STATE OF EPIDEMIOLOGICAL EVIDENCE FOR HEALTH IMPACTS OF ULTRAFINE PARTICLES

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Abstract

There has been increasing interest in the effect of ultrafine particles (UFP) on human cardiovascular and respiratory health. The adverse health impacts due to particle exposure are currently attributed to the mass concentration or the chemical composition of particles smaller than 10 μm (PM_{10}) or 2.5 μm ($PM_{2.5}$) in diameter. However, it has been hypothesised that it is actually UFP (< 0.1 μm) measured in terms of number concentration, as opposed to mass concentration, that might be responsible for the observed health effects. This paper presents the results of a critical literature review aimed at analysing the current state of epidemiological evidence for the effects of UFP on human health. In summary, the array of epidemiological studies conducted thus far suggests that UFP exposure is associated with human mortality, and respiratory and cardiovascular morbidity. This holds true despite the considerable gaps in knowledge that remain, and despite the inconsistencies found between some studies, resulting from some deficiencies in the study designs. The limited number of epidemiological studies conducted thus far indicates that there are comparable health effects of fine and ultrafine particles, which appear to be independent of each other. Fine particles show more immediate effects whilst ultrafine particles show more delayed effects on mortality. However, at present the database is too limited (in terms of both number of studies and number of subjects) and geographically restricted, to allow clear conclusions on the mode of action and/or generalisation to other settings. Consequently, it is recommended that further, better-designed studies be initiated to improve the understanding of health impacts of UFP.

Keywords: ultrafine particles, health effects, epidemiological research, mortality, morbidity, respiratory, cardiovascular

1. Introduction

While an association between ambient particulate matter (PM), and respiratory and cardiovascular disorders has been long been recognised, it is not clear which fraction of PM is responsible for the observed health implications. The adverse health effects of particle exposure are currently attributed to the mass concentration of particles smaller than 10 μm (PM_{10}) or 2.5 μm ($PM_{2.5}$) in diameter, although it has been hypothesised that it is ultrafine particles (UFP, < 0.1 μm) that might be most toxic and thus responsible for the observed health effects. Ambient UFP originate primarily from combustion sources (e.g. mobile sources such as on-road vehicles; and stationary sources such as electrostatic precipitators, bag houses etc) (Cass et al. 2000). UFP only constitute up to 8% of the mass of PM in ambient air, however they are present in very high numbers, have much greater surface area than larger particles and may be deposited in greater numbers in the lungs. Toxicological studies also indicate that UFP are more potent in inducing cellular damage than larger particles and can access circulatory system and move from lungs to other organs more easily (Morawska et al. 2004).

The aim of this study was to review the state of epidemiological evidence for the health impacts of UFP. This research was restricted to the studies reported in peer-reviewed literature, and those that

directly investigated ambient UFP or their specific fractions, or those that linked health effects to complex mixtures of pollutants were excluded. The authors are of the opinion that even if UFP were important components of such mixtures, the absence of good characterisation and quantification of the composition of all fractions of ambient PM means that the effects from UFP cannot be decoupled from the effects of other components of PM.

2. Epidemiological Evidence of UFP Impacts on Human Health

2.1. Overview of Studies and Summary of Main Findings

A number of epidemiological studies have addressed the association between ambient UFP concentrations and the mortality/morbidity of urban populations, however this number is relatively small. Thus far, only thirteen epidemiological studies have reported on respiratory and cardiovascular mortality or morbidity due to exposure to UFP: one study (Wichmann et al. 2000) – reported on both respiratory and cardiovascular mortality; seven studies (Osunsanya et al. 2001, Pekkanen et al. 1997, Penttinen 2001, Peters et al. 1997, Timonen et al. 2004, Tiittanen et al. 1999, von Klot et al, 2002) – reported on respiratory morbidity; and five studies (de Hartog et al. 2003, Pekkanen et al. 2002, Ruckerl et al. 2006, Vinzents et al. 2005, Henneberger et al. 2005) – reported on cardiovascular morbidity. The vast majority of these studies were conducted within the framework of the European "Exposure and risk assessment for fine and ultrafine particles in ambient air" (ULTRA) program, by the same teams of researchers from Finland, Germany and the Netherlands. Noteworthy, the same datasets for the particle concentrations were used in several studies for the investigation of different health outcomes.

