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Review

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Exposure assessment of ultrafine particles in epidemiologic time-series studies

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The health effects of fine-particulate air pollution ($PM_{2.5}$, aerodynamic diameter <2.5 μm) observed in epidemiologic time-series studies may partly be due to the high number concentration of ultrafine particles (aerodynamic diameter <0.1 μm) in urban air. The key uncertainty is how well daily variations in the ultrafine particle concentration measured at a central site correlate with the variations in average personal exposure. Due to a lack of research data, this correlation has been estimated indirectly in this review on the basis of studies on the sources, ambient air levels, spatial variability, indoor air levels, and lung deposition of ultrafine particles. It is concluded that central site monitoring may give a somewhat worse proxy for human exposure to ultrafine particles than to $PM_{2.5}$ in time-series studies.

Key terms epidemiology, exposure, fine particles, indoor air, indoor-to-outdoor ratio, particle modes, review, time-series studies, urban air.

There is convincing evidence from numerous time-series studies that daily variations in ambient particulate air pollution, usually measured as the mass concentration of particles smaller than 10 μm in aerodynamic diameter (PM_{10}), are associated with mortality and hospital admissions due to cardiovascular and respiratory diseases (1, 2). This evidence has already led to legislative actions both in Europe and in the United States. It has been suggested that the adverse health effects are more strongly associated with the mass concentration of fine particulate matter ($PM_{2.5}$, particles <2.5 μm in aerodynamic diameter) than that of larger particles (3). Otherwise, it is not known which characteristics of particulate matter are responsible for the health outcomes. Currently, the two most favored hypotheses are chemical composition of particulate matter, especially transition metals, and the large number concentration of ultrafine particles (particles smaller than 0.1 μm in diameter) in urban air.

There have been relatively few epidemiologic studies on ultrafine particles. Most panel studies, but not all (4), have suggested that ultrafine particles are more strongly (5, 6), or as strongly (7–9), associated with respiratory health than PM_{10} (particulate matter <10 μm in aerodynamic diameter) or $PM_{2.5}$ are. Toxicologic studies have shown that ultrafine particles are more toxic to animals than larger particles when the mass doses are equal. In fact, the toxic effects have had a higher correlation with the particle number or surface area concentration than with the mass concentration (10). The adverse effects of ultrafine particles may be partly mediated by increased oxidative stress in affected tissues and by their ability to reduce phagocytic activity in alveolar macrophages (11). The latter may facilitate the penetration of ultrafine particles into the lung interstitium (12). It has also been hypothesized that ultrafine particles may induce blood coagulation and thereby increase the risk of myocardial infarction (13).

The effect estimates for particulate air pollution on health are largely based on time-series studies. A major factor that may produce bias in these estimates is the measurement of human exposure. Time-series studies usually use data on ambient-air monitoring from one central site of a city as proxy for average personal exposure. However, it is known that particle concentrations at a central site can correlate rather poorly with personal exposures to particles on a given day because personal exposure is influenced by several factors other than ambient-air concentration, such as indoor penetration, indoor sources, and personal time activity. In order to analyze the effect of this error in the exposure

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measurement, it is useful to break down the daily difference between true personal exposures to, and measured ambient-air levels of, particles into the following two components: (i) the daily difference between the measured ambient-air concentration and the *average* personal exposure concentration in the study population and (ii) the daily differences between the average and *true* personal exposures. The second type of error is a Berkson error and cannot produce bias in epidemiologic time-series studies using data on central-site monitoring as a proxy for exposure (14). In contrast, the first component has a great potential to produce bias.

A constant daily difference between the measured ambient-air pollutant concentration and the average personal exposure concentration in the study population has some effect on the interpretation of the effect estimates from time-series studies (14). However, bias is mainly introduced into time-series studies if this difference is not constant but, instead, is correlated over time with the actual ambient-air pollutant concentration. If there is no correlation, as has been suggested (15), indoor sources cannot bias the observed association between the ambient-air concentration and health in a time-series study (14).

This question can also be addressed directly if the correlation is measured over time between the ambient-air concentration and the average personal-exposure concentration, as has recently been done for PM_{10} and $PM_{2.5}$ in several studies conducted in The Netherlands (16–18) and Finland (19). These studies have shown that there is a moderate correlation between the outdoor concentration and the average personal exposure concentration of PM_{10} (around 0.6), and a high correlation between the outdoor concentration and the average personal exposure concentration of $PM_{2.5}$ (around 0.8).

