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Importance of sources and components of particulate air pollution for cardio-pulmonary inflammatory responses

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1. Introduction

Particulate air pollution is regarded as a serious health problem worldwide (WHO 2005). Reductions in the levels of particulate matter (PM) have been reported to reduce the health impact of air pollution (Heinrich et al., 1999; Clancy et al., 2002; Pope, III et al., 2009). Different epidemiological studies show surprisingly little variation in the size of the risk estimates for changes in various health outcomes with increased air pollution. However, the APHEA[1] and NMMAPS[2] studies, in which associations between PM and health outcomes were investigated in many different cities, indicated some heterogeneity in the size of risk estimates (Samet et al., 2000; Samoli et al., 2005). This heterogeneity in risk estimates could at least in part be due to the contribution of specific emissions from different sources to the PM mixture. Epidemiological studies have not compared the importance of different sources, but investigations include air pollution from industry (Ghio 2004), biomass burning (Smith-Sivertsen et al., 2009) and traffic (Brunekreef et al., 2009). In addition, there are some discrepancies in epidemiological studies with respect to the importance of the various size fractions of PM. Compared to the fine PM fraction, the coarse fraction contains most of the non-combustion PM (Brunekreef and Forsberg 2005) which may have a different health impact. Experimental studies indicate that particles from different sources may have different effects. This review will focus on the effects of PM in experimental investigations, including vehicle exhaust, road dust and wood smoke particles. The importance of particle size and composition will also be addressed. The review comprises studies on humans, animals and cells in culture.

Exposure to PM has primarily been associated with morbidity and mortality due to pulmonary and cardiovascular diseases, but other organs may also be affected (WHO 2006). A key process in the development and acute exacerbations of these diseases is inflammation.

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[1] APHEA: Air Pollution and Health in Europe A
[2] NMMAPS: National Mortality and Morbidity of Air Pollution Study

Inflammation involves a variety of cells, including migrating immune cells that may enter inflamed organs. In the lung the first line of defence includes the phagocytising macrophages and the epithelial cells (Figure 1). These cells may release a variety of signalling molecules, such as chemokines, cytokines, leukotrienes and prostaglandins, in addition to adhesion molecules.

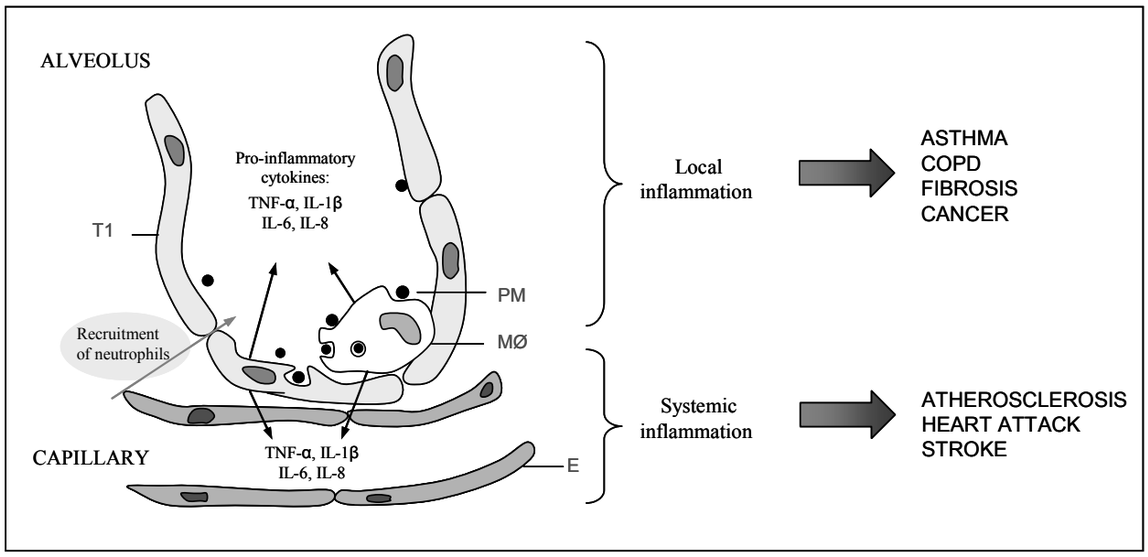

Fig. 1. Illustration of how particle-induced inflammation may affect pulmonary and cardiovascular diseases. T1 = Type 1 epithelial cell, MØ = macrophage, E = endothelial cell, PM = particulate matter (Figure from (Kocbach 2008))

Ambient particles comprise a large variety of different components, such as allergens, metals, organic compounds and microbial components. This review will focus on two groups of components commonly associated with PM, polycyclic aromatic hydrocarbons (PAH) and metals. An important question is whether particles from different sources or different components of particles trigger the release of the same signalling molecules, or whether qualitative and quantitative response differences exist. In addition to effects on the respiratory system the particles may through different mechanisms affect the cardiovascular system, to elicit or exacerbate a vascular inflammatory response. The particles or its components may also trigger cell death that *in vivo* may lead to the loss of functions or start a remodelling process of tissues. Therefore cell death will also be a part of this review, whereas DNA damage is excluded.

