	FVC, FEV _{1.0}	Effect on FVC, FEV _{1.0} by both TSP and SO ₂ . Study areas were residential, suburban and industrial.
Ackermann-Lieblich et al, 1997 (234) - 8 areas, Switzerland, 1991–1993	18–60 years, 3115 never-smokers, 39% male	PM ₁₀ R ₁ 10–33	FVC, FEV _{1.0}	Effect on FVC, FEV _{1.0} by NO ₂ , SO ₂ and PM ₁₀ , most consistently for PM ₁₀ .

(continued)

in particular for neonatal deaths. Three more recent studies have also examined infant mortality (table 5), two of them also using annual averages. In Rio de Janeiro, mortality from pneumonia (14% of infant deaths) but not total infant mortality (dominated by perinatal mortality) was associated with TSP levels (202). In the Czech Republic, neonatal mortality likewise showed only a suggested association, whereas postneonatal mortality, in particular respiratory mortality, was more associated with the annual PM_{10} levels (203). In the more elaborate US study already mentioned, individual estimates of PM_{10} exposure during the first 2 months of life were similarly associated with total and, especially, respiratory postneonatal mortality (204), whereas the OR per $10 \mu g/m^3$ for all other causes was 1.00 (95% CI 0.99—1.00).

Evaluation

Population-based cross-sectional studies have suggested an association between restrictions in activity, leading to work and leisure-time loss, as well as bed disability among children, and particulate air pollution levels over several previous weeks. Similar associations have been observed for school absences and lung function decrements among children and also suggested for respiratory hospital admissions among both children and adults. Preterm delivery and low birthweight has been associated with particulate air pollution during the week of delivery and 3 months before, respectively. A relation between sudden infant death syndrome and particulate air pollution has also been suggested, but data are not convincing, partly due to unclear exposure specifications regarding an appropriate particulate measure, averaging time, and exposure timing. Similar caveats apply regarding neonatal and postneonatal mortality, although the suggestion of an association particularly for respiratory postneonatal mortality is strong.

Health effects of long-term exposure

Long-term effects have been studied mainly with cross-sectional methodology and in a few cohort studies, as illustrated in table 6 (on pages 73-75) (88, 89, 203, 204, 210—247). Although the aim in cross-sectional studies is often to investigate long-term effects on health, observed effects can be due to short-term as well as long-term exposure. Long-term exposure may have effects that become manifest in the human organism as either chronic or acute diseases. In addition, the prevalence of an outcome is affected by both its incidence and its duration. Cross-sectional studies are therefore often problematic to interpret. Nevertheless, the more extensive evidence from cross-sectional studies has been reviewed first in this section, followed by the few cohort studies reported to date. It has been pointed out that,

since the variance in air pollution concentrations decreases as sampling (averaging) time increases, long-term studies intrinsically have less power than short-term studies. Unless individual long-term exposure can be adequately ascertained and there is sufficient mobility among the subjects, studies of long-term changes in health will tend to be studies of spatial differences in exposure with a longitudinal measure of health effects (248). Even so, a longitudinal follow-up will correctly observe the disease incidence, regardless of variations in disease duration, which may be desirable. Selection by the "healthy worker effect" (ie, sensitive persons avoid areas with high exposure) may be problematic, particularly in cross-sectional studies.

Cross-sectional studies

Mortality. Most of the early studies were large cross-sectional studies utilizing population mortality data and long-term average air pollution measurements from public monitoring networks in the United States (210—218). These cross-sectional analyses found that a proportion of total mortality (generally some 3—8%) appeared to be attributable to air pollution, especially SO_4 or fine particulate matter, despite attempts to control for demographic, social, health and other factors in the population in statistical modeling. It was, however, also shown that these results could be sensitive to the variables introduced into the models, and one conclusion by the mid-1980s was that individual-level data were needed for adequate control of confounding. One late analysis of this type suggested that $PM_{2.5}$ and SO_4 levels were more significantly and consistently associated with increased mortality than PM_{10} and TSP concentrations. The ranges of estimated effects for the various particulate measures on total mortality were 4—9% for SO_4 , 3—8% for $PM_{2.5}$, and 0—6% for PM_{10} and TSP (218). A more local study from Utah among chiefly nonsmokers found both nonmalignant and malignant respiratory mortality to be associated with variations in air pollution between the three studied areas over time, attributing 30—40% of respiratory mortality to air pollution (219).

Respiratory symptoms or disease. Two of the cohort studies to be described in this section have also reported cross-sectional results. The study of Seventh-Day Adventist nonsmokers in California included people who were resident within 8 km of their 1977 residence for at least 10 years and who completed the respiratory symptom questionnaires of the National Heart and Lung Institute in 1977 and again in 1987. Individual cumulative exposures (hours/year) to air pollutants above four threshold levels were estimated using residence zip codes and interpolated dosages from air-monitoring stations. Cross-sectional analyses of 1977 questionnaire

data were presented for SO₂ and TSP (220) and oxidants and NO₂, as well as combined analyses of all pollutants and interactions (221). The TSP thresholds were 60, 100, 150, and 200 µg/m³. The OR for COPD symptoms was 1.22 per 750 hours/year of exposure above a TSP concentration of 200 µg/m³ ($P < 0.00001$). Associations were also statistically significant for oxidants above 100 ppb and SO₂ above 40 ppb. In a multiple regression using all three air pollutants, TSP remained significant ($P < 0.01$), a finding suggesting that TSP was either more strongly associated with symptoms of COPD or was the best surrogate representing the mix of highly correlated pollutants (221). From the US Six Cities Study, an analysis of health examinations in 1975–1978 and air pollution levels in the previous year found that cough, bronchitis, and lower respiratory illness were significantly associated with mean TSP levels across cities — with OR values of 1.11, 1.11, and 1.08 (all three $P < 0.05$) for a 10 µg/m³ increase, respectively (222). Surprisingly, however, the within-city analysis (for year-to-year and region-to-region variability) produced negative associations for all the outcomes. A later analysis of 1980–1981 questionnaire data from this cohort found that the prevalence of reported chronic cough, bronchitis, and chest illness was associated with all the particle measures (TSP, PM₁₅, PM_{2.5}, SO₄). For PM₁₅ the OR values were 3.7 (95% CI 1.0–13.5), 2.5 (95% CI 1.1–6.1), and 2.3 (95% CI 0.8–6.7) for the most, compared with the least, polluted city (40 µg/m³ difference) (223).