A portable monitor for measurements of ultrafine particle number concentrations has only recently been marketed. Even ambient air measurements of these particles at a fixed urban site are rare. Therefore, there are no studies on the correlation between the ambient-air and personal-exposure concentrations of ultrafine particles. In this review, we try to estimate the potential of central-site monitoring data representing variations in the average personal exposure to ultrafine particles and also compare this potential to $PM_{2.5}$. Data on particulate concentrations at central sites, spatial variability, indoor-to-outdoor ratios, concentrations in indoor air, and estimated lung deposition in Helsinki, Finland, are used as examples in the discussion.

Sources and properties of atmospheric aerosols

Particulate matter is any substance, except pure water, that exists as a liquid or solid in the atmosphere. Particles in ambient air consist of three main size classes. The ultrafine particles have a diameter below 0.1 μm, the accumulation mode particles usually have a diameter between 0.1 and 1.0 μm (or 2.5 μm), and the coarse mode particles are generally larger than 2.5 μm. The ultrafine particles consist of two modes, the nuclei mode (<25 nm) and the Aitken mode (25–100 nm). The Aitken mode usually dominates the number concentration of ultrafine particles. Particles smaller than 2.5 μm in diameter are generally referred to as "fine", and those larger than 2.5 μm in diameter are termed "coarse" (20).

Ultrafine particles dominate ambient-air particles by number, but they rarely account for more than a few percent of the total mass (figure 1). Therefore, they can

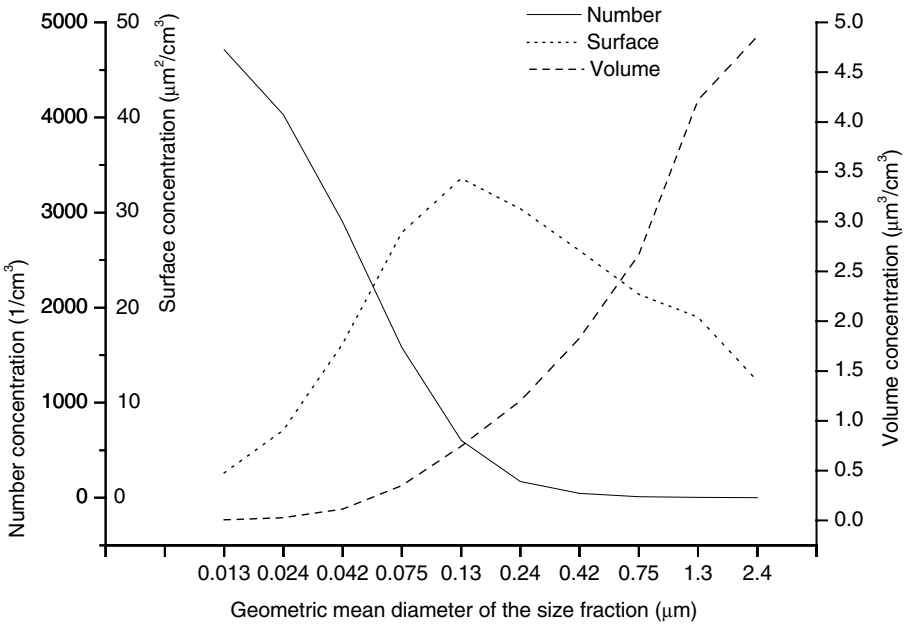

Figure 1. Median number, surface area, and volume concentrations of ambient-air particles in the size fractions measured in 1996–1997 in Helsinki (30).

usually not be seen in the volume size distribution (21). In some cases, ultrafine particles form a substantial fraction of the surface-area size distribution of ambient-air particles. Ultrafine particles are formed in local combustion processes and from the gas-to-particle conversion (nucleation and condensation) of atmospheric gases. They are usually so-called secondary particles. However, it is hard to make a distinction between secondary particles and the primary particles emitted from gasoline or diesel-powered vehicles. For instance, Shi et al (22) have observed that solar radiation affects the emission of ultrafine particles from cars. The atmospheric lifetime of ultrafine particles in high concentrations is very short, but in concentrations observed in urban air it can be a few hours (20).

The accumulation mode usually accounts for most of the aerosol surface area and a substantial part of the aerosol mass (figure 1). The main source of particles in the accumulation mode is the condensation of different condensable vapors, like the condensation of inorganic and organic acids onto existing ultrafine particles, a process which makes them grow into this size range. The other sources are the coagulation of ultrafine particles and cloud processes (20). The formation of accumulation mode particles usually takes several hours, and therefore most of them are from long-range transport. The atmospheric lifetime of accumulation mode particles is relatively long, sometimes over a week.