2. Traffic and wood combustion

Traffic is considered to be a major PM source in most developed countries. Emissions include particles from the tailpipe, crank case, tyre and break wear and particles generated from road pavement abrasion, sanding and resuspension (WHO 2005; Kupiainen et al., 2005; Zielinska et al., 2008; Thorpe and Harrison 2008) Combustion particles emitted from vehicles consist mainly of spherical primary carbon particles with diameters ranging from 20 to 30 nm, which tend to aggregate (Kocbach et al., 2005) (Figure 2). In contrast to larger

sized particles, like the more arbitrarily-shaped mineral particles from road wear, the small diameters of the primary carbon particles provide a relatively large surface area per mass unit. A large surface area implicates a greater potential for adsorption of various components to the particle surface, including metals, organic compounds, allergens and bacterial components like endotoxins. The contribution from residential wood combustion to ambient PM concentrations is highly dependent on the season, but in the cold season wood smoke may contribute substantially to increased levels of PM locally. Similar to combustion particles from traffic, emissions from wood stoves generally consist of aggregates of small carbon particles. However, under very poor combustion conditions spherical organic carbon particles dominate wood smoke emissions, whereas inorganic ash particles are emitted from complete high-temperature combustion (Kocbach et al., 2009). The size and composition of both traffic- and wood smoke-derived particles varies substantially in time and space, depending on the source, fuel type and post-formation processes.

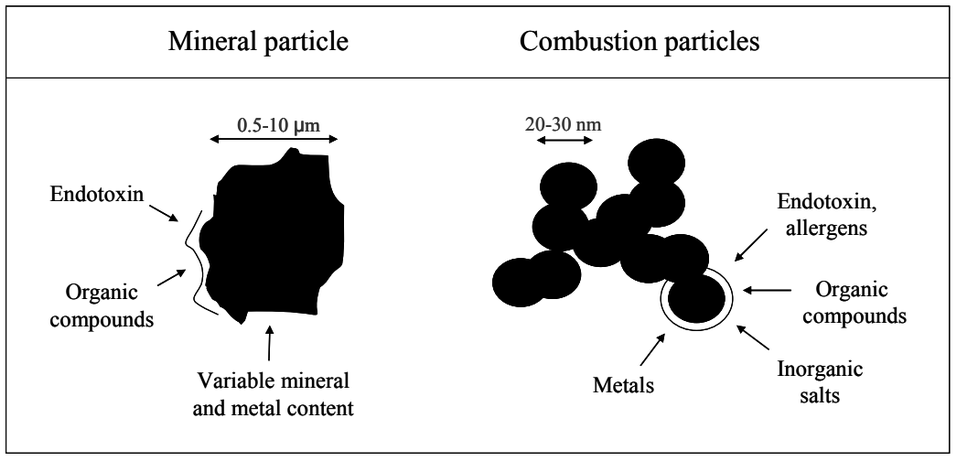

Fig. 2. Schematic figure of mineral particle from road abrasion, and combustion particles consisting mainly of aggregates of small spherical carbon particles (Figure from (Kocbach 2008))

2.1. Experimental studies of traffic-related particles

Experimental studies of traffic-related particles have mainly been conducted with concentrated ambient particles (CAPs) originating from motor-vehicle exhaust or collected from an urban location, and with freshly generated or sampled diesel exhaust particles (DEP). In addition, sampled road dust PM and particles of various minerals and stone types that may be found as components of road dust have been used. Studies with gasoline and biodiesel particles are emerging. Overall, this experimental research indicates that traffic-related PM may induce several changes in processes that have been linked with the development and progress of cardiopulmonary diseases. This includes increased formation of reactive oxygen species (ROS), reduction and activation of antioxidant defence, release of pro-inflammatory cytokines, increased allergy-related responses, mild though time-persistent airway inflammation, changes in autonomic nervous system regulation and changes indicative of increased risk of myocardial infarction.

2.1.1 Combustion particles from traffic

Most of the experimental studies on health effects of particles from tailpipe emissions have been conducted with DEP. This may be due to the fact that the PM emissions from diesel engines are greater, and thus more accessible for studies, than the PM emissions from gasoline engines. Inflammation-related changes induced by DEP in studies with human volunteers include increased levels of inflammatory markers in bronchoalveolar lavage (BAL) fluid (e.g. neutrophils, reduced levels of antioxidants, cytokines), in bronchial mucosal biopsies (e.g. cytokine expression) or in blood (e.g. platelets), increases in airway resistance, and increased number of alveolar macrophages with reduced capacity to ingest particles *in vitro* (Salvi et al., 2000; Stenfors et al., 2004; Mills et al., 2005; Tornqvist et al., 2007). An increase in the number of neutrophils in bronchial and alveolar fractions has also been detected in human volunteers exposed to CAPs (Ghio et al., 2000). Effects on the cardiopulmonary system are reported from human exposure studies using pure ultrafine (< 100 nm) carbon particles, indicating a potential of the particle core itself to induce effects. Already after 2 hours of exposure to these particles, small increases in airway resistance and reductions in carbon monoxide diffusing capacity were detected in healthy subjects, though in the absence of a detectable pulmonary inflammatory response (Pietropaoli et al., 2004). Furthermore, comparable exposure levels were associated with vascular effects, in the form of alterations in expression of adhesion molecules on blood leukocytes (Frampton et al., 2006).

Whereas the human clinical studies are limited to a few hours of observation, both short and long term effects may be studied in animals. However, most experimental studies with animals are carried out at relatively high exposure levels, limiting the usefulness of these studies compared to real life, low level, and long term exposure of humans. Using exposure levels comparable to measured ambient air concentrations, Elder and colleagues studied the effects of freshly generated vehicle exhaust emissions in old, health-compromised rats (pre-treated with LPS) in an on-road mobile laboratory (Elder et al., 2004). Both single and repeated exposures to particles significantly increased the expression of ICAM-1 on the surface of alveolar macrophages, indicative of inflammatory cell activation. Also increased plasma endothelin (Et-2) was observed, suggesting changed vascular endothelial function. Exposure to DEP is known to exacerbate allergic asthma in mouse models and exposure to DEP amplifies the allergen-induced allergic inflammation characterised by high levels of cytokines like IL-4 and IL-5 (Takano et al., 1997; Inoue et al., 2008). Moreover, exposure to diesel exhaust has been found to enhance virus-induced exacerbation of allergic inflammation in mice (Jaspers et al., 2009). Recently, Provoost and co-workers (2009) suggested that inhaled DEP modulates immune responses in the lung via stimulation of the function of pulmonary dendritic cells, known to be crucial mediators in regulation of immune responses (Provoost et al., 2010). In general, studies in animal models support findings from experimental studies with humans with regard to the potential of DEP to induce increased levels of inflammatory mediators in BAL-fluid, lung tissue and blood (Nemmar et al., 2009).