Portney & Mullahy (224) used the US National 1979 Health Interview Survey, in which 80 000 persons nationwide responded to questionnaires. The analyses concerned only 1318 persons who resided within 20 miles (about 32 kilometers) of the nearest O₃ and TSP monitoring stations and were also in the subset that answered questions on chronic respiratory illnesses and smoking habits. The results suggested that sinusitis and hay fever were associated with O₃ exposure but that more serious chronic respiratory disease (chronic bronchitis, emphysema and asthma) were associated with average TSP levels over the previous 6 years. In a similar survey, the first National Health and Nutrition Examination Survey (NHANES I), 3874 adults answered a detailed questionnaire and were examined by a physician (225). The OR associated with a 10 µg/m³ increment in annual average TSP was 1.07 (95% CI 1.02–1.12) for reported chronic bronchitis and 1.06 (95% CI 1.02–1.11) for a respiratory diagnosis by the examining physician, whereas asthma showed no association.

In the United Kingdom, nontrivial positive regression coefficients, adjusted for ethnicity and poverty score, were obtained in an analysis for respiratory admissions to hospitals in relation to 2-year electoral ward averages of BS, NO₂, and, for children, also SO₂. For asthma, only NO₂ and, for children, SO₂ showed posi-

tive associations. Only the association of all respiratory admissions among children <5 years of age with NO₂, however, was statistically significant (249). The prevalence of phlegm among 23-year-olds, as reported in questionnaire studies, showed OR values of up to 1.5 and a significant trend over five exposure categories of annual averages of BS (median 30.2 in highest versus 11.0 in lowest category) (226). Cough did not show a significant association, and no association was found for wheeze with BS or for any outcome with SO₂. In a study of children in 24 communities in the United States and Canada (250), respiratory symptoms (227) and lung function (230) were investigated in relation to annual air pollution levels. Bronchitis was related to all the particulate measures (H⁺, SO₄, PM_{2.1}, PM₁₀), most strongly to H⁺, and also with similar strength to O₃ and SO₂ (not significant) (227). No other associations were found. Similarly, a Swiss study across 10 communities found bronchitis to be associated with PM₁₀ levels with an OR of 2.2 (95% CI 1.2–4.9) between the most and least polluted community. An OR of 3.1 (95% CI 1.6–5.8) was observed for chronic cough and was very similar for nocturnal dry cough, but, in this situation too, no association was found for asthma or for allergy (228). A study of adults in Beijing, with very high particulate levels, found several symptoms to be associated with particle levels in the three compared areas, with the strongest effect on cough and wheeze (229).

In a Dutch study investigating exposure contrasts near roads to elucidate air pollution effects, children's symptoms of cough, wheeze, runny nose and asthma, but not bronchitis or atopy, were related to living close to freeways, density of truck traffic, and BS measured in schools (251). The effect was found mainly among girls. Outdoor BS levels ranged from 14.9 µg/m³ close to the freeways to 7.4 µg/m³ at greater distances, whereas no gradients were found for PM₁₀ or PM_{2.5}. The indoor BS levels were in the same range. Several other studies have also found an elevated prevalence of respiratory symptoms or asthma (251–257) or hospitalization for wheezing bronchitis or asthma among young children (258, 259) to be associated with living near busy roads, measures of traffic intensity, or modeled NO₂ concentrations. Other studies found no association for asthma-related respiratory symptoms (260) or the prevalence of active asthma (261). In all of these studies, some measure of road traffic intensity rather than air pollution measurements was used in the analyses, most were cross-sectional studies but some were case-referent.

Lung function. Children in the US Six Cities Study were studied cross-sectionally on two occasions, in 1974–1977 and 1980–1981. Neither study found any association between pulmonary function levels and

particulate measures (TSP and SO_4 , in the latter study also PM_{15} and $\text{PM}_{2.5}$) (222, 223). In an analysis of lung function in relation to annual mean air pollution levels for US and Canadian children (230), $\text{FEV}_{1.0}$ was related to particulate measures (H^+ , SO_4 , $\text{PM}_{2.1}$, PM_{10}), most strongly to H^+ (OR -3.5% , 95% CI -2.0 – 4.9% for a 52 nmol/m^3 increase in H^+). The percentage decrement was similar (more than -3%) for FVC, MMEF (maximum midexpiratory flow), and PEF (peak expiratory flow) and, for all four pulmonary function measures, was around -2% for a $17.3 \text{ } \mu\text{g/m}^3$ increase in PM_{10} . Spirometric measurements and questionnaire data from young people in 44 cities from the US NHANES II National Health Survey were analyzed against annual mean levels of SO_2 , NO_2 , TSP and O_3 in the preceding year (231). Due to an insufficient overlap of pollution monitoring stations, each pollutant was considered in a separate regression. TSP, O_3 , and NO_2 were all significantly associated with FVC, $\text{FEV}_{1.0}$ and PEF in regression models, the TSP relationship being the least significant and also a magnitude smaller than for O_3 over the range of exposure (approximately -0.05% versus -0.1%).

Two of the previously mentioned studies of road traffic and children's health also investigated lung function and found impairments to be associated with traffic density (254, 262). Only in the more recent study were air pollution measurements made, and the association was observed also with BS measured indoors in schools (262).

Among adults, a study based on the US NHANES I survey found that the quarter-yearly average of TSP exposure was associated with FVC (-2.25% for a $34 \text{ } \mu\text{g/m}^3$ increase in TSP at the mean of $87 \text{ } \mu\text{g/m}^3$) and $\text{FEV}_{1.0}$, but not MMEF or the $\text{FEV}_{1.0}/\text{FVC}$ ratio (232). In another study of adults with exposure to very high particulate levels in Beijing, a clear decrease in adult FVC and $\text{FEV}_{1.0}$ was associated with increases in both TSP and SO_2 (233). Likewise, in a Swiss study of adults, significant and consistent effects on FVC and $\text{FEV}_{1.0}$ were found for PM_{10} , SO_2 , and NO_2 , most consistently for PM_{10} with a 3.4% decrease in FVC per $10 \text{ } \mu\text{g/m}^3$ (234).

Case-referent studies and cohort studies

The long-term effect of air pollution, including particles, on the incidence of lung cancer has been studied with both case-referent and cohort methodology. This evidence has been recently evaluated (263, 264) and will not be reviewed in detail in our report, although the cohort results are discussed briefly under the relevant study. Overall, the observed excess risk for lung cancer of 20–40% in areas with high particulate levels does not appear inconsistent with extrapolations based on occupational data, primarily including workers exposed to

diesel exhaust particulate (263). Apart from lung cancer, the case-referent approach, which requires incident disease data, has rather seldom been applied to other chronic respiratory health effects in relation to long-term air pollution exposure, and, when it has, measurements or estimates of air pollution exposure, including exposure to PM, are usually lacking. One example is a study of COPD in Athens, which noted an OR of 2.0 (95% CI 1.2–3.3) for subjects with long-term urban residence, compared with rural or mixed residence, adjusted for gender, age, smoking, and socioeconomic indicators (265). PM exposure was not measured or estimated, but it was known to be elevated in the urban area.

