What is causing the health effects of particles?

Key points

- Both short-term and long-term exposure to ambient levels of PM_{10} are consistently associated with respiratory and cardiovascular illness and mortality as well as other ill-health effects. The associations are believed to be causal.

- It is currently not possible to discern whether there is a threshold particle concentration below which there are no adverse effects on the whole population's health.

- The effects on health are likely to be dominated by exposure to particles in the long term. Using the health effects coefficients published by COMEAP (1998), estimates for the UK indicate that short-term exposure to the levels of PM_{10} prevalent in 2002 led to 6,500 deaths and 6,400 hospital admissions brought forward that year, although it is not possible to discern by what length of time the events were brought forward. Coefficients published by COMEAP (2001) also indicate that for each 1 $\mu g\ m^{-3}$ decrease in $PM_{2.5}$ over the lifetime of the current population of England and Wales between 0.2 and 0.5 million years of life will be gained (COMEAP, 2001), equivalent, on average, to 1.5–3.5 days per individual. These estimates assume both linearity in the relationship between particle concentration and health outcome and the absence of a threshold.

- The effects of particles on health are likely borne predominantly by susceptible subgroups of the population, such as those with pre-existing lung, heart or other disease and/or the elderly and children.

- The balance of evidence currently available suggests that it is combustion-derived components of PM_{10} – which are comprised predominantly of fine and ultrafine carbon-containing particles and may be enriched with trace metals or specific organic compounds – that are primarily responsible for the harmful effects.

- There is generally less evidence to connect secondary inorganic PM and coarse particles with adverse health effects. However, the latter, in particular, cannot be ruled out since certain sources of these particles may be enriched with components of putative high risk (for example, soluble trace metals). The coarse fraction also contains biological material such as pollen and may be proportionally enriched with endotoxin, both of which factors can lead to adverse health effects.

- The lack of information on quantitative relationships between adverse health effects and specific components of PM_{10} (if different from the relationship

with total PM_{10}) makes it difficult to assess the impact of future changes to the PM_{10} mix, arising from strategies aimed at reducing PM_{10} overall, upon population health.

- Recently, the World Health Organisation (WHO) has recommended the development of air quality guidelines for $PM_{2.5}$ alongside the retention of measurement of PM_{10} for public health protection. Health-based guidelines for $PM_{2.5}$ should be derived with the use of $PM_{2.5}$ data since simple scaling of the PM_{10} limit value using the prevailing $PM_{2.5}/PM_{10}$ ratio does not lead to extra targeting of health benefits. WHO also recommended a re-evaluation of the value of black smoke as an indicator for traffic-related air pollution.

- Experimental evidence suggests that one mechanism by which particles exert their effects is by causing oxidative stress (probably via the generation of free radicals), which leads to inflammation.

3.1 Introduction

58. The evidence for adverse human health effects associated with both short-term (over several days) and long-term (over many years) exposure to ambient PM_{10} has been comprehensively reviewed elsewhere (COMEAP, 1998; WHO, 2000; EPAQS, 2001; WHO, 2003; USEPA, 2004). The adverse health effects include respiratory morbidity (wheeze, reduced lung function) and mortality; cardiovascular morbidity and mortality; and cancer. There is a widespread consensus that associations are causal.

59. In order to provide a context for the rest of the report, this chapter briefly reviews current understanding of the health effects of exposure to PM_{10} and its constituents in the UK. It does not draw new conclusions about the health effects of particles. The literature cited is representative, not exhaustive.

60. Current standards for ambient PM in the UK and elsewhere in Europe relate to PM_{10}, which consequently provides the vast majority of data against which adverse health effects have been quantified. However, ambient PM_{10} is physically and chemically diverse, as is described in Chapters 2 and 6, and it has generally not yet been possible to establish causal relationship(s) between the health effects and specific properties of PM_{10} that are more convincing than the relationship with total PM_{10} inhaled. Some of the chemical species contained within PM_{10} (for example, trace metals and polycyclic aromatic hydrocarbons) can exert considerable toxicity in their own right. However, exposure to PM causes adverse health effects that often exceed those that can be predicted on the basis of the toxicity of the known individual constituents. The review in this chapter of possible effects of chemical species within PM is in the context of this non-specific toxicity rather than the well-known toxicity of individual chemical components.