The coarse mode is formed by mechanical processes and consists of manmade and natural dust particles (eg, road dust). It is responsible for a large part of the mass of ambient aerosol (20). In urban air, the total number concentration of ultrafine particles is over five orders of magnitude higher than the number concentration of coarse particles (7, 23).

Vehicular traffic is one of the major sources of ultrafine particles. Traffic also causes a significant amount of re-emission of coarse, deposited particles from road surfaces. Local point sources, like energy power plants, emit particles and gases, but the release height is so high that their effects on local urban air quality are significant only during unfavorable meteorological conditions. In contrast, traffic emissions released at low heights affect urban air quality directly. Long-range transport from distant sources, such as power plants, industrial sites, traffic, and natural sources (eg, Boreal forest) is the main source of accumulation mode particles. The chemical composition of particles reflects their source and, therefore, also varies with the size of the particles. In fine particles ($PM_{2.5}$), there are sulfates, organic and elemental carbon, ammonium, nitrates, lead, and some trace constituents, whereas coarse particles ($PM_{10-2.5}$) are largely composed of crustal material (silicon compounds, iron, aluminum) (20). The mass of ultrafine particles is dominated by carboneous material, but it also contains sulfate, ammonium, nitrate, and other inorganic material (24, 25).

Aerosol spectrometers that continuously measure the number size distribution of ambient aerosol particles are complex and expensive (26). On the other hand, condensation nuclear counters (CNC), which measure the total number concentration of particles, are less expensive and easier to operate. The typical size distribution obtained by aerosol spectrometers like the scanning mobility particle sizer (SMPS) is 7–600 nm (or 3–600 nm), depending on the CNC used. The typically used models are CPC, TSI model 3022A (50% detection at 7 nm) and CPC, TSI model 3025 (50% detection at 3 nm). However, model 3022A is able to detect a 100 times higher particle concentration than model 3025, the former therefore being more suitable for urban conditions. It is important to note that most of the particles measured by CNC are ultrafine (ie, particles smaller than 0.1 μm). The average number concentration of particles measured by a CNC is higher than that of particles in the size range of 0.01–0.1 μm, as the particles smaller than 10 nm are very numerous.

The total particle number concentration measured by a CNC is highly correlated ($r^2 > 0.95$) with the number concentration of ultrafine particles (27), and, therefore, the former can be used as a proxy for the latter. Overall, CNC monitoring, together with PM_{10} and $PM_{2.5}$, or better PM_1 (particles <1 μm in aerodynamic diameter) (28) mass measurements, gives a fairly good picture of the daily variations in the concentrations of the main classes of particles in ambient air (ie, the number concentration of ultrafine particles and the mass concentrations of accumulation and coarse mode particles). Therefore, the issues discussed in this review for the mass concentration of accumulation mode particles also apply to $PM_{2.5}$ and vice versa.

Particulate concentrations in ambient air at a central site

There are large differences between European cities in the wintertime average concentrations of PM_{10}, ranging from <20 μg/m^3 in Nordic countries to around 40–60 μg/m^3 in central Europe and >90 μg/m^3 in Athens (29). The size-fractionated number distributions of urban aerosols were compared for 3.5 months between three European cities in the first epidemiologic ULTRA study in winter in 1996–1997 (30) and again for 6 months in the second ULTRA study in winter in 1998–1999 (27). Aerosol spectrometers shown to give comparable readings in earlier intercomparisons (26, 31) were placed at urban background sites (ie, at least 50 meters from the closest major road). The results showed that there were large

differences between Helsinki and the central European cities (Amsterdam, Erfurt) in the number concentration of accumulation mode particles and the mass concentration of $PM_{2.5}$ (table 1), but there were few differences in the number concentration of ultrafine particles.

Both the number concentration of ultrafine and accumulation mode particles and the mass concentration of $PM_{2.5}$ had a relatively large daily variability. The variability within the interquartile range was two- to threefold for all the particulate measures (table 1).

The relatively high number concentration of ultrafine particles in Helsinki could partly be explained by the low concentration of accumulation mode particles, which scavenge ultrafine particles. This possibility has been suggested as an explanation for the recently increased number concentrations of ultrafine particles in Erfurt, Germany, where the number concentration of accumulation mode particles has been decreasing (32). Accumulation and coarse mode particles are also a sink for condensable vapors, and therefore they can also hinder the formation of ultrafine aerosol particles (33). Average concentrations of ultrafine particles comparable to the ULTRA data have been observed in Los Angeles in the United States (24) and in Brisbane, Australia (34). Much higher concentrations have been measured near busy motorways (35, 36).