In comparison to the large amount of experimental studies conducted with DEP, only a few studies have investigated the effects of combustion particles emitted from gasoline engines. Recently, gasoline emissions were found to induce both inflammatory and vascular effects in different rodent model systems, whereas many indicators of general toxicity were not

increased, suggesting a modest health effect of the inhaled particles (McDonald et al., 2007). Intratracheally instilled diesel and gasoline PM from a range of vehicles induced similar effects on toxicity, whereas the production of the pro-inflammatory cytokine TNF was slightly higher for diesel than gasoline (Seagrave et al., 2002). The health impacts of the development of new engines and after-treatment technologies remain to be investigated. Both the application of diesel particle filters as well as using biodiesel fuel instead of diesel fuel seemed to reduce particle emissions (Rudell et al., 1999; McDonald et al., 2004). However, the few studies currently available indicate that biodiesel particles may have a greater toxic potential than diesel particles on a mass basis. For instance, biodiesel emissions induced pulmonary and systemic inflammation of similar or more severe degree than DEP in mice (de Brito et al., 2010).

In vitro studies have demonstrated that exposure to DEP leads to the formation of ROS and release of a range of inflammatory mediators from airway epithelial cells (Takizawa et al., 2000; Bonvallot et al., 2002). The mechanisms involved in this inflammatory response are still under investigation, but DEP has been found to trigger phosphorylation of mitogen activated protein kinases (MAPK) and activation of several transcription factors that are known to regulate pro-inflammatory mediator release, including nuclear factor κB (NFκB), activator protein-1 (AP-1) and Stat 3, (Takizawa et al., 2000; Bonvallot et al., 2002; Cao et al., 2010). The expression of the epidermal growth factor receptor (EGFR) is also increased during DEP exposure, and EGFR is believed to play a key role in the early signalling pathways activated by DEP (Cao et al., 2010). Interestingly, all these signalling pathways are also activated in human volunteers exposed to DEP (Pourazar et al., 2005; Pourazar et al., 2008). Another possible mechanism for the DEP-induced effects was recently proposed by Jardim and co-workers, who found altered micro-RNA expression in bronchial epithelial cells after DEP exposure. Micro-RNAs are small non-coding RNAs that have been suggested to be important in maintaining the lung in a disease-free state through regulation of gene expression. The micro-RNAs affected by DEP exposure could possibly be involved in regulation of inflammatory response pathways (Jardim et al., 2009).

Although airway epithelial cells are the most commonly applied model for *in vitro* studies of DEP, a range of other mono- and co-cultures of different cell types have also been applied. DEP for instance functionally activated dendritic cells, and caused the release of a range of inflammatory mediators (Porter et al., 2007). Moreover, human bronchial epithelial cells activated by DEP induced maturation of dendritic cells via thymic stromal lymphopoietin (Bleck et al., 2008). DEP and the organic extracts of DEP have also been reported to induce apoptosis and necrotic cell death in macrophages through the generation of ROS (Hiura et al., 1999). The responses of epithelial cells to DEP seem to be amplified in the presence of monocytes (Chaudhuri et al., 2010). Such a cellular interaction has previously also been demonstrated with pure carbon particles that are commonly used as model particles for DEP (Drumm et al., 2000). With respect to cardiovascular effects of combustion particles, a co-culture model consisting of primary lung and heart cells from rats showed that soluble mediators released from lung cells after exposure to pure carbon particles induced release of inflammatory mediators from cardiac cells, supporting the hypothesis that particle-induced cardiac inflammation and disease may involve lung-derived mediators (Totlandsdal et al., 2008).

With respect to the influence of the physicochemical properties of DEP on the inflammatory responses, the importance of the organic fraction has been investigated in several studies using various solvent extracts. In human bronchial epithelial cells organic extracts of DEP induced the formation of ROS and the release of the inflammatory mediator GM-CSF to a similar extent as the native DEP, whereas the stripped carbonaceous core was less potent (Bonvallot et al., 2001; Baulig et al., 2003). Similarly, Ohtoshi and co-workers showed that DEP induced the release of GM-CSF and IL-8 from human airway epithelial cells, whereas charcoal and graphite, used as models for the carbon core of DEP, did not affect GM-CSF or IL-8 release (Ohtoshi et al., 1998). However, another study reported that DEP-induced cytotoxicity in promyelocytic cells was due to the particle core of DEP rather than the organic fraction (Matsuo et al., 2001). Taken together the *in vitro* studies conducted with DEP demonstrate that the particle core itself as well as organic compounds adsorbed to the particle surface may contribute to the inflammatory effects.

