Question A2

What new health evidence is available on the role of other fractions or metrics of PM, such as smaller fractions (ultrafines), black carbon, chemical constituents (metals, organics, inorganics, crustal material and PM of natural origin, primary or secondary) or source types (road traffic including non-tailpipe emissions, industry, waste processing …) or exposure times (for example, individual or repeated short episodes of very high exposure, 1 hour, 24 hours, yearly)?

Answer

Since the 2005 global update of the WHO air quality guidelines (WHO Regional Office for Europe, 2006), a considerable number of new studies have been published, providing evidence on the health effects of size fractions, components and sources of PM. Health effects are observed with short-term (such as hours or days) and long-term (such as years) exposures to airborne particles.

A. Fractions or metrics of PM other than $PM_{2.5}$ or PM_{10}

1. The 2005 global update of the WHO air quality guidelines noted that, while there was little indication that any one property of PM was responsible for the adverse health effects, toxicological studies suggested that fossil fuel and biomass combustion processes may be a significant contributor to adverse health outcomes. Since then, further information has become available to amplify the earlier conclusions. Epidemiological and toxicological studies have shown PM mass ($PM_{2.5}$ and PM_{10}) comprises fractions with varying types and degrees of health effects, suggesting a role for both the chemical composition (such as transition metals and combustion-derived primary and secondary organic particles) and physical properties (size, particle number and surface area);
2. Three important components or metrics – black carbon, secondary organic aerosols, and secondary inorganic aerosols – have substantial exposure and health research finding associations and effects. They each may provide valuable metrics for the effects of mixtures of pollutants from a variety of sources.
    a. New evidence links black carbon particles with cardiovascular health effects and premature mortality, for both short-term (24 hours) and long-term (annual) exposures. In studies taking black carbon and $PM_{2.5}$ into account simultaneously, associations remained robust for black carbon. Even when black carbon may not be the causal agent, black carbon particles are a valuable additional air quality metric for evaluating the health risks of primary combustion particles from traffic, including organic particles, not fully taken into account with $PM_{2.5}$ mass.
    b. No new toxicological evidence has been presented to support a causal role for such inorganic secondary aerosols as ammonium, sulfates and nitrates. However, epidemiological studies continue to report associations between sulfates or nitrates and human health. Neither the role of the cations (for example, ammonium), nor the interactions with metals or absorbed components (for example, organic particles) have been well documented in epidemiological studies (see Answer C8). Even when secondary inorganic particles (especially sulphate particles) may not be the causal agents, they are a valuable additional air quality metric for evaluating health risks.

c. There is growing information on the associations of organic carbon with health effects, and carbonaceous primary emissions are one of the important contributors to the formation of secondary organic aerosols (a significant component of the $PM_{2.5}$ mass). The evidence is insufficient to distinguish between the toxicity of primary and secondary organic aerosols.

3. The new evidence suggests that short-term exposures to coarse particles (including crustal material) are associated with adverse respiratory and cardiovascular effects on health, including premature mortality. Data from clinical studies are scarce; toxicological studies report that coarse particles can be as toxic as $PM_{2.5}$ on a mass basis. The difference in risk between coarse and fine PM can, at least partially, be explained by differences in intake and different biological mechanisms.
4. There is increasing, though as yet limited, epidemiological evidence on the association between short-term exposures to ultrafine (smaller than 0.1 μm) particles and cardiorespiratory health, as well as the health of the central nervous system. Clinical and toxicological studies have shown that ultrafine particles (in part) act through mechanisms not shared with larger particles that dominate mass-based metrics, such as $PM_{2.5}$ or PM_{10}.

B. Source types

A variety of air pollution sources have been associated with different types of health effects. Most of the evidence accumulated so far is for an adverse effect on health of carbonaceous material from traffic (see also Question C1). A more limited number of studies suggest that traffic-generated dust, including road, brake and tyre wear, also contribute to the adverse effects on health.

1. Coal combustion results in sulfate-contaminated particles, for which epidemiological studies show strong evidence of adverse effects on health.
2. Sources of PM emission relevant to health also include shipping (oil combustion) power generation (oil and coal combustion) and the metal industry (such as nickel).
3. Exposure to particles from biomass combustion – most notably residential wood combustion – may be associated not only with respiratory, but also with cardiovascular health.
4. Desert dust episodes have been linked with cardiovascular hospital admissions and mortality in a number of recent epidemiological studies.

C. Exposure times – for example, individual or repeated short episodes of very high exposure, 1 hour, 24 hours, yearly

1. Epidemiological studies show further evidence that long-term (years) exposure to $PM_{2.5}$ is associated with both mortality and morbidity. The evidence base is weaker for PM_{10}, and hardly any long-term studies are available for coarse particles.
2. There is also strong evidence from epidemiological studies that daily (24-hour average) exposures to PM are associated with both mortality and morbidity immediately and in subsequent days. Repeated (multiple day) exposures may result in larger health effects than the effects of single days.
3. While acute and long-term effects are partly interrelated, the long-term effects are not the sum of all short-term effects. The effects of long-term exposure are much greater than

those observed for short-term exposure, suggesting that effects are not just due to exacerbations, but may be also due to progression of underlying diseases.

4. There is significant evidence from toxicological and clinical studies on effects of combustion-derived particles that peak exposures of short duration (ranging from less than an hour to a few hours) lead to immediate physiological changes; this is supported by epidemiological observations.

Rationale

(a) The role of other fractions or metrics of PM

In the 2005 global update of the WHO air quality guidelines, evidence on the effects on health of different chemical constituents in PM was based on toxicological studies. An integrated science assessment for PM was published by the EPA in 2009 to support the review of the national ambient air quality standards. The integrated science assessment used evidence from both epidemiological and experimental studies to conclude that "there are many components contributing to the health effects of $PM_{2.5}$, but not sufficient evidence to differentiate those constituents (or sources) that are more closely related to specific health outcomes" (EPA, 2009). Despite the increased number of studies (especially epidemiological) after 2009, the general conclusion remains the same.

Black, elemental, and primary and secondary organic carbon

Black carbon concentration is usually estimated by light absorption methods that measure the light absorption of particles retained in a filter – in absorption units. On the other hand, elemental or organic carbon is determined using thermo-optical methods, also on filter samples – in mass concentration units. Black carbon absorption units can be converted to mass concentration units.

The main sources of carbon(aceous) particles are diesel powered engines, the residential burning of wood and coal, power stations using heavy oil or coal, the field burning of agricultural wastes, as well as forest and vegetation (fires). Consequently, black carbon is a universal indicator of a variable mixture of particulate material from a large variety of combustion sources and, when measured in the atmosphere, it is always associated with other substances from combustion of carbon-containing fuels, such as organic compounds (WHO Regional Office for Europe, 2012). Organic carbon not only originates from combustion, but also originates from atmospheric processes and emissions from vegetation. An example of such an organic compound is isoprene. Due to a lack of data, health studies have not been able to separate primary and secondary organic particles.

Epidemiological studies

Since the 2009 EPA integrated science assessment, a number of epidemiological studies have evaluated associations between individual constituents of PM and health. The particle constituents most often included in the studies have been sulfate and black carbon. The WHO Regional Office for Europe has recently published a report that evaluates systematically the health significance of black carbon (Janssen et al., 2012). Estimated effects on health of a 1-$\mu g/m^3$ increase in exposure were greater for black carbon particles than for PM_{10} or $PM_{2.5}$, but estimated effects of an interquartile range increase were similar. Two-pollutant models in time-series studies suggested that the effect of black carbon particles was more robust than the effect of PM mass. Sufficient evidence was found for an association between daily

outdoor concentrations of black carbon and all-cause and cardiovascular mortality, and cardiopulmonary hospital admissions. Evidence was also judged sufficient for an association between long-term black carbon concentration and all-cause and cardiopulmonary mortality.