The number concentration of ultrafine particles measured at urban sites has been several times higher than those measured at remote sites. In the downtown area of Helsinki, the 24-hour average concentrations were over 10 000/cm^3, whereas in a rural area (Luukki) outside the city the corresponding concentrations were around 3000/cm^3, and at a remote site (Hyytiälä) they were around 2000/cm^3 (33, 37). Surprisingly, Pakkanen et al (25) found no difference in the mass concentration of ultrafine particles between downtown Helsinki and the rural area (Luukki). However, the study included only ten 48-hour measurements and measured the mass, not number, concentration of ultrafine particles.

In Helsinki, the largest source of $PM_{2.5}$ is long-range transport, reflected, for example, in the high correlation of the number and volume concentrations of accumulation mode particles with $PM_{2.5}$ (table 2). In contrast, the likely source of ultrafine particles is engine emissions from local vehicular traffic. Therefore, it is no surprise that the correlation of ultrafine particles with $PM_{2.5}$ is fairly poor. The number concentration of ultrafine particles correlates better ($r \approx 0.7$) with the measures of elemental carbon, such as black smoke concentration (r=0.65–0.93) (7), absorbance of $PM_{2.5}$ filters (r=0.56 winter and r=0.76 spring) (28), or black carbon concentration (r=0.77) (8), as these measurements reflect the influence of a common particulate source (ie, direct engine emissions from urban vehicle traffic).

The number concentration of ultrafine particles correlates highly with nitric oxide (NO) and nitrogen dioxide (NO_2) concentrations, but the correlation is somewhat lower with carbon monoxide (CO) concentrations

Table 1. The 24-hour average number concentrations of ultrafine (0.01–0.1 µm in diameter) and accumulation mode (0.1–0.5 µm in diameter) particles and the corresponding $PM_{2.5}$ (particulate matter <2.5 µm in diameter) mass concentrations in 1996–1997 in Amsterdam, Erfurt, and Helsinki (30).

Particle	N	25th percentile	50th percentile	75th percentile	Maximum
Ultrafine (1/cm^3)					
Amsterdam	81	11 800	14 900	22 000	47 100
Erfurt	101	10 400	17 000	25 000	38 000
Helsinki	85	12 100	15 600	18 600	46 500
Accumulation mode (1/cm^3)					
Amsterdam	78	959	1670	2590	9160
Erfurt	101	1140	1870	3170	6700
Helsinki	85	649	905	1200	2390
$PM_{2.5}$ (µg/m^3)					
Amsterdam	99	13.9	23.7	35.4	80.7
Erfurt	101	19.8	38.9	55.0	147
Helsinki	97	6.3	8.5	11.7	38.3

Table 2. Spearman's rank correlations between the 24-hour average number (n) and volume (vol) concentrations of ultrafine (UF, 0.01–0.1 µm in diameter) and accumulation mode (AC, 0.1–1 µm in diameter) particles and the corresponding mass concentrations of particulate matter with an aerodynamic diameter of <1 µm (PM_1), an aerodynamic diameter of <2.5 µm ($PM_{2.5}$), and an aerodynamic diameter of <10 µm (PM_{10}), carbon monoxide (CO), nitric oxide (NO), and nitrogen dioxide (NO_2) in 1998–1999 in Helsinki (27).

	UF_n	AC_n	UF_{vol}	AC_{vol}	PM_1	$PM_{2.5}$	PM_{10}	CO	NO	NO_2
UF_n	1.0	0.53	0.83	0.31	0.30	0.25	0.24	0.43	0.76	0.81
AC_n		1.0	0.86	0.93	0.86	0.85	0.57	0.47	0.57	0.50
UF_{vol}			1.0	0.68	0.63	0.60	0.41	0.53	0.73	0.74
AC_{vol}				1.0	0.88	0.92	0.68	0.31	0.38	0.31
PM_1					1.0	0.92	0.63	0.39	0.38	0.32
$PM_{2.5}$						1.0	0.76	0.32	0.29	0.23
PM_{10}							1.0	-0.03	0.15	0.16
CO								1.0	0.60	0.44
NO									1.0	0.73
NO_2										1.0

(table 2). Consequently, NO and NO_2 are relatively good proxies for ultrafine particles. The lower correlation of ultrafine particles with CO than with NO_2 may be due to several factors. NO and particulate emissions from traffic have more similar, continuously increasing associations with the speed of the vehicle, whereas CO emissions are high at low speeds and then decrease at higher speeds. In addition, diesel vehicles are an important source of both particles and NO_x, but they emit less CO than gasoline vehicles do.