Organic extracts of DEP have been found to influence a wide variety of endpoints, including increased production and release of the chemokines IL-8 and RANTES from peripheral blood mononuclear cells (PBMCs) (Fahy et al., 1999) and oxidative stress followed by cell death in epithelial cells and macrophages (Li et al., 2002). In the latter study, epithelial cells seemed to be more susceptible to the cytotoxic effects than macrophages. DEP organic extracts also increased the IL-4 production and histamine release from human basophils (Devouassoux et al., 2002). DEP favoured Th2 cell recruitment by immune cells from allergic patients by differentially regulating the Th2-recruiting chemokine MDC and the Th1 recruiting chemokine IP-10 (Fahy et al., 2002). The specific organic compounds that account for the biological effects induced by DEP and its extracts remain to be determined. Some likely candidates have however been identified, including PAH like benzo[a]pyrene (B(a)P), phenanthrene and 1-nitropyrene (1-NP) (see paragraph on PAH) (Baulig et al., 2003). Another study fractionated organic DEP extracts into different polarity fractions and identified that the quinone-rich polar fraction was more potent than the more studied aromatic fraction (PAH) in inducing ROS and apoptotic cell death, whereas the aliphatic fraction had no effect (Xia et al., 2004).

2.1.2 Road dust particles

Sampled road dust particles have been observed to elicit pro-inflammatory effects in cells *in vitro* (Hetland et al., 2000; Holopainen et al., 2004; Karlsson et al., 2006) These particles, originating from road wear, sanding or resuspension of settled dust, consist mainly of crystalline or amorphous minerals. The highest concentrations of these particles occur during dry winter or spring days, particularly in countries using studded tires. Effects of mineral particles from stone often used in road pavement have been investigated in some detail in animal and cell studies to determine the importance of mineral structure or released metals (Hetland et al., 2001b; Ovrevik et al., 2005). The crystalline structure appears to be important for the toxicity of mineral particles (Guthrie, Jr. 1997; Warheit 2001), and the amorphous forms of silica are less toxic (Fubini and Hubbard 2003). It has not been possible to identify any specific mineral that explains the potential of the most toxic particles, but particles with a high content of feldspar minerals seemed to be less potent than other mineral particles (Ovrevik et al., 2005; Becher et al., 2007). Some studies indicate that particle-associated ROS does not correlate with pro-inflammatory or apoptotic responses to

mineral particles (Ovrevik et al., 2006), but that cellular ROS may be involved (Becher et al., 2007), as has been observed with combustion particles. Cellular uptake did not seem necessary for pro-inflammatory responses, but seemed to be involved in apoptosis (Refsnes et al., 2006). The pro-inflammatory responses to quartz seemed to involve to some extent the same signalling pathways as activated by carbon or other particle components, e.g. EGF-receptor and MAPK (Ovrevik et al., 2005). The importance of these pathways in pro-inflammatory responses to asbestos has been reported (Mossman et al., 2006), but has not been shown for minerals found in road dust. To what extent mineral particle-associated metals are involved in the responses is still unclear. Some studies indicate that metals are not of major importance, whereas others report that metals in mineral particles contribute to their effects (Hetland et al., 2001a; Aust et al., 2002; Ovrevik et al., 2006).

2.2 Residential wood combustion particles

In a human clinical study, exposure to wood smoke at levels relevant for indoor exposure in developed countries was linked with an increase in markers of inflammation and oxidative stress in the lower airways. Analyses of the blood and urine of the volunteers indicated that wood smoke exposure also was associated with systemic inflammation, blood coagulation and lipid peroxidation (Barregard et al., 2006). Preliminary data from another inhalation study showed increased levels of glutathione due to wood smoke exposure, indicating activation of the antioxidant defence, possibly due to oxidative stress (Boman et al., 2006; Jokiniemi et al., 2008). In subchronic exposure models wood smoke has been linked with modest effects on both pulmonary and systemic inflammation (Burchiel et al., 2005; Reed et al., 2006; Barrett et al., 2006) Furthermore, Ramos et al. (2009) reported that subchronic exposure to wood smoke produced pulmonary effects similar to tobacco smoke in Guinea pigs. These effects included a moderate alveolar inflammation with an influx of macrophages and neutrophils, accompanied by increased apoptosis in macrophages. In accordance with studies on particles from other sources, also wood smoke particles caused the formation of ROS, lipid peroxidation, activation of the nuclear transcription factor NFκB and release of the pro-inflammatory mediator TNF-α in macrophages (Leonard et al., 2000).

In a co-culture of monocytic and epithelial cell lines, it has been demonstrated that the organic compounds adsorbed to wood smoke particles accounted for most of the inflammatory response (Kocbach et al., 2008a). Although PAH are possible candidates for inflammatory effects of particulate matter, the content of PAHs did not seem to account for the effects induced by the organic extract in the monocytes (Kocbach et al., 2008b). In order to identify the biologically active organic compounds of organic extracts of wood smoke particles Kubatova et al. (2006) applied fractionation of organic extracts of wood smoke particles in combination with chemical analysis, and identified the mid-polarity and non-polar compounds, including oxy-PAHs, as inducers of oxidative stress in a macrophage cell line (Kubatova et al., 2006). Since the organic chemistry of wood smoke particles varies considerably with the combustion temperature, it is important to keep in mind that also other groups of organic compounds are likely to contribute to the biological effects induced by PM from different combustion conditions. Recently, it has been demonstrated that particles from different combustion conditions induced differential pro-inflammatory response patterns in a macrophage cell line. Particles from poor combustion seemed more cytotoxic than particles from more complete combustion conditions (Jalava et al., 2010). The

physicochemical properties of emitted wood smoke particles strongly depend on the combustion conditions. Further studies are needed in which the influence of combustion conditions on the biological effects of wood smoke particles is investigated (Kocbach et al., 2009).