There are, typically, considerable intercorrelations between particle constituents in ambient air, especially between constituents from the same source. This is only one reason why the detection of associations in epidemiological studies is not enough to judge causality. The WHO Regional Office for Europe report on black carbon concluded that black carbon per se may not be responsible for the observed health effects, but that black carbon could be interpreted as an indicator for a wide variety of combustion-derived chemical constituents (WHO Regional Office for Europe, 2012). The more robust associations observed for black carbon than for $PM_{2.5}$ in two-pollutant models in short-term epidemiological studies were interpreted to suggest that black carbon is a better indicator of harmful particle substances from combustion than is total particle mass.

Organic carbon has been included in epidemiological studies less often than black carbon. In most studies published after the 2009 EPA integrated science assessment, (total) organic carbon has been found to be associated with short-term changes in cardiovascular (Delfino et al., 2010a; Ito et al., 2011; Kim et al., 2012; Son et al., 2012; Zanobetti et al., 2009) and respiratory health (Kim et al., 2008), or with changes in the levels of inflammatory markers (Hildebrandt et al., 2009).

In epidemiological studies, the effects of combustion-derived organic carbon are difficult to separate from those of black carbon and/or elemental carbon because of a high correlation due to the common source: combustion processes (WHO Regional Office for Europe, 2012). Elemental carbon is most strongly associated with primary combustion particles and primary organic carbon, whereas secondary organic aerosol formation is delayed with respect the primary emissions, because secondary organic carbon is formed during longer range transport in the atmosphere. Secondary organic carbon also has a significant biological component, but this part of PM has hardly been studied in relation to health effects. A series of panel studies have reported that while total organic carbon has not been associated with the outcomes, associations have been observed for primary organic carbon (and not secondary organic carbon compounds) (Delfino et al., 2009b; 2010a; 2011). In one study, primary organic carbon was associated with markers for systemic inflammation, whereas secondary organic carbon was associated with a marker for pulmonary inflammation (Delfino et al., 2010b).

Only one study, since the 2005 global update of the WHO air quality guidelines, has evaluated associations between long-term exposure to organic carbon and health (Ostro et al., 2010). For organic carbon, associations were observed for both ischaemic heart disease and pulmonary mortality, whereas elemental carbon was only associated with ischaemic heart disease mortality. It should be noted that organic carbon is a very complex mixture of primary and secondary organic aerosols that may contain specific components with important health outcomes, such as hazardous air pollutants (HAPs); thus, the health impact of organic carbon may greatly vary from site to site and time to time

Clinical studies

Healthy human subjects exposed for 2 hours to ultrafine clean – that is without any components adsorbed on the surface – carbon particles at concentrations of 10 $\mu g/m^3$ and 25 $\mu g/m^3$ showed a high overall deposition fraction in the respiratory system (0.66 ± 0.12 at rest; mean ± SD) which increased with exercise (0.83 ± 0.04; mean ± SD) (Frampton, 2001).

Asthmatic subjects showed an even higher deposition (0.76 ± 0.05) than did healthy subjects while breathing at rest (Frampton et al., 2004). The effects of ultrafine carbon particles were observed in both heart rate variability and cardiac repolarization, but there were no changes in soluble markers of either systemic inflammation or coagulation. In a more recent study, no vascular impairment or effect on blood clotting were observed in volunteers exposed for 2 hours to 70 µg/m^3 of ultrafine carbon particles (Mills et al., 2011). In this same study, and in Lucking et al. (2011), it was shown that removing the particles from diluted diesel engine exhaust also prevented adverse effects on the cardiovascular system. The difference is explained by the differences in composition, with black carbon particles (soot) being rich in (semi)volatile organic particles and metals. There are no studies reported that used exposure periods longer than 2 hours.

Toxicological studies

Inhalation of ultrafine carbon particles (38 nm, 180 µg/m^3 for 24 hours) caused increased heart rate and decreased heart-rate variability in rats, but there was no inflammatory response and no change in the expression of genes having thrombogenic relevance (Harder et al., 2005). In spontaneously hypertensive rats exposed to similar ultrafine carbon particles (172 µg/m^3 for 24 hours), blood pressure and heart rate increased with a lag of 1–3 days. Inflammatory markers in lavage fluid, lung tissue, and blood were unaffected, but mRNA expression of hemeoxygenase-1, endothelin-1, endothelin receptors, tissue factor, and plasminogen activator inhibitor in the lung showed a significant induction (Upadhyay et al., 2008), which is an indication of a cardiovascular (or even systemic) effect without adverse effects at the port of entry – that is, the lung. Given differences in the deposited dose in the respiratory systems of rats and human beings, the concentration used in this study is high, but not unrealistic when extrapolated to human exposures. Yet, clean carbon particles alone are unlikely to result in detrimental effects at current outdoor levels. Although not a true toxicological study, Biswas et al. (2009) were able to demonstrate that a substantial portion of soot-induced reactive oxygen production (associated with oxidative stress and inflammation) could be attributed to the (semi)volatile organic fraction on the carbon particle core, suggesting that organic particles otherwise not recognized as PM can be responsible for a substantial part of the toxicity of the carbonaceous fraction of PM.

Likewise, but not yet studied, other particles (such as sulfates) may also act as carriers. Verma et al. (2009b) have shown, for Los Angeles in summer, that both primary and secondary organic particles possess high redox activity; however, photochemical transformations of primary emissions with atmospheric ageing potentially enhance the toxicological potency of primary particles, in terms of generating oxidative stress and leading to subsequent damage in cells.

The WHO Regional Office for Europe review (2012) concluded that black carbon particles may not be a major direct toxic component of fine PM, but it may operate as a universal carrier of a wide variety of chemicals of varying toxicity to the lungs, the body's major defence cells and (possibly) the systemic blood circulation.

Coarse particles

The number of studies on the health effects of PM_{10} is vast, and the number of studies on $PM_{2.5}$ is increasing rapidly. In the 2005 global update of the WHO air quality guidelines, it was noted that, for coarse particles ($PM_{10-2.5}$), there was only limitedly epidemiological data. The availability of epidemiological data has significantly increased since 2005. In 2009, the

EPA integrated science assessment concluded – based on data from epidemiological, controlled human exposure, and toxicological studies – that there was "suggestive evidence of a causal relationship between short-term exposure to coarse PM and cardiovascular and respiratory health effects and mortality". The integrated science assessment further stated that there was "not sufficiently evidence to draw conclusions on the health effects of long-term exposure to coarse PM". Since 2009, evidence of the short-term effects of coarse particles on cardiorespiratory health and mortality has increased significantly.

Epidemiological studies

The latest systematic review by Brunekreef & Forsberg (2005) made the scientific community aware again of the potential health risks associated with coarse particles. The review concluded that coarse PM has at least as strong short-term effects on respiratory health as $PM_{2.5}$; also, for cardiovascular effects, some supportive evidence was found. For mortality, evidence was concluded to be stronger for $PM_{2.5}$. The few long-term studies did not provide any evidence of an association with potential health risks.

Taking into account the newest evidence on the effects of coarse PM on cardiorespiratory health (Chen et al., 2005; Halonen et al., 2008, 2009; Peng et al., 2008; Perez et al., 2009a; Zanobetti et al., 2009), the EPA integrated science assessment for PM concluded that, in general, short-term epidemiological studies reported positive associations between mortality and cardiovascular and respiratory hospital admissions (EPA, 2009). For cardiovascular outcomes (admissions and physiological effects), effect estimates of coarse PM were found to be comparable to those of $PM_{2.5}$. On the other hand, it was noted that studies on respiratory admissions were conducted in a limited number of areas, and no associations of coarse PM on lower respiratory symptoms, wheeze, or medication use were reported (in panel studies). Published after the integrated science assessment, one study reported associations between daily coarse PM concentrations and wheeze in children with asthma (Mann et al., 2010).

After the 2009 EPA integrated science assessment, several new studies reported associations between coarse particles and cardiovascular (Atkinson et al., 2010; Chen R et al., 2011; Malig & Ostro, 2009; Mallone et al., 2011), respiratory (Chen R et al., 2011) or total mortality (Meister, Johansson & Forsberg, 2012; Tobías et al., 2011). Expanding the geographical spread of studies on respiratory admissions, a study in Hong Kong (Qiu et al., 2012) reported positive associations between coarse PM and (total) respiratory, asthma, and chronic obstructive pulmonary disease admissions. Effect estimates for coarse PM were somewhat lower than those for $PM_{2.5}$, and in two-pollutant models they decreased more than the estimates for $PM_{2.5}$; yet the associations remained for respiratory and chronic obstructive pulmonary disease admissions.