The number concentration of ultrafine particles has a strong diurnal pattern (figure 2). There is a fivefold increase in the level of ultrafine particles starting during the morning rush hours. Therefore, a measurement of the 24-hour average concentration is too crude for ultrafine particles. The higher peak during the morning rush hours compared with that of the afternoon rush hours is probably due to poorer atmospheric mixing in the early morning hours before sunrise, which occurs between 0700 and 0900 during the wintertime in Helsinki. On the other hand, sunrise increases the atmospheric formation of new ultrafine particles (33). There is also a similar, but smaller (twofold) increase in the number concentration of accumulation mode particles (figure 2).

Spatial variation in particulate concentrations

Epidemiologic studies on the short-term health effects of particulate air pollution generally rely on levels of particles measured at one or a few central monitoring sites. However, it is clear that there is spatial heterogeneity in the absolute concentrations of particles in the city, so that the few monitoring sites cannot accurately represent the absolute levels of particles everywhere in the city. On the other hand, differences in the absolute levels do not bias the results of time-series studies on the associations between ambient-air particles and health. Therefore, the focus of examining possible bias is on correlations between the central-site monitor and other monitors in the city, and not on absolute concentrations of particulate matter.

$PM_{2.5}$ is dominated by accumulation mode particles that originate mainly from long-range transport. Therefore, the mass concentrations of $PM_{2.5}$ are fairly evenly distributed everywhere in Helsinki. In addition the correlation of the 24-hour average concentration of $PM_{2.5}$ between the different monitoring sites in Helsinki is very high ($r>0.9$).

In Helsinki, the total number concentrations of particles were measured with four CNC, three of which were placed in the city within 3 kilometers of each other and one was placed in Luukki, a rural site 22 kilometers northwest of the city center (37). The correlations for the 1-hour total number concentration between the city sites ranged from 0.6 to 0.88. The correlation was highest on days with high traffic density, like weekdays, and between the sites mostly affected by traffic. The number concentrations also varied closely with the traffic density. This correlation was observed to be a function of lag time. The optimal lag times were a few minutes, which matched the estimated times required for air parcels to travel from major roads to the measuring sites. When the wind speed was high, the correlation was not so strongly dependent on the lag time. Fairly high correlations ($r\sim0.6$) were also observed between the city sites and the rural site. This finding suggests that factors other than traffic density (eg, meteorology) also affect the atmospheric concentration of ultrafine particles.

Particulate concentrations in indoor air

People spend typically 80–90% of their time indoors. Therefore, particulate concentrations indoors rather than

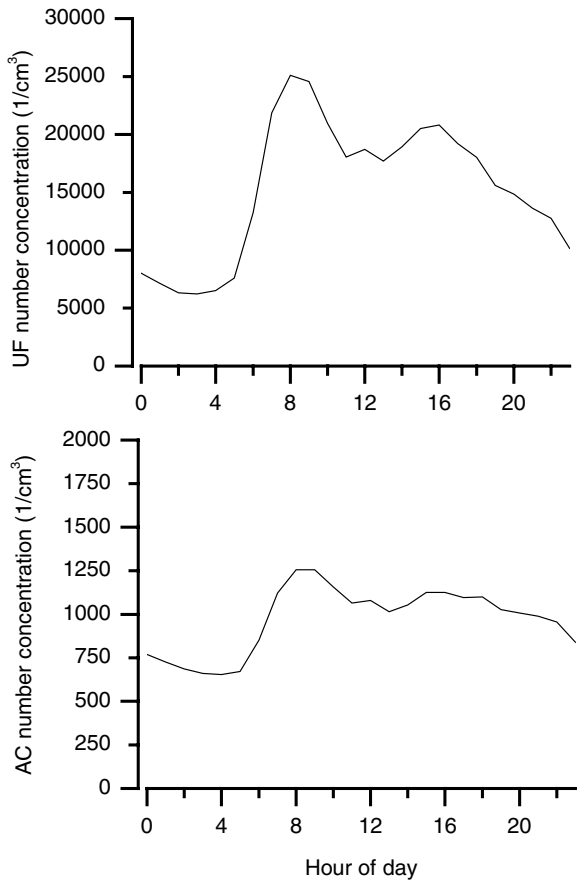

Figure 2. Average diurnal variations in the 1-hour number concentrations of ultrafine (UF, 0.01–0.1 μm in diameter) and accumulation mode (AC, 0.1–1 μm in diameter) particles in 1996–1997 in Helsinki (30).