2.3 Vehicle exhaust versus wood smoke particles

Relatively few studies have compared the inflammatory effects induced by traffic-derived particles and wood smoke. In a contact co-culture consisting of monocytes and pneumocytes particles from these two sources induced different response patterns. Traffic-derived particles elicited higher levels of IL-6 and IL-8 as compared to wood smoke particles, whereas wood smoke induced a greater reduction in proliferation (Kocbach et al., 2008a). Similarly, inhalation of particles from wood smoke and diesel induced to some extent different responses in rats with respect to both toxicity and inflammation, partly dependent on gender (Seagrave et al., 2005). As described above the mechanisms involved in the inflammatory responses induced by DEP seem to involve activation of EGFR, activation of MAPK and activation of different transcription factors like NFκB, AP-1 and Stat3. Although the mechanisms involved in the wood smoke particle-induced inflammation have been less well characterised, it seems likely that some of the same pathways may be activated. The organic fraction seems to be of importance for the inflammatory effects induced by particles from both sources, although it is likely that different organic compounds are involved. There are, however, experimental *in vivo* studies suggesting that the organic fraction is not of major importance for inflammatory effects (Gerlofs-Nijland et al., 2009; Happo et al., 2010). Little is known about how the metal content influences the inflammatory responses induced by particles from traffic and wood smoke. However, metals may contribute to the inflammatory responses, as has been shown for ambient PM (Gilmour et al., 1996; Kodavanti et al., 2008). Regardless of particle source, it should also be noticed that endotoxins adsorbed to the particle surface in the atmosphere are potent inducers of inflammatory responses, and may account for more than 70 % of the release of inflammatory mediators in various cell systems (Becker et al., 2005; Kocbach et al., 2008b). Biological components have also been shown to contribute to the inflammatory responses induced by PM in healthy volunteers (Alexis et al., 2006).

3. Particle size

Since the trimodal distribution of particle size in ambient air has important implications for exposure and effects in humans, the importance of size for particle-induced lung inflammatory effects has been scrutinised. Model particles with defined chemical composition as well as ambient particles from nano- to micrometer size range have been studied. The potential of different model particles to induce adverse biological responses/adverse health effects, in particular inflammation, has been assessed in various animal studies and some *in vitro* studies. Most of these studies have shown that upon instillation in animals, small-sized particles have a much greater potential to induce lung inflammation than larger particles of similar composition. However, when adjusting for the relatively larger surface area of small-sized particles compared to that of larger particles, the differences in responses have tended to disappear. Thus it has been hypothesised that particle surface area is crucial in driving pathological changes, including inflammatory

responses (Oberdorster, 1996). In support of this, Tran et al. (2000) showed that total particle surface area in the lung was the dominant metric, when quantifying the neutrophilic inflammation after exposure to different low-solubility, low-toxicity particles as TiO_2 and $BaSO_4$ in inhalation experiments with rats. Similar studies with ultrafine and fine carbon black or polystyrene corroborated that the smaller particles induced a much stronger lung inflammation *in vivo* or pro-inflammatory responses *in vitro* (Brown et al., 2001; Donaldson et al., 2002; Monteiller et al., 2007). These differences could also be attributed to the differences in surface area. Even with different nano-sized particles (10 to 45 nm carbon), the inflammatory potential of the particles was related to the surface area (Stoeger et al., 2006). Several studies suggest a threshold dose for the particle surface area-dependent effects (Tran et al., 2000; Stoeger et al., 2006; Monteiller et al., 2007). The surface area notion has, however, been challenged by Warheit and co-workers (Warheit et al., 2006; Warheit et al., 2007a), finding that ultrafine TiO_2 and quartz was not more potent than the respective fine particles, after installation in rat lungs. The authors conclude that the surface reactivity corresponded better to the responses than particle size and surface area. However, their study of TiO_2-particles did not exclude that the crystallinity of the particles may be of importance. In a recent article Sager et al. (2008) suggested that the results of Warheit et al. (Warheit et al., 2007b) with TiO_2 particles, could be the result of insufficient dispersion of the ultrafine particles. By using a more appropriate dispersion for ultrafine TiO_2 particles, Sager et al. (2008) observed a much stronger response of these particles than of fine ones. However, after adjusting for surface area, the ultrafine TiO_2 particles were only slightly more inflammatory than the fine-sized particles. This result was not specific to TiO_2, since ultrafine versus fine carbon black showed similar response patterns as TiO_2 (Sager and Castranova, 2009). Different *in vitro* studies with lung cells have supported a role of particle surface area for inflammatory responses. Hetland et al. (2001b) exposed human lung epithelial cells to different size fractions of quartz and observed a linear relationship between cytokine responses and particle surface area. However, mineral particle-induced apoptosis (a form of cell death) seemed mostly to depend on particle size, whereas composition and surface reactivity appeared to be more important for the pro-inflammatory potential of the particles (Schwarze et al., 2007).

Even though particle size and surface area may be important for triggering cellular responses, several studies suggest that surface reactivity may override the role of the former metrics. A study on rats exposed to well characterised particles of diesel, carbon black and silica supports the importance of surface chemistry compared to ultrafine size in biological effects (Murphy et al., 1998). The studies of Duffin et al. (2007) and Monteiller et al. (2007) support the notion on the importance of surface reactivity. Monteiller showed that similarly sized TiO_2 elicited greater effects compared to carbon black, but less than DQ12, a type of quartz. Furthermore, in the Monteiller study the response to TiO_2 exposure was greater than the response to carbon black, but less than to DQ12, indicating that surface reactivity is important in addition to surface area (Monteiller et al., 2007).