It should be noted that in the Hong Kong study, as in most of the studies, coarse PM was calculated by subtracting measured $PM_{2.5}$ from measured PM_{10}. This means that there is more measurement error for coarse PM than for $PM_{2.5}$, which would make associations between coarse PM and health more difficult to find – an issue brought up also by the integrated science assessment. Compared with fine particles, coarse particles also vary more spatially and infiltrate less efficiently into indoor air, which makes further assessment of exposure to coarse PM in epidemiological studies more challenging.

After the EPA integrated science assessment, only two studies were published on the long-term effects of coarse PM; both of them were conducted in the United States and used the same models to estimate concentrations of coarse PM. In the first study (Puett et al., 2009),

coarse PM was not associated with mortality or coronary heart disease incidence among women in two-pollutant models. In the second one (Puett et al., 2011), there was limited evidence of coarse PM having an effect on cardiovascular health among men, mainly on the incidence of ischaemic stroke.

The EPA noted in the 2009 integrated science assessment that the composition of coarse PM can vary considerable between cities, but that there is limited evidence on the effects of the various biological and chemical components of coarse PM. However, there is one source of coarse PM for which evidence has started to accumulate – desert dust, which consists mainly of crustal material (see the dedicated paragraph under the heading "(b) The role of source types").

Practically no studies compare the effects on health of coarse PM from different sources. One study included source-specific PM_{10}: exhausts, fuel oil combustion, secondary nitrate and/or organic particles, minerals, secondary sulfate and/or organics and road dust had statistically significant associations with all-cause and cardiovascular mortality (Ostro et al., 2011). At high latitudes, the levels of road dust are at their highest during wintertime, when studded tires are in use and the roads are sanded to increase friction. In a recent mortality study conducted in Stockholm, Sweden, effect estimates for coarse PM were slightly higher during wintertime than during other times of the year (Meister, Johansson & Forsberg, 2012).

Clinical studies

Although not a direct comparison, Graff et al. (2009) arrived at the conclusion that, in their studies of human beings (2 hours, 90 $\mu g/m^3$), exposure to coarse PM produces a measurable mild physiological response in healthy young volunteers that is similar in scope and magnitude to that of volunteers exposed to fine PM, suggesting that both size fractions are comparable in inducing cardiopulmonary changes in acute exposure settings. No other new evidence since 2005 has been published.

Toxicological studies

Very few studies have compared the toxicity of coarse PM (10–2.5 µm) and fine PM (smaller than 2.5 µm). The few studies available usually collected PM on filters and used in vitro assays or intratracheal exposures to assess the relative hazard, often in relation to the sources of emission. Since the inhalability and, therefore, the deposition efficiency in the respiratory tract of coarse particles is substantially lower, the interpretation of the risk of coarse versus fine PM has to be considered in that context. This also explains the lack of experimental inhalation studies of coarse particles. Wegesser, Pinkerton & Last (2009) compared these two fractions, collected during wildfires in California, and concluded that the hazard expressed per unit mass is roughly the same – with some evidence that fine PM is more toxic in terms of inflammatory potential and cytotoxic responses. In a different study, these effects were attributed to the insoluble components of the mixture and are not caused by an endotoxin (Wegesser & Last, 2008). The intratracheal exposures in rats and mice, as well as in vitro studies, suggest that similar effects can be observed for coarse and fine PM in the bioassays of lung cells (Gerlofs-Nijland et al., 2007; Halatek et al., 2011; Gilmour et al., 2007; Jalava et al., 2008; Happo et al., 2010) and that coarse PM can be even more hazardous than fine PM. Again, given that the deposition efficiency and pattern of coarse and fine PM differ largely, the health outcomes in a population can differ at equal mass exposures.

Ultrafine particles

There is a general consensus that ultrafine particles are defined as particles smaller than 100 nm in mobility diameter and mostly stem from combustion processes in urban settings (Peters, Rückerl & Cyrys, 2011). Emitted primary ultrafine particles are transformed rapidly due to coagulation, adsorption and secondary particle formation. Also, new particle formation takes place in the atmosphere and may give rise to a high number concentration of particles in the nucleation and Aitken modes (0–20 nm and 20–100 nm). This is of special relevance in areas (urban, industrial and rural) with high photochemistry (Reche et al., 2011). Therefore, ultrafine particles have greater spatial and temporal variability than the fine particle mass concentrations. Typically, they are characterized by particle number concentration, which is the metric most measurement devices employ. Research on nano-size material is applicable to assessing the potential toxicity of ultrafine particles and has shown that not only their size, but also their composition, surface chemistry and surface charge are important (Bakand, Hayes & Dechsakulthorn, 2012). Although ultrafine particles are defined by size and number, this fraction may contain such components as metals and polycyclic aromatic hydrocarbons. The following discussion is based on their physical properties only.

Epidemiological studies

Based on epidemiological studies, there is still limited evidence on the effects on health of ultrafine particles (Rückerl et al., 2011), although the potential for such effects was considered to be large in a recent synthesis of opinions of experts (Knol et al., 2009).

Compared with the assessment in the 2005 global update of the WHO air quality guidelines, links were observed between daily changes in ultrafine particles and cardiovascular disease hospital admissions, as well as cardiovascular disease mortality (Hoek et al., 2010). A link between ultrafine particles or total number concentrations and cardiovascular disease hospital admission was observed in European multicentre studies (von Klot et al., 2005; Lanki et al., 2006) as well as in some single-city analyses (Andersen et al. 2008a, 2010; Franck et al., 2011). The evidence for respiratory hospital admissions was mixed (Andersen et al., 2008a; Leitte et al., 2011; Iskandar et al., 2012; Leitte et al., 2012). The link between ultrafine particles or total number concentrations and natural cause mortality appeared to be more robust in time-series analyses (Berglind et al., 2009; Breitner et al., 2009; Atkinson et al., 2010).

Links between daily changes in ultrafine particles and markers of altered cardiac function, inflammation and coagulation were suggested by several, but not all, studies (see reviewed studies within Rückerl et al. (2011) and Weichenthal (2012)) and were further supported by recently published studies (Rich et al., 2012b).

Clinical studies

A few recently published clinical studies support pre-2005 studies that suggested increasing evidence for ultrafine particles in eliciting health effects during and after 2-hour exposure periods (Mills et al., 2007; Langrish et al., 2009; Mills et al., 2011). However, most studies were performed with a mixture of particles and gases, which do not allow statements to be made about the contributions of ultrafine particles. In the clinical setting, the removal of very high particle numbers by filters prevented the otherwise occurring arterial stiffness and increases of blood clotting (Bräuner et al., 2008). Similar observations were made in health

subjects and patients with coronary heart disease that were wearing a very simple, yet highly efficient face mask while walking in highly polluted areas in Beijing, China (Langrish et al., 2009). Observations in healthy young volunteers exposed to pure elemental carbon particles implied that heart function was not affected by these controlled exposures. This was confirmed by a very similar exposure in a study (Mills et al., 2011) that looked at measurements of arterial stiffness and blood clothing in healthy subjects. The presence of a susceptible population has not been shown, and no studies could be identified that have applied exposure periods longer than 2 hours.

Toxicological studies

Substantial advances have been made in understanding the action of ultrafine particles. Ultrafine particles have the ability to translocate from the alveolar space into tissues and to spread systemically, reaching many organs, including the heart, liver, kidneys and brain (Kreyling, Hirn & Schleh, 2010). Ultrafine particles exhibit systemically a multitude of biological responses due to their reactive surfaces within human beings (Bakand, Hayes & Dechsakulthorn, 2012). The study of ultrafine particle toxicology has made substantial advances, as properties of particles smaller than 100 nm are intensively studied for engineered nanoparticles. Specific toxicological actions include impairment of phagocytosis and breakdown of defence mechanisms, crossing tissues and cell membranes, injury to cells, generation of reactive oxygen species, oxidative stress, inflammation, production of cytokines, depletion of glutathione, mitochondrial exhaustion, and damage to protein and DNA, most of which also occurs with larger size PM (Bakand, Hayes & Dechsakulthorn, 2012). Biodistribution studies also suggest that the effects of ultrafine particles may very well be observed in organs other than those that correspond to the port of entry – for example, the central nervous system (Kleinman et al., 2008; Kreyling et al., 2013). In light of different biodistributions on inhalation and the likelihood that ultrafine particles can escape natural defence mechanisms, such as phagocytosis, it is likely that ultrafine particles will also be linked to biological pathways and responses that differ from larger size particles (fine and coarse PM).