those outdoors can have a large effect on personal exposure. Particles generated indoors can confound the association of health with particles generated outdoors only if the particles from these two origins have similar toxicity and if their concentrations correlate. It has recently been suggested that there is no such correlation for PM_{10} (15), but no such studies are available for ultrafine particles. Although there are indoor sources of ultrafine particles, such as smoking, cooking, and cleaning (38, 39), we assume that the concentrations of ultrafine particles generated indoors are not correlated with those that penetrate into indoor environments from outdoors. Therefore, the indoor sources have not been discussed in this review in more detail; instead we focus on the relationships between the outdoor and indoor concentrations of ultrafine particles.

In addition to indoor sources, the particulate concentration in certain size ranges indoors is determined by the outdoor concentration of similar particles, and the air exchange (ventilation) rate and the filtration, deposition, and re-emission of these particles in the building. The amount of filtration that occurs when outdoor particles move indoors (penetration coefficient) is one of the most effective processes with which to keep indoor particulate levels low. The rate of the deposition and re-emission of indoor particles depends on the amount of accumulation of particles on indoor surfaces, and this amount is influenced, for example, by cleaning. These processes can be modeled in a simple indoor model (40) or in a detailed aerosol dynamic model for indoor particles (39).

Filtration removes smaller particles from the air through diffusion, and larger particles are removed through deposition because of gravity and impaction. Deposition on indoor surfaces occurs through the same mechanisms. For accumulation mode particles, none of these loss mechanisms is significant, and therefore this mode has the least amount of filtrated and deposited particles. Air filtration can effectively reduce the penetration of ultrafine particles from outdoors to indoors (39) and can lead to substantial changes in the indoor total number concentration and number size distribution of particles originating from outdoors.

The air exchange rate is commonly measured as times per hour the whole air volume is exchanged in a building. If the air exchange rate is high, like ≥3, as is often the case in office buildings and other workplaces or in houses with windows and doors open, the indoor particulate concentrations can accurately follow even rapid changes in outdoor particulate concentrations (34, 40–42). However, a low air exchange rate somewhat delays the change in the indoor concentration, and the short-lasting peaks in the outdoor concentration are less clearly reflected indoors. In a measurement campaign in Helsinki, the total number concentration of indoor particles followed the outdoor concentration with approximately a 20-minute delay during the night, when the mechanical ventilation was not on (air exchange rate 0.3/hour), but the delay was less than 10 minutes in the daytime, when the ventilation was on (air exchange rate 3.7/hour) (41). Another factor that may blunt the short-lasting peaks in the outdoor concentration of ultrafine particles indoors is coagulation triggered by high particle numbers.

Long et al (42) determined nighttime infiltration factors for nine homes with no indoor sources in the New England area of the United States. There were large differences between homes, but the lowest indoor-to-outdoor ratios were observed for the smallest particles (0.5 for particles 0.02–0.03 μm in diameter) and the largest particles (0.3 for coarse particles, 2.5–10 μm in diameter). The highest ratios (0.70–0.73) were observed for particles between 0.08 and 0.5 μm in diameter. The infiltration factors were lower in the fall and winter than in the summer. Higher average indoor-to-outdoor ratios (around 1) were observed for both ultrafine and accumulation mode particles in residential houses in subtropical Australia, where usual air exchange rates varied between 2 and 5 per hour (34). Again, there were large differences between homes.

Few studies have evaluated the correlation between outdoor and indoor concentrations of ultrafine particles. When major indoor sources were excluded, a high correlation (r=0.94) was observed in a laboratory with the windows closed (4). The indoor levels were about half of the outdoor levels (4). A somewhat lower hourly correlation (r=0.73) and 12-hour correlation (r=0.83) were observed in an elementary school during one winter month in Utah, in the United States (38).

Aerosol concentrations inside office buildings have been studied as a function of corresponding outdoor concentrations in two different measurement campaigns in Helsinki. In office building 1 (41), there was an EU7 type filter that removed about 90% of the ultrafine particles but only about 70% of the accumulation mode particles (table 3). In office building 2 (43), only 30% of the ultrafine particles and 10% of the accumulation mode particles were removed by a less efficient EU3 type filter.