Only three cohort studies have been reported on the health effects on adults as a result of long-term particulate air pollution. In the Californian Seventh-Day Adventist cohort, Cox regression (for mortality and incident disease), logistic regression (for symptom data), and linear regression (for lung function) methods were used for analyses in a cohort of 6338 subjects. The incidence of lung cancer, based on follow-up to 1982 (17 cases), was related to both TSP (RR 1.72, 95% CI 0.81–3.65, see table 6) and O_3 (236, 244); in a multi-pollutant analysis, O_3 was possibly superior (236). With extended follow-up to 1992 (16 men, 20 women), the relation to PM_{10} was strong for the men and was weaker and nonsignificant for the women (245). Associations were similar for O_3 and SO_2 for the men and appeared to be stronger for SO_2 for the women. The authors observed that the gender differences for O_3 and PM_{10} appeared to be partially due to gender differences in exposure, mainly in that men spent more time outdoors, particularly in the summer. In the 1982 follow-up, the incidence of all malignant neoplasms combined showed an elevated risk for the women only (244), whereas myocardial infarction and total natural-cause mortality did not show any relationship to TSP, O_3 , or NO_2 (235, 237). With mortality follow-up to 1992, a weak, nonsignificant association with PM_{10} was observed for total mortality only for the men. The PM_{10} associations appeared to be due to nonmalignant respiratory disease (RR 1.18, 95% CI 1.02–1.36 per 43 days/year above $100 \text{ } \mu\text{g/m}^3$ for both genders combined) and to lung cancer, particularly among the men (247). The results for lung cancer mortality regarding other air pollutants and gender differences were similar to those for lung cancer incidence. In 1987, 3914 subjects received a 10-year follow-up questionnaire on new symptoms. Whereas bronchitis and total COPD were associated chiefly with TSP (RR 1.33 and 1.36 per 1000 hours/year above $200 \text{ } \mu\text{g/m}^3$ in 1973–1977, respectively), the development of asthma showed some association with O_3 (RR 1.40 per 500 hours/year above $200 \text{ } \mu\text{g/m}^3$ 1977–1987, 95% CI 0.99–2.34) (240), mainly observed for men (3.12, 95% CI 1.61–5.85), possibly because they spent more time

outdoors (239). For both genders, asthma development was, however, similarly associated with TSP (RR 1.74 per 1000 hours/year in excess of 200 $\mu\text{g}/\text{m}^3$ 1973–1977, 95% CI 1.11–2.72) and SO_4 (RR 2.85, 95% CI 1.03–7.40, per average annual increase of 7 $\mu\text{g}/\text{m}^3$) (240, 244). Multipollutant analyses could not differentiate clearly between these pollutants in relation to asthma (240). For a subset of this cohort, $\text{PM}_{2.5}$ was estimated from airport visibility data (242). This particulate measure showed an especially strong relationship to all malignant neoplasms among women (244). For a subcohort that performed spirometry in 1993, a decrement of 7.2% in $\text{FEV}_{1.0}$, compared with the predicted level, per 54 days/year when PM_{10} exceeded 100 $\mu\text{g}/\text{m}^3$, was observed for the men whose parents had asthma, bronchitis, emphysema, or hay fever, but not for the men without this familial background or for the women (246). A similar decrement (6.3%) was associated with O_3 . The authors suggested that this gender difference could be due to the marked gender differences in time spent outdoors and in exposure to occupational air pollutants or to a stronger “healthy worker effect” among the women, as suggested in this cohort. PEF lability was similarly increased among all the women and men (0.8% and 0.6% per 54 days/year above 100 $\mu\text{g}/\text{m}^3$ PM_{10} , respectively).

Two other US cohort studies have examined mortality in relation to particulate air pollution using Cox proportional hazard regression modeling. In the US Six Cities Study, a 14- to 16-year follow-up was conducted for 8111 adults in the six cities (88). The adjusted total mortality rate ratio for the most polluted city compared with the least polluted city was 1.26 (95% CI 1.06–1.50). Plotting of the city-specific total mortality rate ratios against various pollutants suggested that $\text{PM}_{2.5}$, PM_{10} , and SO_4 particles best described the rate gradient across the cities, whereas TSP, H^+ , SO_2 , and O_3 correlated less well with the city-specific rate ratios. An analysis with $\text{PM}_{2.5}$ levels instead of simple city indicator variables in the model gave a rate ratio of 1.26 (95% CI 1.08–1.47) across the range of $\text{PM}_{2.5}$ in the most versus the least polluted city (18.6 $\mu\text{g}/\text{m}^3$), and the results were very similar for PM_{10} and SO_4 . The estimate was 1.37 (95% CI 0.81–2.31) for $\text{PM}_{2.5}$ and lung cancer mortality and 1.37 (95% CI 1.11–1.68) for cardiovascular mortality, whereas for all other mortality the rate ratio was not elevated.

The second study linked air pollution data from 151 US metropolitan areas in 1980 with individual risk factors for 552 138 persons resident in these areas when enrolled in the second American Cancer Society Cancer Prevention Study. Mortality was followed until December 1989 (89). The adjusted mortality risk ratios for the most polluted versus the least polluted area were 1.15 (95% CI 1.09–1.22) for 19.9 $\mu\text{g}/\text{m}^3$ SO_4 and 1.17

(95% CI 1.09–1.26) for 24.5 $\mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$ when SO_4 and $\text{PM}_{2.5}$ were used in the model. Whereas SO_4 was associated with an increased risk of cardiopulmonary and lung cancer death (1.26, 95% CI 1.16–1.37, and 1.36, 95% CI 1.11–1.66) and $\text{PM}_{2.5}$ was related to cardiopulmonary but not lung cancer mortality (1.31, 95% CI 1.17–1.46, and 1.03, 95% CI 0.80–1.33), there was no association for either particulate measure with mortality from other causes.