2.1.1. Study designs

The studies were limited to the investigation of the acute health effects of short-term exposures, which evaluated the impact of day-to-day variation in ambient pollution on health. These studies have correlated morbidity and mortality with daily pollution levels. The general approach was to compare the health effects associated with various fractions of PM. Study outcomes ranged from mortality counts of populations to changes in specific parameters or biomarkers in individuals.

While the results of all studies except Vinzents et al. (2005) were described as providing exposure-response relationships, the measurements were conducted at single, fixed-point locations representing "urban background" levels and they only provided information on ambient concentration-response relationships across the population studied. Namely, data was collected at individual monitoring sites located in mixed-use urban areas (residences, offices, schools, hospitals etc) close to the centre of the cities and approximately 40-50 m away from the major roads. The main sources of air pollution at these locations were traffic and domestic heating, as well as the power plants (in Erfurt and Kuopio). Particle number concentrations in different size classes were measured with the mobile aerosol spectrometers and condensation particle counters were used to measure the total number concentration of particles with a lower detection limit of 0.007 μm. $PM_{2.5}$ were measured with Harvard impactors and PM_{10} were measured with TEOM. Elemental carbon (EC) and organic carbon (OC) were determined from the ambient carbon monitors. Confounding factors (data on gaseous pollutants and meteorological variables of temperature, barometric pressure, relative humidity and wind speed) were collected from existing networks.

Unlike other investigations, the study by Vinzents et al. (2005), conducted in Denmark, assessed the relationship between time-resolved personal exposure to both traffic- and indoor-related number concentrations of UFP and oxidative DNA damage in mononuclear blood cells. Condensation particle counters (TSI 3007; TSI, St. Paul, MN, USA) which provided continuous measurement of the number concentrations of UFP were carried in the backpacks of fifteen healthy non-smoking subjects, with the inlet tube placed in the breathing zone. This allowed for the study of exposure-response relationships associated with variations in outdoor exposure for individuals, due to differences in traffic density and meteorological conditions.

The following is a summary of the main findings of these epidemiological studies with respect to the health effects of UFP.

2.1.2. Mortality studies

- A study on daily mortality conducted in Germany (Wichmann et al. 2000) showed comparable and independent increases in mortality in association with ultrafine and fine particles.
- The mortality data suggested that fine particles have immediate health effects whereas UFP have more delayed effects. The immediate effect of exposure was found to be respiratory disease mortality whereas the delayed effects generally involved an increase in cardiovascular disease mortality.

2.1.3. Respiratory morbidity

- Panel morbidity studies with asthmatic subjects indicate that both fine and ultrafine particles are associated with the respiratory health of the exposed population (Peters et al 1997; Pekkanen et al. 1997; Tiittanen et al. 1999; von Klot et al. 2002). A decrease in respiratory functions (e.g. peak expiratory flow) and an increase in symptoms and medication use were associated with elevated particle concentrations of UFP, independently from fine particles.
- There is an indication that the acute effects of UFP number on respiratory health are stronger than that of the mass of fine particles (Penttinen 2001).
- The acute effects of UFP on respiratory health of adult asthmatics are more profound than for children with asthma symptoms (Pekkanen et al. 1997; Tiittanen et al. 1999).
- Inflammatory events in the lungs take several days to develop (von Klot et al, 2002). It is likely that a lag time exists between exposure to UFP and the acute respiratory health effects of the exposed population. Cumulative effects over 5 days seem to be stronger than same day effects (Peters et al. 1997).