Overall, existing literature suggests that surface area is an important determinant for lung inflammation and health effects in the airway system. For low-toxicity particles the surface area might be the strongest driving force, whereas for high-toxicity particles the surface reactivity may dominate over the importance of particle surface area. Soluble factors may

modify the importance of surface reactivity. For example, the pronounced effect of the bacteria toxin LPS has been thoroughly investigated (Becker et al., 2002). Recently this response has been linked to an IL-1/inflammasome-mediated mechanism (Giamarellos-Bourboulis et al., 2009). The current state of knowledge might question the use of mass as the most appropriate metric and underlines that the surface area may be a better or additional metric, at least for low toxicity particles.

With respect to inflammation and cardiovascular effects, the importance of particle size has been much less studied. Ultrafine particles of various compositions may be translocated from the airways to the cardiovascular system (Nemmar et al., 2002). The extent to which this occurs is unclear and might be small (Kreyling et al., 2002), thus questioning the importance of direct nano-sized particle exposure for cardiovascular responses. An alternative hypothesis to translocation of ultrafine particles as a driving force for cardiovascular inflammation, states that particle-induced lung inflammation is reflected in a systemic response, which then triggers the cardiovascular system. If this were the case, the lung inflammatory response would be decisive and depend on the particle surface area and reactivity. A third possibility is that particles are carriers of metals or organic substances, which may be translocated from the lung to the cardiovascular compartment. Since small particles with large surface area could bind larger amounts of various substances, they would have a greater potential to give systemic effects than larger particles based on this hypothesis. Presently, it is unclear to what extent these different mechanisms operate eliciting cardiovascular inflammation. The studies of Totlandsdal and colleagues support an indirect mechanism, with the release of inflammatory mediators from the lung reaching the heart and initiating a pro-inflammatory response (Totlandsdal et al., 2008). Ansteinsson et al. observed that metals that may be attached to particles, have the potential to trigger cytokine release from cardiac cells (Ansteinsson et al., 2009). A forth possibility through activation of nerve cell reactions is not discussed here.

4. Particle components

Several experimental studies have attributed biological effects of combustion particles to adsorbed organic compounds and metals. Therefore this review focuses on two groups of components commonly associated with particles from traffic and residential wood smoke, PAH and metals. The content of these particle-associated components varies significantly in time and space, as it strongly depends on the type and condition of the emitting source. Biological effects of particle-associated components are commonly studied by carrying out the exposure with particle extracts prepared with various solvents (see above), which subsequently may be fractionated and analysed chemically. These studies may be further supported by studies carried out with pure particle components, administrated singly as well as in combination.

4.1 PAH

Following their release PAH will undergo a number of chemical modifications in the air that modify their biological properties. The type and degree of modification depends on the type and level of the chemical components available as well as the temperature and time to allow for reactions (Vione et al., 2004a; Vione et al., 2004b; Vione et al., 2006). Some of the reactions

take part directly after leaving the primary source; others take place in the atmosphere. PAH and oxy-PAH are emitted as by-products of almost every type of combustion technology in urban environments, including diesel- and petrol-fuelled motor vehicles, residential heating, fossil fuel combustion in energy and industrial processes, municipal and medical incinerators. The oxy-PAH originate from reactions between PAH and hydroxyl radicals, nitrate radicals, other organic and inorganic radicals and ozone or from photo-oxidation of PAH by singlet molecular oxygen (Andreou and Rapsomanikis 2009). However, the secondary combustion of diesel soot and associated compounds during after-treatment introduces the formation of new pollutants including various nitro-PAH. The stereo-isomers formed differ from those formed upon atmospheric nitration of PAH (Heeb et al., 2008).

Since the PAH are lipophilic, they are easily transferred to hydrophobic components of the surfactant or into the lipid layer of the cellular plasma membrane. PAH seem to induce their effects through activation of the aryl hydrocarbon receptor (AhR) and the AhR nuclear translocator (Arnt), followed by the upregulation of Cyp1A1 and 1B1. The Cyp metabolise PAH, leading to the formation of ROS and reactive metabolites that may damage macromolecules. Recent findings on single PAH indicate that, in addition, the lipophilic compounds may penetrate into the plasma membrane and change properties linked to lipid fluidity or ion transport. Single PAH may modulate the composition of plasma membrane microdomains (rafts) in a specific way, affecting inter- and/or intracellular signalling (Tekpli et al., 2010a; Tekpli et al., 2010b). This seems to cause changes in ion transport of K^+ and Ca^{2+} and change intracellular pH by activating ion channels (NHE1) as well as via lysosomal rupture. However, the importance of these processes with regard to the whole mixture of organic compounds in the absence or presence of particles is not known.

Some PAH may react directly with macromolecules in tissues, whereas others are converted by enzymes into reactive metabolites within the cells. PAH may elicit pro-inflammatory effects in the lung, possibly through ROS formation (Nel et al., 2001; Xia et al., 2004). Benzo[a]pyrene (B[a]P), one of the important aromatic hydrocarbons in DEP, has been reported to elicit over-expression of keratinocyte chemo-attractant (KC), the murine functional analog of IL-8 in lung. It also triggered the recruitment of neutrophils in bronchoalveolar lavage fluids (Podechard et al., 2008). Oxygen, nitrogen radicals and reactive electrophilic metabolites of the PAH can attack or covalently bind to nucleophilic sites on cellular macromolecules within the cell. In this way several cellular macromolecules including lipids, proteins and DNA may be modified and various damage signalling pathways may be triggered. PAH that have entered cells may bind to cellular receptors such as the aryl hydrocarbon receptor (AhR) and indirectly modify the cellular response to more classical hormone receptors such as estrogen receptors (ER) and EGFR. These types of classical cellular signals are known not only to be involved in cell survival and proliferation, but also in the triggering of inflammatory responses as well as cell death pathways, much depending on the size, duration and the site of formation of the initiating signal.