Evaluation

Large cross-sectional studies in the United States provided an initial impetus for research on the health effects of particles, but they were unable to answer questions regarding short-term versus long-term effects. The lack of individual data also makes these studies vulnerable to confounding. Cross-sectional studies of symptoms rather consistently suggest that chronic bronchitis, cough, and related symptoms are related to particulate air pollution, whereas the data regarding asthma or allergy provide less clear support for an association. From the cross-sectional studies on pulmonary function, there is some evidence for a long-term effect of particulate air pollution, especially for adults. In comparison, the evidence regarding the pulmonary function effects of O_3 appears to be stronger for children, and it may be that this difference between adults and children reflect different time scales for the long-term effects of these two pollutants. Two major cohort studies from the United States have strengthened the conclusion that cardiopulmonary mortality, perhaps including lung cancer, is associated with long-term particulate exposure. A 10 $\mu\text{g}/\text{m}^3$ increase in the long-term $\text{PM}_{2.5}$ level was related to an excess total mortality of roughly 10%. Over the range of $\text{PM}_{2.5}$ levels from the least to the most polluted city, the studies estimated increases in total mortality of 26% (over 18.6 $\mu\text{g}/\text{m}^3$) and 17% (over 24.5 $\mu\text{g}/\text{m}^3$). Calculations using Dutch and US male life-table data and the RR estimates from these studies have estimated a possible effect on average life expectancy on the order of 1 to 1.5 years lost (266). The longitudinal follow-up in the third US cohort study, the Seventh-Day Adventist study, found an association between total mortality and PM_{10} levels of similar magnitude among men, but not among women. The broad category of cardiopulmonary mortality did not show a stronger association, but mortality due to nonmalignant respiratory disease and lung cancer did, particularly among men. SO_2 for both genders and O_3 for men also showed strong associations to lung cancer mortality. This study also confirmed a previously reported cross-sectional association of bronchitic symptoms with particle levels and suggested that asthma may be associated with both O_3 and particles or possibly other pollutants.

Summary and concluding remarks

There is consistency in the findings of increased mortality in association with levels of particulate air pollution on the previous day or days. Different gravimetric measures, such as TSP and PM₁₀, and reflectance or visibility measures such as BS or CoH have been used with similar results. It has lately been suggested that the smaller particulate fractions (eg, PM_{2.5} or even smaller) are primarily responsible for the health effects observed. The possibility that particles are a surrogate for other pollutants cannot be completely dismissed. However, the association has been consistently observed even in locations with low levels of other pollutants. The most recent analyses have modeled several pollutants simultaneously, usually with the effect of particles remaining. The size of the effect is around a 0.5–1% increase in mortality for a 10 µg/m³ increase in PM₁₀, and it appears generally to be stronger for respiratory deaths and cardiovascular deaths than when the totality of death counts is considered. Associations have been observed at particulate levels well below 100 µg/m³, and some studies indicate weaker relationships at higher levels.

The studies on hospital admissions and emergency-room visits provide additional evidence for adverse health effects of short-term exposure to particles. Increases in daily admissions range from 0.5% to 3% per 10 µg/m³ of PM₁₀ in most studies. An effect has been found for many respiratory end points and, in some studies, also for cardiovascular conditions. Generally the estimated effect is stronger for respiratory disease such as COPD and pneumonia and lower for cardiovascular disease or specific cardiac disease end points. The results regarding asthma admissions show a larger variability, possibly due partly to a smaller sample size, but asthma visits, particularly of children, appear to be rather consistently associated with particulate air pollution levels, with increases of roughly 1% to 4% reported per 10 µg/m³ of PM₁₀. The results from recent European studies of hospital admissions (0.4–0.9% increase per 10 µg/m³ of PM₁₀ for different end points in different subgroups) are weaker than previous findings from the United States and elsewhere.

Particulate air pollution has also been found to be related to both respiratory symptoms and lung function among healthy persons. Mostly children have been studied. The lung function decrements are only about 0.5–1.5% per 50 µg/m³ increase in PM₁₀ levels. The most consistent effects have been found for PEFR. The decrements are often more strongly related to longer averaging or lag times than to previous-day levels, and therefore there is a possibility of persistent, chronic effects. The results for symptoms are rather inconsistent, although many studies reported high OR values. For the most part the results have been more consistent for lower

respiratory symptoms and cough than for upper respiratory symptoms, with generally a 10–40% excess RR in association with a 50 µg/m³ increase in PM₁₀ levels when an effect was observed. For asthmatics, a somewhat stronger effect on pulmonary function has often been observed, while this stronger effect does not hold true for symptoms. Extra asthma medication, generally bronchodilator use, has mostly been associated with particulate exposure and may modify the observed effect on symptoms and lung function.

Several studies on both mortality and morbidity have convincingly shown that the effect of particles is stronger among the elderly. There still appears, however, to be an effect also in younger age groups. The stronger effect on the elderly is to be expected if the exposure affects susceptible subgroups of persons with underlying disease. An argument has been made that the effect on mortality only represents a harvesting effect of hastening death by a few days. There is scant evidence to elucidate this hypothesis, but available data suggest that it may be partly true but that the effect is also partly more long-term. There is also overall evidence for stronger effects on respiratory and cardiovascular admissions to hospitals and emergency rooms and mortality than on total admissions and mortality, causal association therefore being suggested.

Cross-sectional studies of symptoms rather consistently suggest that chronic bronchitis, cough, and related symptoms are related to particulate air pollution, whereas the data regarding asthma or allergy provide less support of an association. The longitudinal follow-up in one US cohort study confirmed a previously reported cross-sectional association of bronchitic symptoms with particle levels and suggested that asthma may be associated with both O₃ and particulate exposure or possibly exposure to other pollutants. From the cross-sectional studies on pulmonary function, there is some evidence for a long-term effect of particulate air pollution, especially for adults; this evidence received some support from the mentioned US cohort study. Two recent major cohort studies from the United States have strengthened the conclusion that cardiopulmonary mortality is associated with long-term particulate exposure. A 10 µg/m³ increase in the long-term PM_{2.5} level was related to an excess total mortality of roughly 10%. Over the range of PM_{2.5} levels from the least to the most polluted city, the studies estimated increases in total mortality of 26% (over 18.6 µg/m³) and 17% (over 24.5 µg/m³). A possible effect on average life expectancy on the order of 1 to 1.5 years lost was estimated from these data. The longitudinal follow-up in the first US cohort study mentioned found little association between total mortality and particles, although associations were observed for mortality due to nonmalignant respiratory disease and lung cancer, particularly among men.

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Appendix

Recalculation of regression estimates to a common metric

In tables 1—3 of the review, results from various types of analyses have been recalculated to a percentage increase per 10 $\mu\text{g}/\text{m}^3$. In so doing, the following procedure has been followed.