In office building 1 (41) with the EU7 type filter, the hourly correlation between indoor and outdoor particle number concentrations was 0.30 for nucleation mode particles, 0.57 for Aitken mode particles, and 0.91 for accumulation mode particles when the ventilation was high (air exchange rate 3.7/hour) (table 3). The respective numbers were 0.57, 0.84, and 0.87 when the ventilation was low (air exchange rate 0.3/hour). In office building 2 (43) with the EU3 type filter, the ventilation was constantly set at an air exchange rate of around 3/hour, and the hourly correlation between the

Table 3. Effect of the air exchange rate and filtration in a building on the penetration indoors and the lung deposition of ultrafine (UF) and accumulation mode (AC) particles. The fixed outdoor concentrations of UF and AC mode particles were assumed to be 10 000/cm^3 and 1000/cm^3, respectively.

Air exchange rate	Filter	Indoor-to outdoor ratio		Indoor concentration (1/cm^3)		Lung deposition [a] (10^6 particles/day)		Hourly indoor-to-outdoor correlation	
		UF	AC	UF	AC	UF	AC	UF [b]	AC
0.3/hour [c]	EU7	0.1	0.25	1000	250	6500	325	0.84	0.87
3.7/hour [c]	EU7	0.05	0.3	500	300	3250	390	0.57	0.91
3.0/hour [d]	EU3	0.7	0.9	7000	900	45500	1170	0.96	0.90

[a] Lung ventilation 13 m^3/day.
[b] Aitken mode particles only.
[c] Office building 1 (37).
[d] Office building 2 (39).

indoor and outdoor number concentration was 0.96 for the Aitken mode particles and 0.90 for the accumulation mode particles. The slightly smaller correlation for the accumulation mode particles was probably due to human activity, which caused some re-emission of deposited particles from indoor surfaces. The correlation was not calculated for nucleation mode particles, as this mode occurred only infrequently during the measurement campaign.

As discussed earlier in this review, the air exchange rate determines how fast the indoor concentration follows the outdoor concentration. Therefore, at low air exchange rates, the correlation should be lower. However, this was not seen in the aforementioned office building 1 when the periods with ventilation on and off were compared. This finding was due to the fact that the ventilation was off during the night, when there were no rapid changes in the outdoor particle number concentration.

An effective filter in the mechanical ventilation system, as in the preceding office building 1, can greatly reduce the absolute amount of variability in data on particle number concentration (table 3). When the correlation is used as the measure of the relationship between indoor and outdoor concentrations, the correlation coefficient is thereby reduced, as the correlation coefficient is influenced by the variance of the variables.

Lung deposition of particles

As with filters of mechanical ventilation systems, diffusion, deposition with gravity, and impaction determine particle deposition in the respiratory tract. Consequently, ultrafine particles are strongly deposited in the lungs, whereas accumulation mode particles are poorly deposited (44). Ultrafine particles are strongly deposited in the alveolar region, which is considered to be the most harmful site with respect to human health.

We have examined the combined effects of air filtration (expressed as the proportion of particles penetrating indoors) and alveolar deposition using a recently developed indoor air model (40) and the particulate concentration data collected in Helsinki by Koponen et al (41) and Hussein et al (43). Different filtration efficiencies and air exchange rates were used (table 3). No indoor sources were modeled. The alveolar deposition pattern and the deposition and re-emission of particles from indoor surfaces were assumed to be constant. The alveolar deposition probability of particles in the size range 0.01–0.1 μm was assumed to be 50%, and for the size range 0.1–1 μm 10% was used (44) (table 3). Although ultrafine particles usually dominate the total number concentration of outdoor particles, their filtration can be so effective in some buildings that accumulation mode particles make a larger contribution to the total number concentration indoors. When the outdoor number concentration of ultrafine particles was 10 times higher (10 000/cm^3) than the concentration of accumulation mode particles (1000/cm^3), the corresponding ratio could be only 1.7 for indoors in office building 1, with the effective EU7 type filter (ultrafine particles 500/cm^3 versus accumulation particles 300/cm^3). However, for the deposited particle doses in the human lungs, this ratio could be again 8.3, due to the different deposition probabilities of the two particulate modes (table 3).