PAH like B[a]P, phenanthrene and 1-nitropyrene induced similar responses as DEP extracts, when administered to epithelial cells in concentrations corresponding to DEP extracts (Baulig et al., 2003). Several other DEP related chemical compounds such as pyrene, naphthoquinone and phenanthraquinone may also affect pulmonary inflammation (Bommel

et al., 2000; Bommel et al., 2003; Xia et al., 2004; Inoue et al., 2007), but further studies are necessary to clarify their role in the adverse effects induced by DEP.

In order to understand the effect of PAH associated with PM, the effect of some of the most common PAH have often been studied singly in cell culture experiments. The bronchial epithelial cell line (BEAS-2B) released large amounts of IL-8 in response to nitro-PAH (Ovrevik et al., 2010). Nitro-PAH and their metabolite amino-PAH induced both qualitatively and quantitatively different cytokine/chemokine expression profiles. Whereas 1-nitropyrene and 3-nitrofluoranthrene elicited predominantly an IL-8 release their corresponding amines predominantly induced the release of RANTES (Ovrevik et al., 2010). It has been suggested that many inhaled environmental toxic components may trigger the release of inflammatory cytokines via an initial binding to the AhR (Wong et al., 2010). B[a]P that binds to the AhR, increased the mRNA expression and secretion of CCL1 in primary human macrophage culture. Moreover, in exposed mice the level of TCA3 (mouse ortholog of CCL1) in the lung was increased (N'diaye et al., 2006). 1-NP is known to bind to AhR, induce ROS production and activate MAPK (Asare et al., 2008) as well as NFkB (Pei et al., 2002). However, the precise roles for AhR, MAPK and NFkB in the 1-NP-induced IL-8 release are presently not clarified. ROS and nitrogen oxides are often cited as possible mediators in these reactions. Alternatively these molecules lead to a less specific activation of kinases, e.g. by inactivation of their respective phosphatases through binding or oxidizing their thiol groups. Most probably combinations of several factors are needed for the induction of cytokine responses. Often activation of the same cell signalling pathways are found to be involved in eliciting pro-inflammatory effects as well as cell death. Recent unpublished findings by our group suggest that the DNA damage induced by many of the PAH may change the inflammatory cell signalling response into cell cycle arrest, DNA damage repair or apoptotic cell death (Oya et al., personal communication). The reason why PM rich in PAH induces less cytokines than expected from 1-NP exposure alone, may be that cells interact with other PAH, giving rise to DNA damage that via p53 changes the transcriptional activity of NFkB.

4.2 Metals

An increasing number of studies have indicated that different transition metals may act as possible mediators of particle-induced injury and inflammation (Dreher et al., 1997; Molinelli et al., 2002; Pagan et al., 2003; Schaumann et al., 2004; Chen and Lippmann 2009). The focus has often been on transition metals such as iron (Fe), vanadium (V), nickel (Ni), chromium (Cr), copper (Cu) and zinc (Zn) on the basis of their ability to generate reactive oxygen species (ROS) in biological tissues. Most of the evidence pointing to the biological effects of metals originates from studies in animal models and cell cultures. However, in these systems pure metals have been applied in concentrations that are much higher than levels relevant for environmental exposures. Studies using PM containing multiple metals have reported effects that seem to be related to the PM metal content, despite low metal levels. However, it is difficult to determine the roles played by the individual metals in these complex PM mixtures (Chen and Lippmann 2009).

In relatively few studies human volunteers have been exposed to PM analysed for elemental composition, followed by an analysis of the extent of correlation between different metals

and biological responses. A clinical study of CAPs inhalation by Ghio et al. (2000) has been reanalyzed to determine the correlation between the nine most abundant elements and the cellular and biochemical endpoints (Huang et al., 2003). In the correlation analysis a Fe/Se/sulfate factor was associated with increased percentage of neutrophils in BAL fluid, and a Cu/Zn/V factor with increased blood fibrinogen. In another study metal-rich ambient particles $PM_{2.5}$ from a smelter area (Hettstedt) induced a more distinct airway inflammation and increased generation of oxidant radicals in healthy subjects as compared to samples from a non-industrialized area (Schaumann et al., 2004). PM samples with contrasting metal content collected in Utah Valley before closure, during closure and after reopening of steel mill plants have been applied in a human bronchial instillation study to investigate whether soluble components or ionizable metals could influence the biological effects. PM extracts were instilled into the bronchus of human volunteers, and phagocytic cells were obtained after 24 hours. The inflammatory response in the lungs of human volunteers was greater after exposure to aqueous extract collected before the closure and after the reopening as compared to during the shutdown of the plant (Ghio and Devlin 2001). With respect to metal content, the Zn content was 61 and 2 times higher in the aqueous extract from PM before closure as compared to the extracts from during and after reopening, respectively. In contrast, the Fe content was 5 times higher in the extract from after as compared to before the closure. Ni and V were only present in trace amounts and did not differ from year to year (Frampton et al., 1999; Dye et al., 2001; Ghio and Devlin 2001). In a clinical study using single metals rather than complex mixtures, soluble V and Cr instilled into human volunteers caused significant increases in oxidative stress, measured as 8-oxodG concentrations in lymphocytes, whereas other soluble metals (Fe, Ni, Cu and Pt) were not associated with oxidative stress (Sorensen et al., 2003).