2.1.4. Cardiovascular morbidity

- There is association between exposure to UFP and cardiovascular morbidity in a population with chronic heart disease. Panel studies among subjects with coronary heart disease indicate that there are independent associations between both fine and ultrafine particles and the risk of ST-segment depression, which is used as indicator of myocardial ischemia, in the exposed population (Pekkanen et al. 2002).
- There is an indication that the effect of both fine and ultrafine particles on cardiovascular morbidity is at least partly mediated through increased susceptibility to myocardial ischaemia (Pekkanen et al. 2002).
- The results also suggest that inflammation, as well as parts of the coagulation pathway, may contribute to the association between particulate air pollution and coronary events (Ruckerl et al. 2006).
- Elevated concentration of UFP may have a significant immediate effect on physiological measures of cardiovascular functions, such as QTc duration, T-wave complexity and T-wave amplitude (Henneberger et al. 2005). These results provide evidence for a deleterious effect of UFP on myocardial substrates and vulnerability, key factors in the mechanisms of cardiac death.
- Oxidative DNA damage to base pairs in circulating mononuclear blood cells is associated with personal exposure to UFP and short-term higher intensity exposure in traffic is associated with elevated levels of damage (Vinzents et al. 2005). These results indicate that biologic effects of UFP occur at modest exposures, such as those occurring in traffic, which supports the relationship between UFP and the adverse health effects of air pollution. These results reinforce the important role of UFP in causing oxidative stress. Moreover, concern about the health effects of small high-intensity exposures of UFP in ambient air may also be relevant.

Figure 1 (in Appendix) presents the odds ratios and 95% confidence intervals reported in the morbidity studies. It can be seen that the odds ratios were typically greater than or close to 1.00, which suggests some increased risk, while the 95% confidence intervals indicate that these increases do not reach statistical significance since, in general, they include 1.00 within their ranges.

2.2. Uncertainties in the Epidemiological Evidence of the Health Impacts of UFP

Although the vast majority of studies observed pathologic effects associated with UFP, which were independent of fine particles, some results suggest that the effects of larger particles, especially of accumulation mode particles (with the diameters between 0.1 and 1 μm), may be stronger than the effects of UFP. On the other hand, there are a few reports that suggest an opposite tendency.

Analysis of the concentration levels measured in the morbidity studies revealed that, although the studies demonstrated the highly variable size and number distribution, as well as chemical composition of particles, the mean concentrations of UFP were comparable in all centres. The number concentration trends of UFP did not follow the trends of either PM_{10} or $PM_{2.5}$ concentrations, while particle mass concentrations were typically inter-correlated within the studies. The mean number concentration of UFP across the centres typically ranged from 1.00×10^4 to 2.10×10^4 particles/m^3, with the overall mean value of $1.56 \pm 8.56 \times 10$ particles/m^3.

As the UFP concentrations were comparable in all studies, levels of exposure cannot be used to explain the different health outcomes. The inconsistencies found between studies may be due to the study designs. Specifically, all these results were based on the particle concentrations measured at a single monitoring site, which may not be a good proxy measure for the personal exposure of subjects. While the results of the studies were described as providing exposure-response relationships, they actually provided

information on ambient concentration-response relationships across the population studied. However, it is unlikely that the measurements taken at a single monitoring site will give a reasonable estimate of overall outdoor pollutant exposure. Thus, it is not clear what impact this had on the observed (or unobserved) associations between UFP and daily morbidity, and whether the results were due to biases in the measurement of exposure to UFP caused by the monitoring ambient levels of air pollutants at a single sites rather than measuring total exposure of each member of the study population. To quantify the associated risks and health impacts of UFP, it is necessary to obtain a description of the full-range of exposure distribution. To achieve these goals, measurements should be taken at multiple outdoor locations, to gain a better representation of the UFP exposures of large, spatially dispersed populations.

2.3. Sensitive Exposure Groups

So far, no systematic attempts have been reported to identify and define sensitive exposure groups with regard to UFP. It is, therefore, assumed that the subpopulations that have been considered more susceptible to the effects of air pollutants containing particulate matter in general will also be more susceptible to the effects of UFP. Thus, the subpopulations that are likely to be at greatest risk due to exposure to ambient UFP may include:

- Individuals with respiratory disease (e.g. COPD, acute bronchitis, and asthma) and/or cardiovascular disease (e.g. ischemic heart disease);
- Individuals with infectious respiratory disease (e.g. pneumonia) (exposure to UFP might also increase individual susceptibility to respiratory infections);
- Elderly individuals; and
- Children.