Secondary inorganic aerosols

Sulfate is a major component, together with nitrate, of secondary inorganic particles that are formed from gaseous primary pollutants. Because of their high solubility (and low hazard) and their abundance in the human body, these secondary inorganic particles have been suggested to be less harmful than, for example, primary combustion-derived particles (Schlesinger & Cassee, 2003).

Epidemiological studies

It was noted in the 2009 EPA integrated science assessment that secondary sulfate had been associated with both cardiovascular and respiratory health effects in short-term epidemiological studies. At that time, there were more studies available that looked at the cardiovascular effects of PM constituents and sources than at the respiratory effects. Since the integrated science assessment, epidemiological evidence has continued to accumulate on the short-term effects of sulfate on both cardiovascular (Ito et al., 2011) and respiratory (Atkinson et al., 2010; Kim et al., 2012; Ostro et al., 2009) hospital admissions; two studies have linked sulfate also with cardiovascular mortality (Ito et al., 2011; Son et al., 2012). There is also some new evidence on the associations between daily increases in ambient sulfate and physiological changes related to cardiovascular diseases, such as ventricular arrhythmias and endothelial dysfunction (Anderson et al., 2010; Bind et al., 2012).

It should be noted that, similar to black carbon, sulfate is associated with a number of other constituents from the combustion of fossil fuels, such as transition metals and organic compounds. In many areas, sulfates and nitrates are associated with hydrogen and ammonium. Sulfate could be considered to be an indicator of harmful constituents from oil and coal combustion. On the other hand, the situation may be more complex: sulfate has been reported to increase the solubility of iron (Oakes et al., 2012), which may increase the harmfulness of particles. The follow-up study of the Harvard Six Cities Study reported that there was no evident increase in the estimate of the effect of $PM_{2.5}$ mass over time, despite the relatively higher drop in sulfate concentrations, when compared with $PM_{2.5}$ mass during the study period (Lepeule et al., 2012). This suggests that sulfate does contribute to the toxicity of ambient PM. In any case, it is still unclear whether removal of SO_2 (a precursor for sulfate) from the emissions of oil and coal combustion would lead to a significant reduction in the health effects associated with these sources. Also, it is accepted that if new particle formation of sulfuric acid or ammonium sulfate occurs in the atmosphere, these new particles may act as a condensation sink for primary and secondary organic components.

Nitrate is one more indicator of emissions from combustion processes, including traffic exhausts that are rich in oxides of nitrogen. In a mortality study conducted in Seoul, Republic of Korea, there was some evidence of cardiovascular, but not respiratory, effects for nitrate, and even more so for ammonium (Son et al., 2012). In contrast, two studies on hospital admissions found evidence of respiratory, but not cardiovascular, effects for nitrate (Atkinson et al., 2010; Kim et al., 2012). It is noteworthy, in these studies, that sulfate was not associated with cardiovascular admissions, showing that the recent evidence for sulfate is not fully consistent.

Only one recent study has evaluated associations between long-term exposure to nitrate and health. In a study conducted in California (Ostro et al., 2010), both nitrate and sulfate were associated with cardiopulmonary mortality. Sulfate and organic carbon also showed consistent associations in multipollutant models. Multiple analyses of prospective cohort studies in the United States have also associated long-term exposure to sulfate with mortality (Smith KR et al., 2009).

Clinical and toxicological studies

No new relevant evidence or relevant information on the role of secondary inorganic aerosols has been reported since the review by Schlesinger & Cassee (2003), in which it was concluded that these particles have little biological potency in normal human beings or animals or in the limited compromised animal models studied at environmentally relevant levels. As mentioned in Reiss et al. (2007), toxicological evidence provides little or no support for a causal association between particulate sulfate compounds and a risk to health at ambient concentrations. Limited toxicological evidence does not support a causal association between particulate nitrate compounds and excess health risks either. However, it cannot be excluded that the cations associated with sulfates and nitrates (such as transition metals, acidity marked by hydrogen cations), nor absorbed components (such as organic particles) may be the underlying cause of the strong associations between sulfate and health effects, because ammonium sulfate or ammonium bisulfate can be regarded as a relative low toxic material, in comparison with transition metals or polycyclic aromatic hydrocarbons. No toxicological studies have been published that investigated the role of sulfates (or nitrates) in the complex mixture of PM; at present, it cannot be excluded that these secondary inorganic components have an influence on the bioavailability of other components, such as metals.

Transition metals and metal compounds

Epidemiological studies

A few panel and population studies published during or after 2009 have included transition metals (Bell et al., 2009a; de Hartog et al., 2009; Ito et al., 2011; Mostofsky et al., 2012; Ostro et al., 2009, 2010; Suh et al., 2011; Zanobetti et al., 2009; Zhou et al., 2011). A comparison of the relative harmfulness of different metals is not possible at this point, because most of the studies have included only a few transition metals, most often zinc or nickel, and there is substantial variability in the outcomes available. Furthermore, no patterns emerge for transition metals as a general category: depending on the study and outcome, associations may have been found for all, a few, or no metals. Most evidence has been found for an association between nickel and cardiovascular hospital admissions (Bell et al., 2009a; Ito et al., 2011; Mostofsky et al., 2012; Zanobetti et al., 2009).

Clinical studies and toxicological studies

Metal oxides are substances traditionally considered to be relatively inert chemically. However, in very small (ultrafine) size ranges, these particles have been linked with significant oxidative stress mediated toxicity (Duffin, Mills & Donaldson, 2007). Some metals, such as zinc oxide, will dissolve in the body (Gilmour et al., 2006; Charrier & Anastasio, 2011). Zinc ions have many physiological functions, but they can also interfere with the body's homeostasis, leading to such adverse effects as oxidative stress and inflammation. Toxicological examinations of the constituents of ambient air have not identified an individual metal as being a likely cause of human health problems associated with PM (Lippmann et al., 2006; Lippmann & Chen, 2009). A study by Lippmann et al. (2006) did involve 6 months of weekday concentrated ambient particle exposures, in which an association between cardiac function changes and nickel was also observed for short-term responses to pronounced daily peaks in nickel. In this and subsequent subchronic concentrated ambient particle exposure studies, there was no evidence of an association of nickel with chronic effects. Moreover, controlled exposure of young, healthy adults to $PM_{2.5}$ caused an elevation in blood fibrinogen at 18 hours post-exposure. This response was correlated with a copper–zinc–vanadium factor in the PM. In healthy elderly adults, $PM_{2.5}$ exposures decreased heart rate variability, a response not seen in young adults (Devlin et al., 2003).

In Toronto, there was a $PM_{2.5}$-related mean decrease in brachial artery diameter, but no changes in blood pressure in one study; in a follow-up study, involving most of the same subjects, $PM_{2.5}$ exposure produced a significant decrease in diastolic blood pressure. In both studies, the effects were significantly associated with organic carbon. There were suggestive, but not significant, associations with elemental carbon and some metals (cadmium, potassium, zinc, calcium and nickel) in the first study (Urch et al. 2005). In their review, Lippmann & Chen (2009) concluded that if there are health-related effects of specific metals, other than the effects of nickel in ambient fine PM on cardiac function, they are not yet known. Overall, it appears that the cardiovascular effects of ambient air $PM_{2.5}$ are greatly influenced, if not dominated, by their metal contents, especially the transition metals, and that nickel is likely to be a key component (Lippmann & Chen, 2009). An important role for metals is also evident in a study in which a single dose of dusts from two types of tyre were instilled intratracheally in the lungs of rats, and effects were assessed within 24 hours and after 4 weeks. One dust was made from ground tyres of recycled styrene butadiene rubber, while a second dust was made from scrap tyres. Tests were done with administered saline, the

two tyre dusts, and soluble zinc, copper, or both. At very high dose levels (5 mg/kg rat), the exposures induced cardiac oxidative stress (Gottipolu et al., 2008), which was associated with the water soluble zinc and copper.