61. Epidemiological studies have formed the basis of PM standard setting because relating daily or longer term mass concentrations of particles to a wide range of health endpoints is relatively straightforward. Such studies often embrace the whole population and thus reflect the full range of individual sensitivity to inhalation of ambient concentrations of PM. However, the diverse sources and spatial and temporal variability of PM_{10} can complicate the accurate quantification of individual and aggregate-level exposure. A disadvantage of the empirical

methodology of epidemiology is that considerable monitoring data and a large study population are required to yield sufficient statistical power to narrow the confidence intervals (CIs) of results. Consequently, epidemiology is inevitably measurement-led and a lack of epidemiological evidence for an effect or not of particular component(s) of PM_{10} often reflects a lack of sufficient data to test.

62. Toxicology can be used as an alternative approach to understanding the adverse health effects of PM and may involve *in vivo* animal exposures or *in vitro* studies. The advantage of a toxicological approach is control over exposure to individual components or mixtures, but doses are usually high and quantitative extrapolation to human health effects from ambient doses is difficult. In some studies, particle mixtures other than that found in ambient air have been used, and extrapolating from such studies to predict the effects of ambient particles is even more difficult. Nevertheless, toxicology can provide insight into the potential biological cause-effect pathways of specific PM_{10} components and subfractions.

3.2 The health impact of particles in the UK

63. Quantitative estimation of health impacts from exposure to PM assumes linearity in the relationship between exposure and responses as well as the absence of (or existence of a very low) threshold of exposure below which there is no effect.

64. COMEAP has used estimates of population exposure-response relationships from time-series studies to quantify the number of deaths or hospital admissions for respiratory disorders attributable to short-term exposure to PM_{10}. COMEAP (1998) estimated that at the concentrations that prevailed in 1996, exposure to PM_{10} in urban areas in the UK (excluding Northern Ireland) caused 8,100 deaths (all causes) to be brought forward and 10,500 hospital admissions for respiratory complaints to be either brought forward or additionally caused. Using the same COMEAP health-effects coefficients, but basing PM_{10} concentrations on the 2002 maps presented in Chapter 8, updated calculations indicate that short-term exposure to PM_{10} in 2002 in the UK caused 6,500 deaths to be brought forward and 6,400 hospital admissions to occur that were either brought forward or would not have otherwise have happened. Additional morbidity effects include the increased use of bronchodilators on poor air quality days.

65. For these acute responses it is not possible to establish either the extent to which death is brought forward or the split of hospital admissions between those that were brought forward and those that would not have occurred in the absence of exposure to PM_{10}. It may be that the major effect of short-term exposure to PM_{10} is to hasten the death of the elderly and the sick, in which case the impact of air pollution episodes on mortality is relatively small. However, in some cases deaths may be brought forward by weeks or months rather than days.

66. There are very few cohort studies[1] on the chronic health effects of particles in the UK/Europe from which to estimate the health effects from long-term exposure to particles. COMEAP (2001) has applied results from US cohort studies on $PM_{2.5}$, but it is important to stress that the impact of pollution could vary between countries because of differences in particle composition and population lifestyle.

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[1] In a cohort study, the exposure to particles, and the health status, is assessed over time for a subpopulation of specific individuals.

The long-term health effects appear to be dominated by cardiovascular rather than respiratory mortality. The quantitative estimate determined by COMEAP to be most likely, based on current knowledge, is a gain of 0.2–0.5 million life years for the population of England and Wales in 2000 for every 1 µg m^{-3} decrease in annual mean PM$_{2.5}$ over its lifetime. (The range incorporates different assumptions in lag time between hazard reduction and health gain). This estimate corresponds to an average of 2.5 days gained per person for all 52 million people, or 25 days for 5 million people, or 4.5 months for 1 million people and so on, or a mixture of these. Although it is likely that effects are borne only by a subset of the population, the particular distribution of life expectancy gains across individuals cannot yet be identified.