2.4 Monitoring Particle Number or Particle Mass Concentrations

While toxicological studies demonstrate that the primary determinant of the effect of UFP is their number and their surface area, the available data provides only modest epidemiological support for the hypothesis that it is the number concentration of UFP, rather than the mass concentration, that is important in driving the health effects. Nevertheless, given the UFP relevance to human heath, it is not sufficient to only study associations between health outcomes based on the mass of particles e.g. PM_{10} and $PM_{2.5}$. This is best illustrated by developments in Erfurt over a seven year period. While the mass of $PM_{2.5}$ was shown to reduce from 1991 to 1998, the number concentration of UFP was stable and the smallest size fraction of UFP (particles between 0.01 and 0.03 μm diameter) increased steadily over the seven years of observation. These trends clearly demonstrate that the reduction of $PM_{2.5}$ does not automatically mean that the number of UFP is also reduced. Thus, $PM_{2.5}$ cannot be used as indicator for UFP. Identification of the relevant particle fraction with respect to human health is, therefore, crucial for sound regulatory activities.

2.5. Conclusions

Despite the limited array of epidemiological studies conducted thus far, the current state of knowledge on the health effects of UFP does suggest that UFP exposure is associated with respiratory and cardiovascular effects, and that there are comparable health effects of fine and ultrafine particles, which appear to be independent of each other. This holds true despite considerable gaps in knowledge and some inconsistencies that were found between studies. Fine particles tend to show more immediate effects while UFP show more delayed effects on mortality. Therefore, such results or outcomes could serve as pointers for future investigations or formulations of hypotheses, but not as scientifically justifiable conclusions.

Given that there is a poor correlation between UFP (measured by number) and fine particle mass, observed statistical independence (in the multiple regression models) is of significance. Furthermore, given that fine and ultrafine particles often originate from common sources, given the dynamics of particle formation and accumulation, and given the different observed lead-lag relationships between exposure and observed health responses, it is currently difficult to make very strong inferences about independent effects, based on the epidemiological evidence provided so far. Further better-targeted studies in other settings should be initiated to improve the understanding of UFP and health outcomes.

3. Recommendations for Future Epidemiological Studies to Address Gaps in Knowledge of Health Effects of UFP

Knowledge gained from the epidemiological studies reported to date has improved scientific understanding of the impacts of UFP on human health, compared to a few years ago. Nevertheless, further, better-designed studies will provide much clearer answers on the health implications of UFP. The design of such studies can now target the specifics of UFP (e.g. characteristics and dynamics of UFP in atmospheric systems) which differ from

other size fractions and characteristics of ambient PM. The World Health Organization “Guidelines for concentration and exposure-response measurement of fine and ultrafine particulate matter for use in epidemiological studies” (WHO 2002) is an example of the progress in understanding how UFP specifics should be dealt with in study designs with respect to facilitating the usefulness of data. The following are the specific recommendations for future epidemiological studies regarding to health implications of UFP:

1. To quantify the associated risks and health impacts of UFP, it is necessary to obtain a description of the full-range of exposure distribution. Thus, air monitoring should be conducted at multiple outdoor locations, over various distances from the sources of UFP, rather than at a single, centrally located monitoring site, for a better representation of the UFP exposures of large, spatially dispersed populations.
2. Study designs and statistical approaches used should allow for the decoupling of the effects of UFP from those of other particle size modes.
3. Studies should be conducted over longer periods of observation, to enable comparison of effects during periods with high UFP exposure and periods likely to have low exposures. Longer periods of observation would also enable an evaluation of the lag phase between exposure and effect.
4. Studies should be conducted with larger sample sizes to enable better modelling of the role of diverse demographic and clinical variables in the effect of UFP. In addition, studies should specifically target potentially susceptible subgroups and provide information on the susceptibility of particular groups of the population.
5. Taking note of the reported differences in UFP concentrations and other characteristics between different geographical locations (resulting from the differences in the local sources, their strength and characteristics, meteorology, topography etc), as well as the differences in demographic, socio-economic and urban use factors, it is expected that the type and the magnitude of the responses will differ between different locations. It is therefore recommended that future studies be conducted in selected places in Australia to quantify the relationship between exposure to UFP and health outcomes in an Australian setting. The outcomes of such studies would provide appropriate guidance to the decision makers on the most desirable steps in controlling exposure to UFP in Australia.