Despite the toxicological evidence that controlled exposure studies using transition metals can result in detrimental health effects, it is unlikely that these components can explain all of the health effects observed in epidemiological studies at present ambient levels. However, transition metals remain a group of components for which reduction measures will most likely lead to improving the health status of the population.

(b) The role of source types

Extreme caution is required when attributing health effects to sources based on health impact assessment studies that use specific components of PM. For example, when taking black carbon as an indicator in a health impact assessment, to obtain concentration–response functions in Europe, caution is required when attributing health outcomes to sources. Thus, in many cases most black carbon would be attributed to diesel exhaust emissions, but attributing the whole health impact to diesel would be erroneous. This is because several sources, such as gasoline engines and other sources co-emitting with diesel exhaust or varying collinearly with black carbon due to meteorology, would be included – simply because they correlate with black carbon. This is an important limitation when dealing with source-related health outcomes.

The 2005 global update of the WHO air quality guidelines considered the effects on health of particles from biomass combustion in a separate chapter, because of the significance of biomass combustion as an emission source. Therefore, special emphasis has been given to the issue in this review. A WHO workshop in Bonn concluded in 2007 that current knowledge does not allow specific quantification of the health effects of emissions from different sources (or of individual components). In 2009, the EPA integrated science assessment concluded that "there are many components contributing to the health effects of $PM_{2.5}$, but not sufficient evidence to differentiate those sources (or constituents) that are more closely related to specific health outcomes". The integrated science assessment further noted that a number of source types – including motor vehicle emissions, coal combustion, oil burning, and vegetative burning– are associated with health effects and went on to include crustal material as another potentially toxic component. The limited new evidence accumulated after 2009 does not lead to changes in the conclusions.

New epidemiological evidence on the health relevance of various particle sources has come from two types of studies: some studies have simply included chemical constituents known to be indicators of specific sources; others have used statistical source-apportionment techniques to partition the mass of particles between sources. Most studies have been able to identify emission sources for traffic, crustal material, and secondary inorganic aerosols (as indicated by sulfate or nitrate). Depending on location, and monitoring tools also, sources for biomass combustion, industry, oil combustion, coal combustion, cooking, hydrogenated organic aerosols, oxygenated organic aerosols and sea spray may have been identifiable.

Traffic

Traffic is not only a source of combustion particles, but is also a source of road dust that originates from the wear of road surfaces, brakes, clutches and tyres. Simultaneous emissions of gaseous pollutants and noise make estimation of traffic-related PM effects a challenge. The

relative importance of all types of pollutants originating from traffic will be considered in the Answer for Question C1.

Epidemiological studies

Vehicular traffic does not have a unique indicator, but road traffic (especially vehicles powered by diesel fuel) is a major source of black carbon in most urban environments. Consequently, evidence accumulated after 2005 on the health effects of black carbon indicates that both short-term and long-term exposures to particles in vehicle exhausts are harmful. In the more limited number of short-term studies that have been based on source apportionment, $PM_{2.5}$ from traffic has typically been found associated with cardiovascular (de Hartog et al., 2009; Cakmak et al., 2009; Lall, Ito & Thurston, 2011; Lanki et al., 2006; Mar et al., 2006; Ostro et al., 2011; Sarnat et al., 2008; Yue et al., 2007) and respiratory heath (Cakmak et al., 2009; Gent et al., 2009; Penttinen et al., 2006; Sarnat et al., 2008), but not always (Jacquemin et al., 2009; Lall, Ito & Thurston, 2011; Schreuder et al., 2006).

The source category of "crustal material" can be assumed to consist of substantial amounts of road dust, although in some locations natural sources may be important too. Some research groups have even named the source category for crustal material "road dust". The results for crustal material and/or road dust have been slightly less consistent than those for vehicular exhausts. In some studies, the source has been associated with cardiovascular (Andersen et al., 2007; Cakmak et al., 2009; Ito et al., 2006; Ostro et al., 2011; Yue et al., 2007) or respiratory health (Cakmak et al., 2009; Gent et al., 2009). However, there are also studies without evidence of cardiovascular (Lanki et al., 2006; Mar et al., 2006) or respiratory effects (Jacquemin et al., 2009; Lall, Ito & Thurston, 2011; Schreuder et al., 2006).

Only a few of these studies were published after 2009 – that is they have not affected the formulation of the integrated science assessment. In New York City, traffic was associated with cardiovascular hospital admissions, but no effect was observed for soil particles (Lall, Ito & Thurston, 2011). A study conducted in Barcelona, Spain, associated separately $PM_{2.5}$ from road dust and mineral dust, and vehicle exhausts with daily all-cause mortality (Ostro et al., 2011). The health outcomes of the contributions of these components were higher than the ones obtained for the $PM_{2.5}$ bulk mass concentrations.

Some recent studies have linked $PM_{2.5}$ from traffic with birth outcomes. Wilhelm et al. (2012) found both diesel and gasoline $PM_{2.5}$ and geological $PM_{2.5}$ to be associated with low birth weight. The same study group found preterm birth to be associated with diesel $PM_{2.5}$ (but not other categories of traffic PM). Bell et al. (2010) reported motor vehicles and road dust to be associated with lower birth weight.

In conclusion, the evidence on the harmfulness of particles from traffic has increased substantially since the 2005 global update of the WHO air quality guidelines. However, because of limited data and large variability in outcomes and available source indicators and/or categories, traffic cannot be ranked yet relative to other particle sources with respect to harmfulness. The review by Stanek et al. (2011b) concluded that $PM_{2.5}$ from crustal or combustion sources, including traffic, may be associated with cardiovascular effects; for respiratory effects, the evidence for association was judged limited.

Clinical and toxicological studies

Diesel engine exhaust is rich in PM, mostly below 2.5 µm. A large database describes all sorts of adverse health effects due to exposure to diesel engine exhaust. Exposure to diesel engine exhaust in healthy volunteers causes inflammation of the airways (Behndig et al., 2006) and reduces vascular function (Mills et al., 2005). In patients with heart problems (stable myocardial infarction), diesel engine exhaust causes myocardial ischaemia and reduces the clot resolving function (endogenous fibrinolytic capacity) (Mills et al., 2007). Although in certain urban areas diesel engine exhaust particles can be a substantial part of the total PM to which people are exposed, it is not clear if diesel engine exhaust is always more potent than PM on a mass basis. For example, diesel engine exhaust (105 µg/m^3) appeared to be less toxic in inducing plaque development than corresponding exposures to $PM_{2.5}$ (105 µg/m^3, 4 days/week, 5 months), indicating that some components in ambient $PM_{2.5}$, which are not present in diesel engine exhaust, are responsible for exacerbating plaque progression (Quan et al., 2010). In their recent review, McClellan, Hesterberg & Wall (2012) pointed out that, although there are good reasons for concern for health effects due to diesel engine exhaust exposure, significant efforts have been made to abate the composition of diesel engine exhaust in the past few decades, resulting in a more fuel efficient and complete combustion process and the installation of filter traps with substantial lower mass emissions. It seems very likely that this will have a profound effect on the toxicity of diesel engine exhaust, but there is no systematic review available that allows clear conclusions on an increase or decrease of the toxic potency and associated health risks.

Apart from the changing technologies, the composition of the fuel is also changing, by using biodiesel blends. There is a large knowledge gap with respect to the health effects related to replacing petroleum-based diesel with biodiesel fuel. There is conflicting evidence about the extent to which biodiesel fuel exhaust emissions present a lower risk to human health relative to petroleum-based diesel emissions (Swanson, Madden & Ghio, 2007). German studies have shown significantly increased mutagenic effects, by a factor of 10, of the particle extracts from rapeseed oil in comparison to fossil diesel fuel; and the gaseous phase caused even stronger mutagenicity (Bünger et al., 2007). Biodiesel (rapeseed oil methyl ester) has been shown to have four times higher cytotoxicity than conventional diesel under idling conditions, while no differences were observed for the transient state (Bünger et al., 2000). So far, the opposite was found by others: no differences for cytotoxicity with vehicle emissions under idling conditions (Jalava et al., 2010).