67. The above data indicate that life expectancy gains from the reduction of exposure to particles in the long term are about tenfold greater than for a similar magnitude reduction in exposure over the short term. Uncertainties within the long-term estimates include undetected confounding[2], the lag time and the extent to which the long-term health outcomes are driven by the much higher exposures to PM$_{10}$ air pollution in the past (Brunekreef and Holgate, 2002).

3.3 Evidence for adverse health effects from specific physical/chemical components of PM$_{10}$

3.3.1 Fine particles (PM$_{2.5}$)

68. Time-series epidemiological studies, in the UK and elsewhere, that use short (0–3-day) lag times have shown that PM$_{2.5}$ and black smoke are at least as predictive as PM$_{10}$ for certain acute health endpoints.

69. In the West Midlands conurbation, analysis of hospital admissions by age over the period 1994–1996 showed evidence of associations between daily PM$_{10}$, PM$_{2.5}$ and black smoke and respiratory admissions in the 0–14 years age group (Anderson *et al*., 2001). The results for black smoke were more robust between different models than for PM$_{10}$ or PM$_{2.5}$, whereas the coarse fraction (PM$_{10-2.5}$) showed smaller and less consistent associations. Recent updates to this study show stronger associations between adverse health effects and PM$_{2.5}$ and strengthen the conclusion that the active component resides mostly in the fine fraction.

70. In Edinburgh during 1981–1995, a significant positive association was found between black smoke (mean of previous 3 days) and daily all-cause and respiratory mortality in people aged 65 or over, in addition to a significant positive association between PM$_{10}$ and cardiovascular hospital admissions also for people in this age group (Prescott *et al*., 1998).

71. As indicated in Section 3.2, there are no published data on the health effects of long-term exposure to PM$_{2.5}$ (or even to PM$_{10}$) in the UK. Of the US studies

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[2] A confounding factor is a condition or variable that is both a risk factor for disease and associated with an exposure of interest. This association between the exposure of interest and the confounder may make it falsely appear that the exposure of interest is associated with the disease.

used by COMEAP to estimate the health effects of long-term exposure in the UK, the Harvard Six Cities cohort study found $PM_{2.5}$ was significantly associated with cardiopulmonary and cardiovascular mortality (with a non-significant increased risk for $PM_{2.5}$ and lung cancer) (HEI, 2000). The American Cancer Society cohort study also showed a significant association between $PM_{2.5}$ and all-cause and cardiopulmonary mortality as well as lung cancer mortality, but no association between coarse particles ($PM_{15-2.5}$) and mortality (Pope *et al.*, 2002) was found.

72. In the US, healthy human volunteers exposed for 2 h to average fine particle concentrations of 200 μg m^{-3} (inhaled as concentrated air particles) showed transient mild pulmonary inflammation, although no other indicators of respiratory symptoms or decline in pulmonary function (Ghio *et al.*, 2000). Urban fine concentrated air particles also cause lung inflammation and injury in rats (Clarke *et al.*, 1999). This work provides support for the assumed causality of the associations observed in epidemiological studies.

3.3.2 Ultrafine particles ($PM_{0.1}$)

73. Very few data on exposure to ultrafine particles ($PM_{0.1}$) exist on which to base epidemiology. Although a number of sites in the UK now have monitors for both total and size-resolved particle count there are probably still insufficient data for epidemiological analysis.

74. In studies with German and Finnish asthma patients, the exacerbation of symptoms had a stronger association with daily fluctuations of ultrafine than with fine particles. A study on daily mortality in Germany showed fine and ultrafine particles had comparable effects, although the fine particles had more immediate effects and the ultrafine particles showed effects between particle concentration and mortality that were delayed for a few days. The immediate effects were clearer in respiratory cases, whereas delayed effects were clearer in cardiovascular cases (Wichmann and Peters, 2000).