Original data from each publication were extracted in principle in the following order of priority: (i) for point estimates: published beta-coefficient, relative risk or odds ratio (OR), percentage increase; (ii) for random error: standard error (SE) or confidence interval (CI) of beta, SE or CI of the relative risk or OR, SE or CI of the percentage increase, exact P-value, t-value, P-limit (eg, $P < 0.05$). In a few cases the order of priority was altered to retain as many decimals as possible. In all cases the original numbers were first recalculated to beta per unit of exposure and the SE of the beta for the function relating air pollutant x to outcome y . The slope of the function in a single point was obtained by taking the derivative of this original function. For linear regressions, a relative increase was obtained by dividing by the mean of the outcome (median if mean not available). The derivative function was then evaluated at the mean concentration of the air pollutant (median if mean not available). The result was converted to the PM_{10} (particulate matter $< 10 \mu\text{g}/\text{m}^3$) metric by applying the conversion factors given previously (see the Introduction of the review). Finally the relative risk for the chosen increment (10 $\mu\text{g}/\text{m}^3$) was evaluated as $\exp[10 \times (\text{PM}_{10} \text{ derivative at mean})]$, that is, by assuming an relative risk function-

al form, whether the original function assumed this form (log-linear regression models, generally assuming the Poisson distribution) or a linear absolute risk (linear regression models). The percentage increase was then obtained as $(\text{relative risk} - 1) \times 100$. The result may, in principle, be interpreted as the proportional increase in the outcome due to a 10 $\mu\text{g}/\text{m}^3$ increase in PM_{10} from any level, remembering that it is estimated *based on the association (slope) observed at the mean air pollutant concentration in each study*. All the calculations were performed in an Excel spreadsheet, with no rounding of intermediate steps beyond what was built into the program.

It should be noted that the numbers obtained may differ slightly from those of other reviews. Apart from calculation errors in one place or the other and different conversion factors to PM_{10} , several other explanations are possible. A point estimate may also be obtained as the midpoint (directly or on the log scale as appropriate) between published confidence limits. This procedure may even give point estimates that are as consistent and may perhaps even asymptotically more accurately reflect the "true" nonrounded point estimates obtained in a large number of studies. However, after rounding, such indirectly calculated point estimates will in some cases result in a rounded point estimate that differs from the one published in the paper, which we deemed undesirable. Similarly, the choice of using pub-

lished SE or CI values when both are available for calculating the CI may give slightly different results. The rounding of numbers taken from the publications or of intermediate results can also produce noticeable differences in the final result. Furthermore, an alternative method of evaluating the effect of a $10 \mu\text{g}/\text{m}^3$ increase in PM_{10} is to evaluate the original function at, for example, the mean air pollution level and (mean + 10) and take the difference. This procedure will also often produce slightly different results (except in the case of log-linear, including Poisson, models relating the outcome to untransformed air pollutant levels because these assume a constant relative risk independently of the baseline outcome value and of air pollution levels between which the relative risk is evaluated). However, the choice of (mean + 10) minus mean, or mean minus (mean - 10), or even (mean + 5) minus (mean - 5) for a $10 \mu\text{g}/\text{m}^3$ difference near the mean is arbitrary. Therefore, we chose the method which evaluates the effect *at the mean* (eg, using the instantaneous slope of the function *at the mean* by taking the derivative). Finally, as already noted, others may have retained the linear absolute risk assumption for linear models and evaluated the percentage increase for a $Z \mu\text{g}/\text{m}^3$ increase in such models as simply $[Z \times (\text{PM}_{10} \text{ derivative at mean})] \times 100$ rather than $\{\exp[10 \times (\text{PM}_{10} \text{ derivative at mean})] - 1\} \times 100$. As long as $Z \times (\text{PM}_{10} \text{ derivative at mean})$ is smaller than 0.1 (10%), as is the case for most studies evaluated for a difference of $10 \mu\text{g}/\text{m}^3$ PM_{10} , it will make very little difference. Note, however, for example, the larger numbers for Wordley et al (1) in table 2 of the review; these numbers differ very slightly from percentage increases given in the paper as a result of the constant relative-risk assumption we assumed in our calculations. When evaluated over a larger difference than $10 \mu\text{g}/\text{m}^3$ PM_{10} , such discrepancies will be more noticeable. For

the interested reader, percentage increases for a $Z \mu\text{g}/\text{m}^3$ increase in PM_{10} based on the slope at mean air pollution levels and on the assumption of a linear absolute risk can be obtained from our numbers by taking $\{[\ln(\text{tabular value})/100] + 1\}/10 \times Z \times 100$. Assuming a constant relative risk, as we have done, one computes $\{[(\text{tabular value})/100] + 1\}^{(Z/10)} - 1 \times 100$.

As mentioned in the main text, several sensitivity analyses have shown that results are not overly sensitive to regression type or functional form (variable transformations) when the air pollution effect is expressed as the slope at the mean. If one considers that any regression analysis in a sense "pivots" around the bulk of data, which naturally centers around the mean, and that most reasonable functional forms have moderate curvature near the mean, it is perhaps not surprising that the slope at the mean is relatively insensitive to model specification. The differences between linear or log-linear models or different functional forms for dose-response interpretations become more important when the effect at high air pollution levels are considered, and even more so at low levels, or when extrapolation is done beyond the data range. However, from a practical point of view, the major interest is in present-day averages and possible realistic changes and variations around these levels, and, for that purpose, the different models generally produce qualitatively similar estimates of dose-response.

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Exposure

Sources and air concentrations

Airborne particulate matter (PM) is a very diverse material in terms of its physical and chemical properties, and many sources contribute to its atmospheric concentrations. Airborne particles are typically very small, ranging in size from a few nanometers up to 100 μm or more. While all particles in this range can be found in the air, only particles in the range of 0.1–2 μm can remain airborne for long periods (10 days or more). Particles less than about 10 μm , the PM_{10} fraction, are the most important from a health point of view, as such particles reach the thoracic parts of the respiratory tract to a large extent.

Airborne particles can be either directly emitted (primary particles) or formed in the air by chemical reactions or the condensation of gases (secondary particles). Mechanically generated airborne particles are normally larger than 2.5 μm (coarse particles), while the particles formed from gas conversions are smaller than 2.5 μm (fine particles). Due to their different size and formation processes, fine and coarse particles have substantially different properties (chemical composition, atmospheric half-time, temporal and spatial variability).

The annual Swedish emission of primary particles (coarse and fine) is estimated to be about 50 000–100 000 t. Wood combustion for heating is probably the major source, but emission estimates are uncertain. Heavy-duty diesel vehicles, the combustion of heavy oil for energy production, machines, and industrial processes are other important sources. Resuspension of road dust is probably also important; however, no reliable estimates of its contribution are available on a national level.