Comparing different studies to determine the possible adverse effects on health of biofuels is difficult, since all studies have been performed under different conditions. It has been seen that the emissions, as well as the health effects related to changes in emission substances or concentrations, are influenced by: the type of vehicle and/or motor used for the study; which test cycle is run; if the subsequent exhaust is diluted from the tailpipe or not and differences in fuel type; and fuel quality. Within the North American Electric Reliability Corporation programme, various sources of particle emissions were tested for their toxicological profile. For example, $ApoE^{-/-}$ mice were exposed by inhalation 6 hours a day for 50 consecutive days to multiple dilutions of diesel or gasoline exhaust, woodsmoke, or simulated *downwind* coal emissions. From Lund et al. (2007), as well as a meta-analysis by Seilkop et al. (2012), it can be concluded that filtration of particles has little effect on responses − that is, particulate components ranked third to seventh in predictive importance for the eight response variables. This suggests that not only the particles, but certainly also the gaseous fraction of engine exhaust is related to adverse health effects. Although it is beyond the scope of the question,

these observation, as well as those reported from clinical studies by Mills et al. (2005, 2007) mentioned above, point out that exhaust control strategies need to be evaluated for the likely hazard of the remaining mixture of components: a reduction of PM mass may not be accompanied by a similar trend in the reduction of toxicity.

Recent toxicological studies suggest that both tailpipe and non-tailpipe emissions (brake wear and tyre dust) express toxic properties that are similar or sometimes stronger on a per milligram basis than those found for diesel engine soot, for example. This will be discussed in section C1.

Coal and oil combustion

Epidemiological studies

After 2005, only one published epidemiological study based on source apportionment has included a category for coal combustion. Research teams found some evidence of an effect on total and cardiovascular mortality in Washington, DC (Ito et al., 2006). In another study, selenium, an indicator element for emissions from coal combustion, was found to be associated with cardiovascular mortality and hospital admissions in New York City (Ito et al., 2011).

The few epidemiological studies that included an oil combustion source provided conflicting results on the effects of the emissions on respiratory and cardiovascular health: some studies reported an effect (Andersen et al., 2007; Gent et al., 2009; Ostro et al. 2011) whereas others did not (Ito et al., 2006; Lall, Ito & Thurston, 2011; Lanki et al., 2006). Sometimes no effect was observed for oil combustion, as obtained from source apportionment, but an effect existed for vanadium, an indicator element for emissions from oil combustion (Bell et al., 2010; de Hartog et al., 2009).

It should be noted that the source category "secondary inorganic particulate air pollution" (typical indicator is sulfate) has been associated with cardiorespiratory health in most studies published since 2005. The category includes particles from coal and oil combustion, since vanadium and nickel (tracers of heavy oil combustion) are often found in this association with secondary sulfate (Viana et al., 2008, a paper on source apportionment in Europe), but also includes particles from vehicle exhausts.

Toxicological studies

Several studies based in the United States have reported toxicological evaluations of short-term exposure to coal-fired power plant emissions (Godleski et al., 2011). In general, these emissions – weather aged and/or oxidized, and diluted or not – showed very little (if any) adverse effects in rat's responses to the inhaled aerosols studied. Godleski et al. (2011) also reported that no specific toxic constituent could be identified that explained the subtle effects. Barrett et al. (2011) reported that downwind coal combustion emissions are able to exacerbate various features of allergic airway responses, depending on the timing of exposure in relation to allergen challenge, and that these symptoms were related to both the particulate and gaseous phase of the emissions. A large number of studies have been published on residual oil fly ash PM. This type of dust is rich is transition metals (see section on "Transition metals and metal compounds" above), such as vanadium and nickel, all of which possess strong redox activity associated with the ability to cause oxidative stress.

Industry

Epidemiological studies

Obviously, a heterogeneous group of emission sources can be referred to as *industry*; and, consequently, the source category "industry" differs between epidemiological studies. Depending on location, the category might consist of one dominant source, or be a mixture of industrial sources or even other combustion sources. Eight short-term epidemiological papers published since 2005 have included a source category (or several) for industry.

In papers based on the ULTRA Study conducted in three European cities, industry was not associated with harmful physiological changes (Jacquemin et al., 2009; Lanki et al., 2006; de Hartog et al., 2009). Lall, Ito & Thurston (2011) reported a source category called "steel metal works" to be associated with respiratory, but not cardiovascular, hospital admissions in New York City. In contrast, in Atlanta, Georgia, a source category "metal processing" was associated with cardiovascular, but not respiratory, admissions (Sarnat et al., 2008). Concerning mortality, emissions from incinerators in Washington, DC, or from the industry sector in Barcelona (Spain) were not associated with total or cardiovascular mortality (Ito et al., 2006; Ostro et al., 2011), whereas emissions from copper smelters were associated with both (Mar et al., 2006).

A few recent studies have looked at the long-term effects of emissions from industry, by linking distance from one or several point sources with health. The problem in most of these studies has been the lack of individual level adjustment for confounders. In some studies, even area level adjustment was not conducted (excluded from this review). Furthermore, it is seldom possible to separate between the effects of particles and gaseous pollutants. No general conclusions can be made based on the limited new data.

In a study by Monge-Corella et al. (2008), proximity to the paper, pulp or board industries was not associated with lung cancer mortality in Spain. Living near a nickel and/or copper smelter was reported to be associated with increased cardiovascular mortality in Harjavalta, Finland (Pasanen et al., 2012). An estimate of long-term exposure in the study was based on levels of nickel in soil humus. The result should be interpreted cautiously because the highest emissions occurred in the past (follow-up 1982–2005). In another study of a copper smelter (Pope, Rodermund & Gee, 2007), a strike at the facility was associated with decreased mortality. However, the strike occurred in 1967/1968, after which emission standards were tightened. Emissions before tightening regulation from municipal waste incinerators were associated with non-Hodgkin's lymphoma in France (Viel et al., 2008).

In a Canadian study with individual level confounder adjustment, living in the proximity of point sources was associated in small children with the development of asthma (Clark et al., 2010), but not with inflammation of the middle ear (MacIntyre et al., 2011). The category of "point sources" included all kinds of industrial facilities, from power plants and waste treatment facilities to shipyards, which limits the use of results to some extent. A study conducted in Texas reported a slightly increased risk for neural tube defects (Suarez et al., 2007), but not congenital heart defects (Langlois et al., 2009), around industrial point sources (petroleum refineries, primary metal or smelter facilities and the chemical industry).

Toxicological and clinical studies

No useful information could be identified to support the importance of industrial sources other than power plants and/or coal emissions. This is due largely to toxicological and

clinical studies having not been performed near sources of industrial emissions. In other words, the evidence is mainly derived from PM samples of which PM composition has been determined and used for source apportionment. For example, Steerenberg et al. (2006) identified, in a small data set, that industrial combustion and/or incinerators were associated with respiratory allergy. Specific data on the toxicity of industry emitted PM other than combustion-derived PM has not been published since 2005.

Biomass combustion

Epidemiological studies

The source category "biomass combustion" includes particles from residential wood combustion (also other types of solid fuels in developing countries), wildfires, and the burning of agricultural residues. In low-income countries, biomass is extensively used for heating and cooking, but it is most important as an indoor source, and the concentrations are substantially higher than outdoor concentrations in middle- and high-income countries. Long-term exposure to biomass PM from indoor use has been associated in low-income countries, for example, with lower respiratory infections (including pneumonia) in children, chronic obstructive pulmonary disease in women, and lung cancer. The 2005 global update of the WHO air quality guidelines concluded that there was little evidence that the toxicity of particles from biomass combustion would differ from the toxicity of more widely studied urban PM. However, there were at that time hardly any studies available on the cardiovascular or mortality effects of ambient biomass PM. In several European countries, high biomass burning contributions to ambient PM may be correlated with high levels of polycyclic aromatic hydrocarbons. Levoglucosan and potassium are very good tracers of biomass burning emissions; thus, these components can and will be used for epidemiological studies.