75. A number of *in vitro* and rat *in vivo* studies have shown that monodisperse ultrafine particles composed of, for example, carbon black, nickel or cobalt are capable of inducing relevant inflammation responses, in which the production of damaging reactive oxygen species (ROS) play a role (Dick *et al.*, 2003).

76. To rationalise the cardiovascular effects associated with particle exposure, it has been hypothesized that, as well as initiating inflammation responses in the lung, ultrafine particles can pass through into the blood circulation and act systemically (Seaton *et al.*, 1995). Measurements of the blood of volunteers who have inhaled radioactively labelled ultrafine carbon particles has recently provided evidence for this (Nemmar *et al.*, 2002).

3.3.3 Coarse particles (PM_{coarse})

77. Some time-series studies have provided limited evidence that coarse particles are associated, independently of fine particles, with mortality and morbidity endpoints such as respiratory hospitalizations. It is likely that endotoxin is more closely associated with aged crustal coarse particles and contributes to some of the health effects of this fraction along with other biological material such as pollen

and spores, which have known health effects. In addition, certain sources of coarse particles may be enriched with components of putative high risk such as trace metals (Section 3.3.5). Some coarse particles may contain agglomerations of fine particles, or fine particles or semi-volatile components adsorbed onto larger particles, that may disaggregate within the lung. Agglomerations of fine particles may also retain the high surface area and surface chemical activation of the subunits.

3.3.4 Total surface area of particles

78. A linear association between daily mortality rate and the estimated surface area concentration of coalescing particles has been demonstrated using historic UK black smoke time-series data and a simple model of the evolution of particle distributions (Maynard and Maynard, 2002). The analysis also indicated the existence of a threshold particle concentration below which particle mass and surface area concentrations were linearly related. Below this threshold (estimated to be ~35 µg m^{-3} for fine particles) mass concentrations may provide a good indicator of health effects and mask the influence of surface area, if the latter is the controlling property, whereas at high particle concentrations effects seemed to be more closely related to surface area. Present day fine particle concentrations in the UK are usually well below this threshold, but the size distribution of particles is unlikely to be uniform everywhere and consistent with this simple model, so the appropriateness of a surface area metric cannot be ruled out.

79. *In vivo* rat studies using monodisperse polystyrene particles with a diameter in the range of 64–535 nm have yielded a linear relationship between the surface area of particle dose instilled against different parameters of lung inflammation (Brown *et al.*, 2001). These findings support the hypothesis that small particles, even of presumed low toxicity material such as polystyrene, can exert inflammatory activity in proportion to their large specific surface area.

3.3.5 Chemical constituents of particles

3.3.5.1 Sulphate, acidity and other major inorganic ions

80. In the West Midlands time-series analysis, health associations with particle sulphate were similar to those of PM$_{2.5}$ although, in both instances, clear effects were difficult to discern. In the US, the Harvard Six Cities cohort study also showed that particle sulphate was significantly associated with long-term cardiopulmonary and cardiovascular mortality. The similar associations for sulphate and PM$_{2.5}$ mean it is possible that sulphate is a surrogate for other components.

81. The evidence from toxicity studies is for low or undetectable toxic potency for sulphate and other major inorganic components of particles, such as nitrate and chloride (Schlesinger and Cassee, 2003).

3.3.5.2 Trace metals

82. Both toxicological studies and *in vitro* assays modelling inflammation have implicated transition metals (often, but not exclusively, the water soluble component) as being the causative agent(s) of cardiopulmonary injury in both healthy and compromised rats. Many of these studies have used real samples of PM$_{10}$ or PM$_{2.5}$ and have shown that the effects are blocked by the addition of

metal chelators to the samples. The balance of mechanistic evidence suggests that the inflammation is promoted by ROS generated by chemical cycling of the metals between different oxidation states.