Regular monitoring of PM_{10} in a few major cities in southern Sweden since the beginning of the 1990s has shown that the average concentration at roof level is around 10–20 $\mu\text{g}/\text{m}^3$. Levels in rural areas are in the lower end of this range. The comparatively small difference between roof-top urban levels and rural levels results from the strong influence of long-range particle transport on the concentrations. The 98th percentile of the daily mean values ranges from about 30 to 50 $\mu\text{g}/\text{m}^3$, and the maximum daily mean concentrations are in the approximate range of 50–100 $\mu\text{g}/\text{m}^3$. At street level, the mean concentrations range from 20 to 40 $\mu\text{g}/\text{m}^3$, and the 98th percentile of the daily means varies from 50 to 100 $\mu\text{g}/\text{m}^3$. The maximum daily mean concentra-

tions are in the range of 100 to 150 $\mu\text{g}/\text{m}^3$, and hourly mean concentrations can exceed 300 $\mu\text{g}/\text{m}^3$. The highest concentrations are measured in spring, probably because of the resuspension of road dust due to the build-up of particles on the road surface during sanding and salting, as well as because of road wear by studded tires in the winter season.

No major changes in concentration are anticipated during the next few decades. There are indications that reduced emissions due to better combustion technology for vehicles and wood boilers will be counteracted by an increase in the share of diesel cars and also by an increase in the use of wood for heating. Moreover, the contribution from the particles transported long-range is estimated to remain about the same as now.

Deposition and clearance

Particle deposition in the airways depends on particle size, density, and shape. Particles of soluble material can take up water in the airways and grow considerably. Deposition is also dependent on respiration pattern, including mouth or nose breathing. Deposition in the alveolar region is highest for particles of 20–30 nm, about 50%.

Recent experiments indicate substantial retained fractions of particles after 24 hours in small ciliated airways (bronchioli), and the clearance of these fractions appears to be rather independent of mucociliary transport. For persons with chronic bronchitis, clearance by coughing is an important mechanism in the larger airways of the lung, in addition to mucociliary transport, but its importance in small ciliated airways is uncertain.

The mechanical clearance of particles from the alveolar region in humans is extremely slow, with a half-time of about 5 years for the majority of the particles. This slow clearance should be relevant for the carbon skeleton of ambient particles. However, particles of many materials typically considered insoluble in water, such as many metal oxides, can be cleared at a much faster rate because they are dissolved in the acid milieu in the phagolysosomes of the alveolar macrophages. Particles deposited in the alveolar region can be transported to the regional lymph nodes, especially toxic particles, such as quartz particles, ultrafine particles, and also rather large inert particles when the inhaled amount is extremely large. In all of these situations there may be a considerable number of particles outside alveolar macrophages.

Health effects

Short-term effects

Experimental studies. Most experimental studies have dealt with sulfuric acid aerosols and persons with asthma, who are more sensitive than healthy subjects to these particles with respect to lung function. In the investigations on ventilatory function, the study design and methods of measuring lung function have been similar. Still, the results have differed remarkably. Significant changes in young asthmatics have, for example, been observed already at $70 \mu\text{g}/\text{m}^3$, whereas concentrations of $1000 \mu\text{g}/\text{m}^3$ or higher have been necessary to induce significant changes in asthmatics in other studies. An explanation for the different results may be that the groups of asthmatics differed in bronchial reactivity. In combined exposure of sulfuric acid aerosols and ozone (O_3), there was no indication of any major synergistic effect. Furthermore, short-time exposure to carbon black particles ($200 \mu\text{g}/\text{m}^3$) and sulfuric acid particles ($100 \mu\text{g}/\text{m}^3$) among healthy subjects and asthmatics did not induce any significant effect on lung function.

The results of the clearance studies seem more consistent than those based on lung function tests. Apparently, there is an effect of sulfuric acid particles on mucociliary clearance at least down to $100 \mu\text{g}/\text{m}^3$ in short-term exposures. The effect seems to increase with duration of exposure. In contrast to the results regarding ventilatory function, asthmatics do not seem more sensitive to exposure to sulfuric acid particles than healthy subjects do.

Healthy subjects exposed to filtered or unfiltered diesel exhaust have shown only small differences in effects. The filtered exhaust had about half as many particles as the unfiltered exhaust (1.4×10^6 and 2.6×10^6 particles/ cm^3 , respectively), but the carbon dioxide concentration was similar (1.7 and 1.9 ppm). In a later study 4.3×10^6 particles/ cm^3 was reported to correspond to $300 \mu\text{g}/\text{m}^3$. There was an increase in airway resistance (R_{aw}) of around 15% for both exposures. In the bronchial portion of the lavage fluid, the number of macrophages was significantly increased only after the exposure to the unfiltered diesel exhaust, whereas the neutrophils increased by a factor of 3–4 after both exposures. The phagocytic activity of alveolar macrophages was significantly reduced after both exposures. In these studies, it was difficult to assess whether the effects were caused by particles or by gases.

In another study with realistic but complex exposures, volunteers with mild asthma were exposed to the atmosphere in a road tunnel for 30 minutes during the rush hour. When the subjects inhaled pollen antigen 4 hours after the end of the exposure, the SR_{aw} and thoracic gas volume (TGV) were significantly increased

when compared with the results of the control exposure, and more asthma symptoms were seen later in the evening after the tunnel exposure. The asthma symptoms correlated both with the concentrations of nitrogen dioxide (NO_2) and particulate matter with diameters of $<2.5 \mu\text{m}$ ($\text{PM}_{2.5}$), but the relationship appeared to be stronger for NO_2 . The late-phase reaction tended to be higher for those with $\text{PM}_{2.5}$ exposure above $100 \mu\text{g}/\text{m}^3$.

There are very limited human data on whether the number, surface area, or mass of particles is the most appropriate way to measure dose. Healthy subjects inhaling cholinergic aerosols with mass median diameters of 3 or $7 \mu\text{m}$ required a three to four times higher mass for the large particles than for the small particles in the tracheobronchial tract to induce the same effect on R_{aw} and forced expiratory capacity in 1 second ($\text{FEV}_{1.0}$). This result may be relevant also for at least some particles in ambient air, as another study indicated a strong correlation between the effects of cholinergic aerosols and the effects of sulfuric acid aerosols on asthmatic subjects.