A systematic review of the health effects of particles from biomass combustion was published in 2007 (Naeher et al., 2007). The review concluded that there was no reason to consider PM from biomass combustion less harmful than particles from other urban sources, but that there were limitedly studies on the cardiovascular effects. However, most of the evidence on the effects of residential wood combustion was still indirect: studies were conducted in areas affected by wood combustion, but no specific indicators of wood combustion were available.

The few studies based on source apportionment (and published since 2005) provide an opportunity to compare the short-term health effects of particles from biomass combustion with particles from traffic – the source with the most evidence on health effects. In a study conducted in Copenhagen (Andersen et al., 2007), particles from biomass combustion were associated with cardiovascular and respiratory hospital admissions, whereas particles from traffic were not. In Atlanta, Georgia (Sarnat et al., 2008), woodsmoke was associated with cardiovascular emergency department visits as strongly as was traffic; neither of the sources was associated with respiratory health. In Phoenix, Arizona (Mar et al., 2006), wood combustion was associated with cardiovascular mortality, with effect estimates slightly lower than those for traffic particles. Finally, in Spokane, Washington (Schreuder et al., 2006), associations with cardiovascular mortality were of similar strength for biomass combustion and traffic. Only in a study conducted in Washington, DC (Ito et al., 2006), was no clear effect of particles from biomass combustion (or traffic) on cardiovascular health (mortality) observed. Altogether, these new studies suggest that cardiovascular effects of particles from biomass combustion may be comparable to those of traffic-related particles.

A recent study conducted in a woodsmoke impacted community provided evidence on the processes through which woodsmoke affects cardiovascular health (Allen et al., 2011). The introduction of portable air filters was associated with improved endothelial function and decreased inflammatory biomarkers; markers of oxidative stress were not affected. In another recent study, exposure to woodsmoke was associated with increased risk of physician visits for ear inflammation among children aged 1–24 months (MacIntyre et al., 2011). There are hardly any studies on the health effects of longer-term exposure to outdoor woodsmoke. In British Columbia, Canada, exposure to woodsmoke was associated with an increased risk of infant bronchiolitis, but not with the development of childhood asthma (Clark et al., 2010; Karr et al., 2009b). In California, $PM_{2.5}$ from biomass combustion was associated with preterm birth, but not with low birth weight (Wu et al., 2011; Wilhelm et al., 2012).

Considering the effects of particles specifically from open biomass burning (wildfires and crop residue burning), there has been a lack of studies on cardiovascular health and mortality. In some studies published after a 2007 review (Naeher et al., 2007), no evidence of short-term cardiovascular effects was reported (Henderson et al., 2011; Morgan et al., 2010). However, one study reported associations between smoke from peat bog wildfires and congestive heart failure (Rappold et al., 2011), and another one reported associations between smoke from burning of sugar cane and hospital admissions for hypertension (Arbex et al., 2010).

Little evidence was found for an effect of wildfire smoke on mortality in the few published studies, since studies often lack statistical power. Significant cardiovascular effects during major forest fires have been reported, although it is not entirely clear what proportion of this could be attributed to exposure to PM (Analitis, Georgiadis & Katsouyanni, 2012). In contrast, evidence has continued to accumulate on the effects of wildfire smoke on respiratory health; in recent studies, not only total respiratory admissions and/or emergency department visits, but also visits due to chronic obstructive pulmonary disease, acute bronchitis, and pneumonia have been considered. Increased use of medication for chronic obstructive pulmonary disease and decreased lung function in schoolchildren have also been reported in association with exposure to PM from open biomass burning (Caamano-Isorna et al., 2011; Jacobson et al., 2012). A study conducted on forest fire-fighters associated exposure to high levels of woodsmoke with pulmonary and systemic inflammation, providing a potential link between exposure and both respiratory and cardiovascular diseases (Swiston et al., 2008). Interestingly, one recent study reported that exposure during pregnancy is associated with a slight decrease in birth weight (Holstius et al., 2012). It is not known, however, whether systemic inflammation mediates the effect.

Clinical and toxicological studies

Wegesser, Pinkerton & Last (2009) demonstrated that fine and coarse PM collected during wildfires are considerable more toxic in the mouse lung per unit mass than PM collected in the same area without fires. This was confirmed by Verma et al. (2009a), who tested PM collected during Los Angeles wildfires (see WHO Regional Office for Europe, 2012 – in which the effects have been summarized, with a focus on wood combustion). A more recent controlled human exposure study from Denmark reported that 3-hour exposure to woodsmoke with up to 354 $\mu g/m^3$ of PM from a well-burning modern wood stove had no effect on markers of oxidative stress, DNA damage, cell adhesion, cytokines or microvascular function in atopic subjects, supporting the suggestion that burning conditions are dominant factors that determine the hazard of the combustion-derived particles. Another

Scandinavian study (Bølling et al., 2012) reported that the hazard of woodsmoke particles seems, to a large extent, to depend on the type of stove and combustion conditions (oxygen supply and water content). These outcomes suggest that a simple risk assessment for woodsmoke is not possible and the toxicity of the emitted PM can vary significantly. Notably, the toxicity seems to be clearly contingent on the organic fraction.

Desert dust

Epidemiological studies

After the 2005 global update of the WHO air quality guidelines, several new studies reported positive associations between short-term exposure to PM_{10} or coarse particles and mortality during desert dust episodes (Chan & Ng, 2011; Jiménez et al., 2010; López-Villarrubia et al., 2012; Mallone et al., 2011; Perez et al., 2009a; Zauli Sajani et al., 2011; Tobías et al., 2011). However, PM_{10} during desert dust episodes was not associated with either cardiovascular or respiratory mortality in Athens (Samoli et al., 2011b).

The results for cause-specific mortality have not been fully consistent for coarse particles: in Taipei, Taiwan, Province of China, coarse PM was associated with cardiovascular (and natural) mortality, but not with respiratory deaths (Chan & Ng, 2011), whereas in Rome both cardiovascular and respiratory mortality were affected. In most studies, PM_{10} or coarse PM were more strongly associated with mortality during desert dust episodes than at other times (Jiménez et al., 2010; Mallone et al., 2011; Perez et al., 2009a; Tobías et al., 2011), but not in all studies (Zauli Sajani et al., 2011; Samoli et al., 2011b). For $PM_{2.5}$, no clear difference in effects between dust days and non-dust days has been observed (Mallone et al., 2011; Perez et al., 2009a; Tobías et al., 2011).

Only two recent studies have looked at the associations between desert dust days and hospital admissions. A study conducted in Hong Kong (Tam et al., 2012), reported an increased rate of hospitalization for chronic pulmonary disease, but not for pneumonia or influenza, during desert dust days. In contrast, in a study in Nicosia, Cyprus (Middleton et al., 2008), desert dust days were associated with an increased rate of hospitalization for cardiovascular, but not respiratory, causes. Saharan dust days in Barcelona, Spain, were found not to be associated with pregnancy complications (Dadvand et al., 2011).

Evidence for an effect of desert dust on human health is increasing, but at the moment it is not clear whether crustal, anthropogenic, or biological components of dust are most strongly associated with the effects. New results by Perez et al. (2012) found that during African dust outbreaks the PM fraction that shows better correlations with health outcomes is the non-African dust. Thus, it is possible that the health outcome of African dust outbreaks over Europe is related to specific components of anthropogenic PM that are enhanced during the outbreaks. A recent review stressed the importance of chemical characterization of desert dust (Karanasiou et al., 2012). The fraction of biological origin, however, remains largely unknown.