83. A time-series epidemiological study in the UK showed no positive association between the daily trace metal composition of PM_{10} or $PM_{2.5}$ and respiratory and cardiovascular mortality and morbidity for one year of measured data (1999–2000) (Beverland *et al*., 2002). The time-series of metal exposure was extended retrospectively for eight years by estimating daily metal concentrations in PM_{10} using the significant relationship of daily metal concentration with air mass back trajectory coordinates. For this 8-year dataset there was a significant association between some of the metal concentrations (for example, water-soluble and total iron, copper and zinc, water-soluble vanadium and total nickel) and cardiovascular admissions, although associations did not remain significant after adjusting for PM_{10} mass. The loss of statistical power is a consequence of a residual strong correlation between metal concentration and PM_{10} mass and limitations in the ability of air mass back trajectory coordinates to explain all variations in particle metal.

84. In the same study, the concentration of a number of trace metals, such as copper, analysed in PM_{10} (and in $PM_{2.5}$) correlated more strongly with the gravimetric concentration of black smoke than with PM_{10} or $PM_{2.5}$, indicating a source of these metals associated with fine primary combustion particles. This is a potential causal link, consistent with other observations that health effects are associated with combustion or traffic-related particle sources.

85. In another UK study, daily samples of PM_{10} taken from six sites with an anticipated variation in ambient particle composition were either instilled in rats *in vivo* or used in *in vitro* cell cultures (Lightbody *et al*., 2003). Although markers of *in vivo* and *in vitro* inflammation were most strongly influenced by PM_{10} mass dose, analysis of the results based on PM_{10} composition showed that the mass of primary particles within PM_{10} (estimated using the Netcen source apportionment model, see Chapter 8) was a strong factor in determining potency, whereas secondary and coarse PM_{10} mass were not. Certain trace metal components – most notably water-soluble zinc, but also water-soluble manganese and the sum of water-soluble trace metal analysed – were also independently significant predictors of a number of toxicological endpoints.

3.3.5.3 Organic components

86. Carbon and organic compounds are major constituents of combustion-generated particles and these, together with secondary organic aerosol, comprise a substantial proportion of PM_{10}. Some organic compounds associated with PM from combustion sources, for example, PAHs and their oxy- and nitro-derivatives, exert inflammatory as well as mutagenic and carcinogenic effects. Oxygenated organics such as quinones can yield ROS. Plausible mechanisms therefore exist to link the organic components of PM_{10} with both acute and chronic adverse health effects. However, there are insufficient measurement data for individual organic components and their variability, in the UK or elsewhere, to attempt an epidemiological quantification of effects, if any.

3.3.6 Interactions between physicochemical properties of particles

87. Some toxicological studies have investigated the net effect of mixtures of model particles and chemical constituents. For example, the ability of monodisperse ultrafine carbon black particles to generate ROS *in vitro*, or rat lung inflammation *in vivo*, is synergistically enhanced by the presence of soluble iron or copper salts (Wilson *et al*., 2002). A mechanistic suggestion for the effect *in vivo* is that selective adsorption of lung surfactant onto carbon particles reduces rates of particle clearance from the lung and increases the effective exposure time. There is also some evidence that sulphate potentiates metal effects: increased metallic ion availability in an acidic environment is a possibility.

3.3.7 Particle source

88. Some epidemiological studies have investigated the health effects of particles categorised by source, rather than by specific physicochemical property. These generally use either multivariate models (for example, factor analysis) or geographical information systems (GIS)-based methods to apportion particles and thus exposure to different sources. Studies of this type have not yet been applied to UK data, although a recent study of the toxicology of PM_{10} from six different UK locations (Section 3.3.5.2) suggests that the concentration of particles, apportioned by modelling, as being combustion-related primary particles was a significant predictor of some toxicological endpoints. US studies have shown that daily mortality in six cities is significantly associated with concentrations of $PM_{2.5}$ apportioned by factor analysis to mobile and coal combustion sources but not to crustal sources (Laden *et al*., 2000).

89. A cohort study in the Netherlands indicated that traffic-related air pollution (as assessed by GIS data for the distance subjects lived from main road) was significantly associated with increased cardiopulmonary mortality (Hoek *et al*., 2002). The relative risk for living near a major road was 1.95 (95% CI: 1.09 – 3.52). A study in Sweden observed a relationship between motor vehicle emission (estimated by dispersion modelling) and lung cancer (Nyberg *et al*., 2000). However, it is important to note that neither of these studies sought to separate the contribution of PM from other traffic-related pollution. A study in Amsterdam showed the relationship between mortality and black smoke was twice as steep for subjects on the main road network compared to subjects living elsewhere (Roemer and van Wijnen, 2001), suggesting traffic was associated with these effects.