Epidemiology. A large number of studies has consistently observed an association between mortality and the levels of particulate air pollution on the previous day or days. Different gravimetric measures, as well as reflectance or visibility measures, have been used with similar results. The measured or estimated daily mean PM_{10} levels ranged from about 30 to $80 \mu\text{g}/\text{m}^3$ during the observation periods in most of the studies. It has lately been suggested that the smaller particulate fractions (eg, $\text{PM}_{2.5}$ or even smaller) are primarily responsible for the health effects observed. The possibility that particles are a surrogate for other pollutants cannot be completely dismissed. However, the association was consistently observed in locations with differing levels of other pollutants. The effect corresponds to around a 0.5–1% increase in mortality for a $10 \mu\text{g}/\text{m}^3$ increase in PM_{10} , and it appears to be stronger for respiratory deaths and cardiovascular deaths. Associations were observed at particulate concentrations well below $100 \mu\text{g}/\text{m}^3$, and some studies even indicate weaker relationships at higher levels. Furthermore, several studies have reported stronger effects in the summer (when PM_{10} levels are usually lower).

The studies on hospital admissions and emergency room visits also provide evidence of adverse health effects resulting from short-term exposure to particles. Increases in the daily morbidity range from about 0.5% to 3% per $10 \mu\text{g}/\text{m}^3$ of PM_{10} in most studies. An effect on many respiratory conditions, such as chronic obstructive pulmonary disease and pneumonia, has been found, as well as an effect also on cardiovascular diseases in some studies. The results regarding asthma admissions show a larger variability, which may be partly due to a smaller sample size, but hospital visits for asthma,

particularly of children, were rather consistently associated with particulate air pollution levels, with increases of roughly 1% to 4% per 10 $\mu\text{g}/\text{m}^3$ increase in the PM_{10} . The results from recent European studies of hospital admissions, indicating excess risks of about 0.4–0.9% per 10 $\mu\text{g}/\text{m}^3$ of PM_{10} for different disorders in different subgroups, appear to be lower than previous findings from the United States and elsewhere.

Particulate air pollution has been shown to be related to both respiratory symptoms and lung function in healthy persons. For the most part children have been studied, often in the age range of 5–15 years. The lung function decrements have been small (ie, corresponding to only about 0.1–0.3% per 10 $\mu\text{g}/\text{m}^3$ increase in PM_{10}). In addition they have often been more strongly related to longer averaging or lag times than to previous-day levels, and, therefore, the question of a possibility of persistent effects is raised. Symptoms of the lower respiratory tract, such as cough and wheeze, have been the most consistently related to particulate exposure, with excess relative risks (RR) of about 2–8% per 10 $\mu\text{g}/\text{m}^3$ increase in the PM_{10} level. For asthmatics, a somewhat stronger effect has often been observed for pulmonary function but not necessarily for symptoms. Extra asthma medication, generally bronchodilator use, has also been associated with particulate exposure, and it may modify the observed effects on symptoms and lung function.

Population-based studies suggest an association between restrictions in activity, leading to work and leisure-time loss, and weekly average particulate air pollution levels. Preterm delivery and low birthweight has also been associated with particulate air pollution during the week and 3 months before delivery, respectively. A relation between sudden infant death syndrome and particulate air pollution has also been suggested, but the data are not conclusive.

Long-term effects

Animal experiments. The review of animal experiments has primarily focused on diesel exhaust particles and ultrafine particles. Rats have primarily been studied for pathological and histological effects in the lung after exposure to diesel exhaust particles. The findings include chronic inflammatory changes involving proliferation and hyperplasia of the alveolar epithelium and type 2 cells, thickening of the alveolar septa, wall fibrosis, and emphysema, as well as activation of inflammatory cells and the release of cytokines and mediators. A comparison of diesel exhaust particles and carbon black in animal inhalation studies has shown that a reduction in lung function and an accumulation of macrophages appears in parallel. This finding suggests that the toxic effect of diesel exhaust particles is in part coupled to the carbon

core. The toxicity of diesel exhaust particles could in part also be mediated via the production of oxygen radicals and the release of different inflammatory mediators.

Animal experiments show that aggregates of ultrafine particles are more toxic than aggregates of fine particles. When aggregates of ultrafine and fine particles have been installed via the trachea or inhaled, the ultrafine particles have induced much stronger inflammatory reactions. The relationship between dose and the alveolar retention half-time of test particles could be well described by one curve for both fine and ultrafine particles when the dose was expressed by the surface area of the particles. This finding suggests that the surface area may be a better measure of the dose than the mass, at least for some health effects.

Diesel exhaust particles introduced by different routes, intraperitoneally, intranasally or intratracheally, may act as an adjuvant to pollen and hence increase the sensitization response. This action has been observed in both human and animal studies (mostly in mice). For example, immunoglobulin (Ig) E production in response to an allergen has been enhanced by diesel exhaust particles. Furthermore, diesel exhaust particles may act as a carrier of pollen allergens and thereby increase the deposition of pollen in the lower airways.

Epidemiology. Large cross-sectional studies of geographic variations in mortality and air pollution in the United States provided an initial impetus for research on the health effects of particles, but they could not answer questions regarding short-term versus long-term effects. The lack of individual data also makes these studies vulnerable to confounding. Several cross-sectional studies of symptoms suggest that chronic bronchitis, cough, and related symptoms are associated with particulate air pollution, whereas the data regarding asthma or allergy are less consistent. From the cross-sectional studies on pulmonary function, there is some evidence for a long-term effect of particulate air pollution. Two major cohort studies from the United States strengthen the conclusion that long-term particulate exposure is associated with cardiopulmonary mortality. These studies controlled for major risk factors, including smoking habits, using information obtained at entry to the cohort. Over the range of $\text{PM}_{2.5}$ levels from the least to the most polluted cities the studies estimated increases in total mortality of 26% per 18.6 $\mu\text{g}/\text{m}^3$ and 17% per 24.5 $\mu\text{g}/\text{m}^3$, respectively. These figures would correspond to an excess total mortality of about 10% for every 10 $\mu\text{g}/\text{m}^3$ increase. A third cohort study from the United States, focusing on Seventh Day Adventists, found an association between PM_{10} levels and cardiopulmonary mortality among men but not among women. Unfortunately, no data in relation to $\text{PM}_{2.5}$ levels were available.

Evaluation

Exposure to particles in the ambient air has been associated with several adverse health effects. This assessment focuses on effects other than cancer. A recent review evaluated the evidence on particles in the ambient air and lung cancer (1). It was concluded that the observed excess risk of 20–40% for lung cancer in areas with high particulate levels did not appear inconsistent with extrapolations based on occupational data, primarily including workers exposed to diesel exhaust particulate. This finding provides a further impetus for restricting exposure to airborne particulate.