Acknowledgments

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Appendix

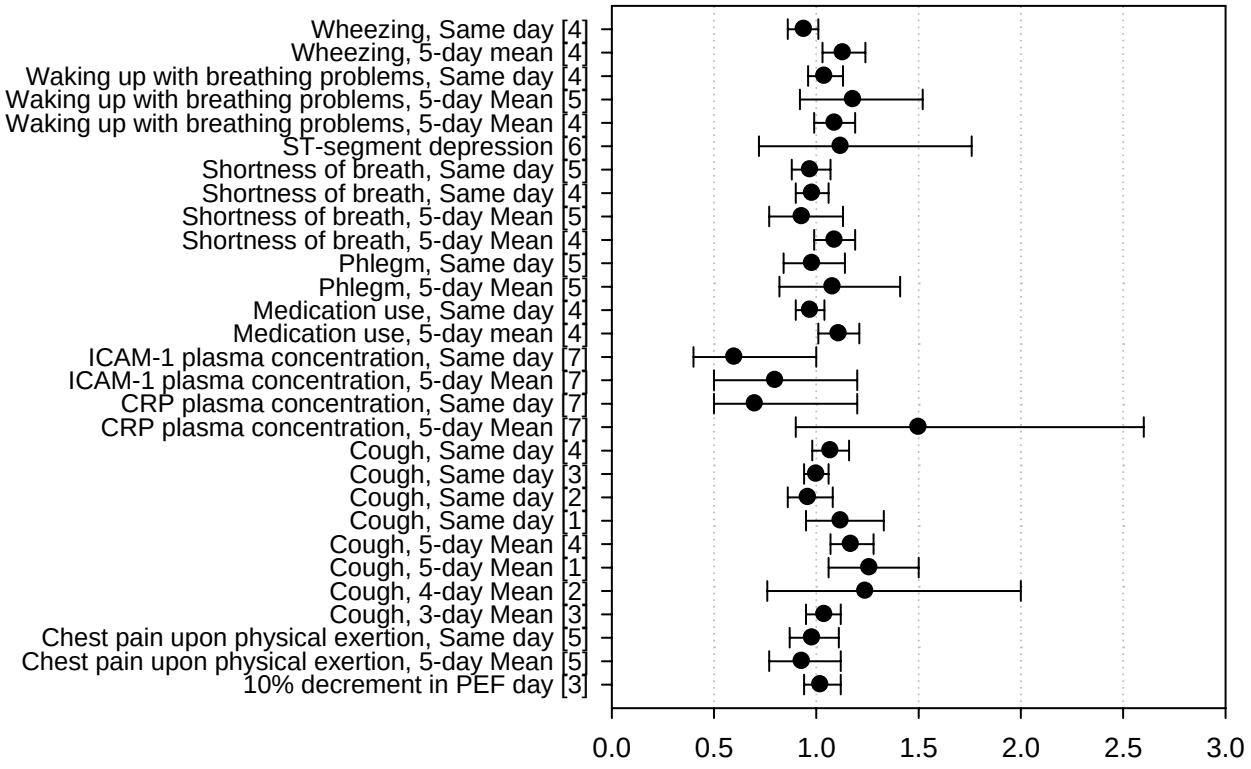

Fig.1. Summary of the results of the morbidity studies on the association of UFP with health outcomes: odds ratios (dots) and 95% confidence interval (bars) for ultrafine particles by study. [1] - Peters et al., 1997; [2] -

Tiittanen et al, 1999; [3] - Osunsanya et al. 2001; [4] - von Klot et al 2002; [5] - de Hartog et al., 2003; [6] - Pekkanen et al., 2002; [7] - Ruckerl et al., 2006.