Thus air filtration in buildings removes ultrafine particles somewhat more effectively than it does accumulation mode particles. This difference is compensated for by the higher deposition probability of ultrafine particles in human lungs. If the filtration and deposition efficiencies remain constant from day to day, they should not have a major effect on how well the variations in outdoor particulate concentrations are reflected in average personal exposure. If the filtration is very effective, it can blunt the appearance of outdoor peak concentrations indoors, and the correlation coefficient between the outdoor and indoor particulate levels decreases. In addition, a strong reduction in the absolute levels

of particles transported indoors may lead to such low concentrations and lung doses that no health effects are observed.

Personal time activity

The preceding discussion has not considered differences and changes in people's daily time activities. These differences add a very unpredictable component to the correlation between the ambient concentration and average personal exposure to particles. Daily changes in personal time activities can produce bias in time-series studies only if they are, on the average, correlated with the concentration of particles measured at the central site. However, this may well be the case, as people may change their daily activities in response to weather and air pollution warnings. They may open or close their windows and change filtration efficiencies and ventilation rates. They may also decide to avoid exercise. Exercise increases lung ventilation and breathing through the mouth and, in turn, reduces the filtration efficiency of larger particles in the upper respiratory tract.

People may also change the time they spend in traffic. Ultrafine particles are locally produced from primary and secondary emissions of vehicle traffic, and therefore they show more spatial variability in absolute levels than accumulation mode particles do. This difference can be seen as a stronger decline in the ultrafine particle number concentration than the $PM_{2.5}$ mass concentration with distance from a busy road (36). Therefore, it can be speculated that the time spent in traffic can potentially produce greater bias in time-series studies on ultrafine particles than in those on $PM_{2.5}$.

Concluding remarks

In this review, the exposure assessment of ultrafine particles in epidemiologic time-series studies has been discussed and compared with those of accumulation mode particles and $PM_{2.5}$. The main requirement for a time-series study to provide an unbiased estimate of the health effects of air particulate matter is that the particulate concentration measured at a central site correlates with the average personal exposure (14). Unfortunately, there are no studies on this aspect for ultrafine particles. Therefore, sources, ambient-air levels, the indoor-to-outdoor ratio, and the lung deposition of ultrafine particles have been examined separately.

In epidemiologic studies, CNC data on the total number concentration of particles can be used as a proxy for ultrafine particles. A CNC, together with continuously acting $PM_{2.5}$ and PM_{10} mass monitors, gives a good picture of the actual concentration and variations in the main classes of urban air particles (ie, ultrafine, accumulation mode and coarse mode particles). More elaborate instrumentation is required for detailed studies on atmospheric physics and chemistry.

There seems to be smaller differences between European cities in the 24-hour average number concentration of ultrafine particles than in the corresponding $PM_{2.5}$ mass concentration. Ultrafine particles also have higher diurnal variability and greater spatial heterogeneity than $PM_{2.5}$. This difference is not surprising, as ultrafine particles are mostly produced by local traffic, whereas accumulation mode particles and $PM_{2.5}$ are dominated by long-range transport. In addition, a high aerosol mass concentration reduces the number concentration of ultrafine particles (45), because accumulation mode particles and coarse mode particles act as a condensation sink for condensable vapors (and therefore decrease the formation of new particles), as well as a coagulation sink for existing ultrafine particles.

Ultrafine particles have lower penetration indoors than $PM_{2.5}$, which is partly compensated by their higher deposition probability in human lungs. Penetration indoors is greatly influenced by the air exchange rate and filtration efficiency of the building, while lung deposition is affected by the physical activity of people. The few available studies show a moderate or high correlation of ultrafine particle concentrations between different city sites and between outdoor and indoor air. The latter correlation is reduced when the air exchange rate is low, which may be common in areas with cold climate. In a sample of 242 residences in Helsinki, the air exchange rate averaged 0.5/hour (46). However, if the air exchange rate and filtration efficiency of the building and the lung deposition efficiencies of particulate fractions do not change from day to day, they should not have a major effect on the correlation between outdoor particulate concentrations and average personal exposure. Changes in people's daily time activities add another, unpredictable component to the evaluation of results from time-series studies on ultrafine particles.

We conclude that the main uncertainty in the interpretation of results from epidemiologic time-series studies on ultrafine particles is the lack of data on the correlation between the outdoor air concentration and average personal exposure. However, the limited data available suggest that central-site monitoring may give a somewhat worse proxy for human exposure to ultrafine particles than to $PM_{2.5}$ in time-series studies. Multicenter studies with repeated measurements of outdoor, indoor, and personal exposure concentrations of ultrafine particles are needed to address this difference.

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