Experimental evidence from asthmatics shows that acute effects on lung function may occur already at levels of 70 $\mu\text{g}/\text{m}^3$ of sulfuric acid aerosols. Exposure in a road tunnel at $\text{PM}_{2.5}$ levels above 100 $\mu\text{g}/\text{m}^3$ was associated with enhanced asthma symptoms after exposure to pollen. However, the specific role of $\text{PM}_{2.5}$ is unclear because of concomitant exposure to other factors, such as nitrogen oxides (NO_x).

Animal experiments provide no clear evidence on possible mechanisms behind the acute effects on respiratory symptoms, hospital admissions, and mortality in association with comparatively low levels of airborne particulate in epidemiologic studies. There is limited evidence from experimental studies that the surface area, and maybe even the number, of particles is more relevant than the mass for observed health effects. Long-term inhalation exposure to high levels of diesel exhaust particulate and fine particulate gives rise to inflammatory reactions in the respiratory tract of experimental animals. Some evidence indicates that diesel exhaust particulate may enhance allergic sensitization.

Quantitative risk assessment

The epidemiologic evidence published during the last decade clearly points to a relation between short-term exposure to particulate air pollution and adverse health effects well below current air quality guidelines in many countries. Unfortunately, only limited support has been provided by experimental studies, and, therefore, there is a lack of understanding of the mechanisms behind the effects, such as those on mortality. There are, however, experimental data indicating that ultrafine particles induce stronger inflammatory reactions than fine particles at the same mass. Considerable uncertainty still exists regarding which characteristics of the particles are important for the observed effects. It is not unlikely that particles originating from different sources, such as diesel vehicles and wood burning, may differ in toxicity. Recent epidemiologic evidence suggests that the fine fraction ($\text{PM}_{2.5}$ or less) is especially harmful. However, quantitative assessments of exposure-response relation-

ships regarding acute effects will be based on PM_{10} , as information on $\text{PM}_{2.5}$ is not available in most studies.

Measurements of PM_{10} in ambient air in Sweden are limited, and, therefore, there are uncertainties as to the quantitative risk assessment. Episodes of increased 24-hour levels of particulate depend primarily on meteorological phenomena, such as the transport of polluted air from Europe and inversion during the winter season. Only a few urban areas measure PM_{10} regularly, and it is therefore difficult to generalize for the whole country. In southern and middle Sweden the highest 24-hour levels generally range from 20 to 60 $\mu\text{g}/\text{m}^3$, and the winter half-year means are from 12 to 15 $\mu\text{g}/\text{m}^3$ (primarily based on roof-top measurements in Stockholm, Göteborg, and Malmö). The particulate levels thus increase roughly by 8–45 $\mu\text{g}/\text{m}^3$ above average during an episode with increased particulate levels (average about 25 $\mu\text{g}/\text{m}^3$ for all measurement stations during heating periods in 1993–1994 and 1994–1995). In general, up to 5 such episodes occur yearly in Sweden. The influence by transport from surrounding countries decreases with latitude, while the importance of inversion episodes increases. It may thus be relevant to generalize the measured values also to northern Sweden.

Table 1 summarizes the evidence on short-term exposure to airborne particulate and some health effects. In an attempt to avoid extrapolation linearly down to the low background levels of Sweden, the estimates have been based on a typical 3-day air pollution episode in which the PM_{10} level increased by 25 $\mu\text{g}/\text{m}^3$. According to the data in the table, roughly 10–30 excess deaths, 50–300 hospital admissions and emergency room visits for respiratory and cardiovascular conditions, and 5000–20 000 person-days of respiratory symptom exacerbations would occur in Sweden if the whole population experienced such an air pollution episode. It is likely that mainly people with particular susceptibility would be affected.

The public health impact of short-term associations between particulate levels and mortality remains

Table 1. Estimated acute health effects following exposure to a 3-day episode of PM_{10} levels increased by 25 $\mu\text{g}/\text{m}^3$ in a population of 1 million. (PM_{10} = particles less than about 10 μm in diameter)

Health effect	Excess risk (% per 10 $\mu\text{g}/\text{m}^3$ PM_{10})	Back- ground rate (per 10 ⁶)	Number of subjects (per 10 ⁶) ^a
Respiratory symptoms (person-days)	2–8	10 000	500–2 000
Hospital admissions & emergency room visits for respiratory and cardiovascular conditions	0.5–3	400	5–30
Excess mortality	0.5–1	100	1–3

^a Excess risk per 25 $\mu\text{g}/\text{m}^3$ PM_{10} multiplied by background rate.

unclear. If the effects primarily involve patients who are terminally ill, the life shortening may be minimal. A few cohort studies indicate an increased mortality also in relation to long-term exposure. The observed effects correspond to an increase of about 10% for every 10 $\mu\text{g}/\text{m}^3$ increase in the $\text{PM}_{2.5}$ level in the two studies presenting data on this particulate measure, or roughly 1100 deaths a year per 1 million subjects. A possible effect on average life expectancy on the order of 1 to 1.5 years lost has been estimated from these data. Cross-sectional studies on respiratory symptoms and lung function provide further support for an effect by particulate air pollution, but these data are unsuitable for use in the assessment of effects resulting from long-term exposure. In view of the limited evidence on the long-term effects of particulate air pollution, no quantitative risk assessment has been performed. Furthermore, relevant information on population exposure to particulate in Sweden is lacking.

Proposed health-based guideline

Short-term variations in PM exposure are associated with adverse health effects even at very low levels of exposure. However, the available evidence does not allow derivation of a threshold below which no effects occur. Associations have been observed in studies where the 24-hour average or estimated PM_{10} level was from 30 to 80 $\mu\text{g}/\text{m}^3$. The evidence is the most limited in the

lower part of the interval, but it would seem appropriate that the long-term goal should lie near the lower end of this range. Thus a health-based guideline for PM_{10} is proposed at 30 $\mu\text{g}/\text{m}^3$ as the 24-hour average. It is probable that certain people are particularly susceptible to airborne particulate, such as asthmatic children and adults. These groups comprise fairly large parts of the population, and, therefore, the public health importance of any effects is great. Recent evidence suggests that the fine fraction ($\text{PM}_{2.5}$ or less) may be especially harmful, but the available information is too limited for a guideline based on this measure.

The available evidence on the health effects related to long-term exposure to airborne particulate is limited. However, epidemiologic findings suggest serious effects well below current standards. The yearly average levels of $\text{PM}_{2.5}$ ranged down to 10 $\mu\text{g}/\text{m}^3$ in the metropolitan areas under study, and it may be reasonable to use this value as a basis for a guideline. It would correspond to a PM_{10} level of about 15 $\mu\text{g}/\text{m}^3$.

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