90. Both types of source-oriented approach consistently identify an association between traffic-derived particles and adverse health effects. The observation that black smoke (generally taken as a current marker for traffic- and combustion-related primary PM) is associated with ill health is consistent with the outputs of these models.

91. Short duration (2 h) controlled human exposure studies with diesel exhaust have shown clear, although mild, local inflammatory effects in the respiratory tract as well as systemic effects in both healthy or asthmatic individuals. A small epidemiological study, mainly based on US railroad workers, has shown a small effect of diesel particles on lung cancer. The mechanism may be a combination of particle-induced oxidative inflammation and the carcinogenic potential of soot-

attached PAH. Diesel exhaust does not of course consist exclusively of particles; animal tests vary in their indications of whether PM is the most important fraction of the diesel exhaust, although inflammation of airways has been shown in healthy human volunteers exposed to resuspended diesel exhaust particulate only (Nightingale *et al.*, 2000).

3.4 Summary of current understanding

92. Epidemiology has consistently demonstrated an association between adverse health effects and PM_{10}. A recent WHO meta-analysis of 33 time-series studies done in Europe gives an estimated 0.6% (95% CI: 0.4–0.8%) increase in total mortality effect for a 10 µg m^{-3} increase in daily PM_{10} (WHO, 2004). The corresponding values for respiratory and cardiovascular deaths are 1.3% (0.5–2.0%) and 0.9% (0.5–1.3%), respectively. These values are similar to those reported previously in the APHEA (Air Pollution and Health, a European Approach) study in Europe and in the NMMAPS (National Morbidity, Mortality and Air Pollution Study) study in the US. For comparison, the COMEAP (1998) exposure-response coefficients used in the calculations for the UK given in Section 3.2 are 0.75% for increase in all-cause mortality and 0.80% for increase in respiratory hospital admissions.

93. The recent evidence from time-series studies is that the displacement of daily mortality and hospital admissions is not of just a few days. An increase in effects estimates with increasing duration of exposure to PM_{10} is consistent with the larger health impacts observed from long-term studies.

94. Despite their broadly consistent adverse health associations, the APHEA and NMMAPS studies both indicated some spatial variability in effects estimates between cities. These can be attributed to differences, *inter alia*, in mean temperature (leading to differences in domestic ventilation and proportion photochemical particles) and the proportion of traffic-related particles. Another source of variability is the distribution of exposures received by individuals making up the population.

95. The apparent general uniformity of time-series risk factors has been used to argue that individual components of PM are of secondary importance to total inhaled mass (Harrison and Yin, 2000). However, although it has generally been difficult to show convincingly that attributes other than size are more important determinants of ill health than others, this may simply reflect the dominance of measurements of PM by mass in the available data. The ability of studies to discriminate between effects of different fractions is also limited when there is a high degree of correlation between different measures of PM.

96. Nevertheless, the balance of evidence suggests overall that it is the combustion-derived components of PM_{10}, which are comprised predominantly of fine and ultrafine particles and may be metal and PAH (and other organic compound) enriched, that are primarily responsible for the harmful effects. These particles also have a high specific surface area. This component of fine/ultrafine carbonaceous particles have low optical reflectivity that likely also explains the associations of health effects with traditional black smoke measurements. Re-evaluation of the value of black smoke as an indicator for traffic-related air pollution has been recommended by WHO (2003).

97. The relationship between ultrafine particles and PM_{10} in ambient air is complex and consequently the assertion that ultrafine particles provide the underlying explanation for the generally consistent associations of PM_{10} with adverse health effects might appear to be a contradiction. A possible rationalisation of this is the considerable spatial and temporal variability of ultrafine particles and the consequent difficulty in correctly quantifying exposure to this component. Data from Germany show that although PM_{10} and $PM_{2.5}$ have declined with time, ultrafine particle concentrations have remained relatively constant and the smallest size fraction of ultrafine particles has continuously increased in the last decade (Wichmann and Peters, 2000). Particle number, and particle surface area, are metrics whose associations with health endpoints have yet to be properly explored, particularly in the UK.