Toxicological studies

Only one study was identified that specifically investigated the adverse effects of an acute exposure to desert dust (Wilfong et al., 2011). Rats received a single dose in the lungs (1, 5, or 10 mg) of PM_{10} collected in Kuwait. At 24 hours, 3 days, 7 days and 6 months, the effects on inflammation, cytotoxicity and pathology were very minimal compared with those of silica dust. Although the evidence is limited and obtained in healthy animals, the hazard per

gram associated with desert dust will most likely be smaller than that of, for example, combustion-derived PM or soluble transition metals. Of particular interest, Godleski et al. (2011) reported that viable pathogens in breathable dusts were identified in desert dust collected in Iraq and Kuwait, suggesting that the source is more complex in nature than sand. Polymenakou et al. (2008) found a large load of airborne microorganisms and pathogens during an intense African dust event in the eastern Mediterranean, and they concluded that the presence of aerosolized bacteria in small size particles may have significant implications for human health via intercontinental transportation of pathogens.

Ocean and sea

Epidemiological studies

Several short-term studies published since 2005 have included a source category for sea salt. With one exception, sea salt has not been associated with health outcomes (Andersen et al., 2007; de Hartog et al., 2009; Gent et al., 2009; Ito et al., 2006; Jacquemin et al., 2009; Lanki et al., 2006; Ostro et al., 2011; Penttinen et al., 2006). In a study by Mar et al. (2006), sea salt was associated with total and cardiovascular mortality. However, the effect was evident only 5 days after exposure, which suggests that chance may have a role in the finding. Recent studies that looked at the associations between individual components of PM and health did not find evidence of an effect for sodium, an indicator for sea salt. The exception is a study by Ito et al. (2011), which reported associations for cardiovascular mortality; however, no effect was observed for hospital admissions. On the other hand, Zanobetti et al. (2009) reported stronger effects of $PM_{2.5}$ on cardiovascular hospital admission in areas with a high sodium content of particles. The authors suggested that the effect may be attributable to emissions from shipping. All in all, there is little epidemiological evidence of the harmfulness of sea salt.

Clinical studies

In Edinburgh, healthy and age-matched volunteers with stable coronary heart disease were exposed for 2 hours to $PM_{2.5}$ (190 ± 37 μg/m^3) and to clean filtered air using a randomized, double-blind crossover study design. After exposure to PM, there were increases in exhaled breath 8-isoprostane, in blood flow and in plasma tissue plasminogen activator ($P < 0.005$); but there were no significant changes in markers of systemic inflammation, and there was no effect on vascular function in either group of subjects (Mills et al., 2008). It was noted that most of the particulate mass consisted of sea salt, and far less PM was derived from combustion sources than was identified in the studies described above. The study provided clear evidence that PM dominated by sea salt and/or sea spray is far less toxic than equal amounts of combustion-derived PM.

Toxicological studies

In no study published since 2005 has the role of sea spray and/or sea salt been investigated, although sea salt is not classified as a hazardous compound and it is plausible that at current exposure levels no harmful effects will occur.

Hazardous waste sites

New studies have found little evidence of an effect of PM originating from hazardous waste sites on conotruncal heart defects or neural tube defects in offspring (Langlois et al., 2009; Suarez et al., 2007).

(c) The role of exposure times

Given that risk estimates of long-term exposure studies are usually much higher than those of short-term exposure studies, guidelines for yearly average concentrations will be of higher relevance than those based on 24-hour averages. It should also be noted that the EC's Second Position Paper on PM (2004) showed that, on a European scale, annual PM_{10} averages and 90.4 percentile values of daily concentrations (equivalent to the daily limit value) of the corresponding year are highly correlated.

Both epidemiological and clinical studies have demonstrated that sub-daily exposures to elevated levels of PM can lead to adverse physiological changes in the respiratory and cardiovascular systems. This suggests that an averaging time of less than 24-hours – for example, 1 hour, similar to ozone – could be considered for air quality guidelines. However, the correlation between the 1-hour maximum and 24-hour average particle concentration is typically high. Furthermore, no studies have evaluated whether, for example, a high 1-hour exposure would lead to a different response than a similar dose given for 24 hours. The same is true for repeated very short-term exposures.

Epidemiological studies

Epidemiological studies published since the 2005 global update of the WHO air quality guidelines provide additional evidence on the effects of long-term (years) exposure to $PM_{2.5}$ on morbidity and especially mortality (see Question A1). There is more limited evidence on the long-term health effects of PM_{10}, and mainly on respiratory outcomes (Question A4). Hardly any studies have evaluated the effects of long-term exposure to coarse particles, and none have evaluated them for ultrafine particles (see "(a) The role of other fractions or metrics of PM" in Question A2 above). For $PM_{2.5}$, there is also new evidence on the effects of (sub-yearly) exposure during pregnancy on adverse birth outcomes (Question A1).

Evidence has continued to accumulate on the associations of daily $PM_{2.5}$ levels with both morbidity and mortality (Question A1), In addition, new epidemiological evidence links daily concentrations of coarse particles with increased respiratory and cardiovascular morbidity, and mortality (see "(a) The role of other fractions or metrics of PM" in Question A2 above). The evidence on the effects of 24-hour exposures to ultrafine particles on cardiorespiratory health is increasing, but is still limited.

Few epidemiological studies evaluate the health relevance of shorter than 24-hour exposures, and they focus mostly on cardiovascular health. Some recent population-based time-series studies have reported associations between hourly ambient PM concentrations and cardiovascular hospital admissions or mortality (Burgan et al., 2010). Unfortunately, in these studies the apparent effects of very short-term exposures are difficult to separate from the effects of 24-hour concentrations due to high correlation. There are also new panel studies that link very short-term changes in ambient PM (or in PM exposure measured with personal monitors) to adverse physiological effects. These studies suggest that physiological changes occur within hours of changes in PM exposure (Burgan et al., 2010; Delfino et al., 2010a; Ljungman et al., 2008; Schneider et al., 2010).

Interesting evidence comes from experimental studies that look at the health effects of traffic-generated air pollution: volunteers may have been asked to cycle, walk, or sit at a bus stop in the midst of busy traffic (Langrish et al., 2012; McCreanor et al., 2007; Weichenthal et al., 2011). The studies suggest that 1–2 hours of exposure may be enough to lead to harmful

physiological changes. In the most susceptible people, these changes might further lead to more serious exacerbations of chronic disease. The problem in these studies is that the effect of traffic-related PM is almost impossible to separate from the effects of gaseous pollutants and noise.

Susceptible population groups and effect mechanism differ for short-term and long-term exposures (Question A3). Even apparently healthy people are susceptible to the effects of long-term exposure to PM, because exposure can potentially accelerate progression of a disease, or perhaps even initiate it, until it is clinically diagnosed. Most susceptible to the effects of short-term exposures are those with an unstable disease. Progression of a disease due to particle exposure may be associated, for example, with acceleration of inflammatory processes, whereas other mechanisms may also play a role in triggering acute exacerbation of diseases, such as changes in autonomic nervous control of the heart in the case of cardiovascular diseases (Question A1; Brook et al., 2010). The fact that effect estimates in epidemiological studies are higher for long-term exposures than for short-term exposures demonstrates that long-term effects are not merely the sum of short-term effects.

Clinical and toxicological studies

Very little data has been published on health effects due to exposures to PM shorter than the usual 1–2-hour duration of clinical studies, whereas the pre-clinical studies have durations between a few hours and several months. In the study by Mills et al. (2007), patients with stable coronary heart disease have more ST-segment depression in their electrocardiogram tracings when exercising during exposure to diluted diesel exhaust (300 $\mu g/m^3$) than they do when exercising during exposure to clean filtered air. The effect of exposure on exercise induced ST-segment depression was highly consistent across patients and repeatable during sequential exercise periods. These findings were from a double blind randomized controlled trial, which would be considered strong evidence (Level 1). ST-segment depression is an important predictor of adverse cardiovascular events, but the magnitude of ST-segment depression in the trial was less than would be conventionally considered clinically significant. It is likely, however, that the magnitude of ST-segment depression would have been greater at higher workloads – trial patients were only asked to undertake gentle exercise in the exposure chamber. It should be mentioned that although exposure levels were high, they may occur in traffic hot spots of tunnels. Unfortunately, several variables – such as animal strain or species, and the type of test atmosphere – prevent statements to be made on the role of exposure times.