98. There is generally much less compelling evidence to connect secondary inorganic particles (that is, ammonium and sodium nitrates and sulphates) and coarse particles with adverse health effects. Associations with sulphate have predominantly come from US studies where sulphate may have been a surrogate for particle acidity. The latter is less of an issue in the UK where particulate matter is generally well neutralised by ammonium.

99. Despite the evidence pointing to finer particles, health effects from coarse particles cannot yet be excluded.

100. Given the evidence emerging for the importance of exposure to traffic-related particles, the public health burden of exposure at such roadside 'hotspots' may be inadequately assessed by the characterization of population exposure using background urban concentrations.

101. An important issue is that of interactions, either between different PM components, and/or between different pollutants. In general, the evidence suggests that associations between PM and health effects are due to PM and that PM is not acting as a surrogate for something else. For example, results from many time-series studies are relatively insensitive to adjustment for a number of gaseous pollutants and human and animal exposure studies also show a direct effect of PM. On the other hand, in the APHEA study, adjustment for NO_2 reduced PM effect estimates by about half, suggesting that PM_{10} or $PM_{2.5}$ mass alone is not sufficient to represent fully the impact of complex air pollution mixtures (Katsouyanni *et al.*, 2001). This may be due to a direct effect of NO_2, but could also be due to NO_2 acting as a surrogate for an unknown traffic-related pollutant. In the latter case, NO_2 may provide a better measure of the more toxic (traffic-related) component(s) of PM than does PM_{10}.

102. Mechanistically, the evidence suggests that in *vivo oxidative* stress caused by particles elicits inflammation and drives the respiratory and cardiovascular effects. In the case of ultrafine particles, this may include systemic effects from direct transfer into the vascular system. The mechanistic link to cancer is less clear but PM yields DNA adducts, which provide unequivocal evidence of exposure and, if the material analysed for adducts includes acids, may provide evidence of these genotoxic compounds reaching sites where genotoxic effects could be expressed.

103. The consistent demonstration of population health effects with PM_{10} indicates that PM_{10} is a relevant metric for air quality standards in spite of the important

issues of PM_{10} composition and the relationship between ambient and personal exposure to PM_{10}. However, as part of their review of the health effects of particles for the CAFE programme (CAFE, 2004), WHO (2003) recommended the development of air quality guidelines for $PM_{2.5}$ alongside the retention of measurement of PM_{10} for public health protection. A health-based $PM_{2.5}$ limit value should be derived from $PM_{2.5}$ data since scaling the PM_{10} limit value according to the prevailing $PM_{2.5}/PM_{10}$ ratio assumes that both fractions have the same toxicity and leads to no extra targeting of health benefits. Furthermore, given that the coarse fraction of PM cannot currently be considered innocuous, development of a $PM_{2.5}$ target would need to be accompanied by health-based targets for the coarse fraction either indirectly via retention of a target for PM_{10} (as recognised by WHO) or directly via a target for PM_{coarse} instead of PM_{10}.

104. Without a better understanding of the relationships between specific components of PM_{10} and their health effects, it is difficult to assess the impact upon population health of future changes to the PM_{10} mix that may result from strategies to reduce PM_{10} overall.

105. There is general consensus that some health effects are dominated by those in susceptible subgroups, for example, the elderly, children, those with pre-existing lung or heart disease or (possibly also) diabetes. These groups are more likely to succumb to the very low extra inflammation they receive from exposure to particle pollution.

106. A consequence of the general agreement that no lower threshold is yet discernible in the exposure-response relationship for particles is that setting an air quality standard becomes a somewhat subjective judgement. This implies that an approach based on reducing the general exposure of the population to particles, rather than a limit value approach, which focuses on hotspots, should be more effective at maximising the total population health gain (CAFE, 2004).