The few *in vivo* animal studies of the response to ambient PM that investigated the contributions from specific air pollution components, either as an individual compound or as part of a mixture, may suggest that some of the PM components are more toxic than others (Chen and Lippmann 2009). For instance, inhalation of CAPs induced oxidative stress in the lung and heart of rats, but not in the liver. Using single-component regression analysis, the content of Fe, Mn, Cu and Zn was strongly associated with the oxidative stress generated in the lung, whereas Fe, Al, Si and Ti was associated with the effects observed in the heart (Gurgueira et al., 2002). Another study indicated that iron-catalyzed generation of ROS may not be a predominant mechanism of $PM_{2.5}$-induced ROS formation (Shukla et al., 2000). However, inhalation of iron particles induced a decrease in total antioxidant capacity and an increase in BAL proteins and IL-1α levels in rat lungs (Zhou et al., 2003). The water soluble Zn associated with PM was suggested to be one of the causal components involved in PM-induced cardiac effects in a study comparing instillation of particles with different levels of Zn, aquatic PM extracts and zinc sulphate in rats (Kodavanti et al., 2008). Moreover, the soluble fraction of an urban air particulate sample (EHC-93) induced lung cell injury and inflammation after instillation into mouse lung. Since a metal mixture containing all the metals in the sample except Zn induced minimal lung effects, Zn was suggested to be the toxic factor in the lung response (Adamson et al., 2000).

When PM collected in a smelter area (Hettstedt) with high levels of Zn, Mg, Pb, Cu, Cd and As was instilled to ovalbumin-sensitised mice it increased the allergic responses, in contrast

to PM with lower metal content collected in another area (Zerbst) in the same region (Gavett et al., 2003). However, PM from both areas significantly increased lung injury parameters and the levels of pro-inflammatory cytokines. This indicates that the metal composition of the ambient PMs may have greater influence on the allergic respiratory disease than other endpoints. The role of chemical composition of PM collected in different European cities dominated by pollution from traffic has been investigated in a study focusing on respiratory inflammation (Steerenberg et al., 2006). By application of cluster analysis, in which chemical constituents of PM were clustered based on the overall response pattern in the bioassays, the cluster containing Ti, As, Cd, Zn, Pb, Hg and organics derived from several combustion processes, were primarily associated with adjuvant activity for respiratory allergy. Clusters of crustal materials (containing Ca, Al, Mg, Fe, Ba, Cu, Cr) were predominately associated with measures of inflammation and acute toxicity. Another study instilled fine PM collected in the US into rat lung, and reported that metal oxides, transition metals (Pb, Mn, Cu, Se, Zn and As), but also carbon (EC, OC) and the organic compounds hopanes and steranes, were important predictors of cytotoxic and inflammatory responses (Seagrave et al., 2006).

The extracts of Utah Valley PM with contrasting metal content have also been used *in vivo* in animal studies and in cell cultures. When aqueous extracts of the Utah PM with high metal content (open plant) were instilled in rats they induced a significant pulmonary injury and neutrophilic inflammation (Dye et al., 2001). Cu, Zn, Fe, Pb, As, Mn and Ni, could have contributed to these effects, in addition to sulfate and cationic salts. In human airway epithelial cells extracts of PM with low levels of metals (closed plant), did not induce cytotoxicity, and only generated a minimal cytokine and ROS response compared to extracts from PM collected before and after the strike with higher metal content (Frampton et al., 1999). Overall, the human epidemiological, clinical and animal toxicological studies of the Utah Valley PMs show a strong qualitative coherence, that identifies soluble metals as important components in PM related health effects.

Residual oil fly ash (ROFA) is a complex mixture of sulphate, nitrate and metals, such as Fe, V and Ni, with the majority of these metals present in high concentrations as water-soluble salts. The ROFA leachate, containing Ni and V induced lung injury (Dreher et al., 1997; Kodavanti et al., 1998). Although BAL inflammatory markers (neutrophil influx, protein leakage, etc) were similar in ROFA- and metal (Ni and V)-exposed animals, gene expression profile studies of inflammation, remodelling and stress response genes, suggest that there are more complex interactions between metal constituents than previous studies have implicated (Nadadur and Kodavanti 2002). Furthermore, Zn has also been found to be responsible component in different oil combustion emission particles (Kodavanti et al., 2002). ROFA-associated transition metals have also demonstrated immediate and delayed cardiovascular responses (Watkinson et al., 1998).

The mechanisms involved in the biological responses induced by metals relevant for PM-induced effects (Zn, V, Cu, As, Ni, Cr and Fe) have been studied in a range of lung- and heart-related cellular systems. Metals in ambient air PM may alter the intracellular redox state with subsequent modulation of the activity of several transcription factors, including NF-kB and AP-1 (Chen and Lippmann 2009). These factors are critical for the expression of a

variety of pro-inflammatory cytokines and adhesion proteins. Several studies suggest that MAPK such as ERK, JNK and p38 mediate metal-induced expression of inflammatory proteins in lung cells and also in cardiac cells (Samet et al., 1998; Lag et al., 2005; Kim et al., 2006; Ansteinsson et al., 2009). Furthermore, activation of MAPKs by the metals As, Cu, V and Zn have been suggested to be mediated through the EGFR (Wu et al., 1999). V and Zn seem to induce tyrosine phosphate accumulation by inhibiting protein tyrosine phosphatases and thereby also inhibiting the dephosphorylation process, whereas other mechanisms might be involved in As-induced MAPK activation (Samet et al., 1999). The mechanisms involved in the EGFR activation induced by Zn have been studied in great detail in epithelial lung cells (Samet et al., 2003; Tal et al., 2006). From the *in vitro* studies of PM the metals Zn, V, Cu and As seem more important for elucidating biological responses than for instance Fe. Although Fe induces production of ROS both *in vivo* and *in vitro*, it does not seem to play an important role for lung injury when applied in a mixture of many soluble metals, such as in ambient PM or ROFA (Chen and Lippmann 2009).

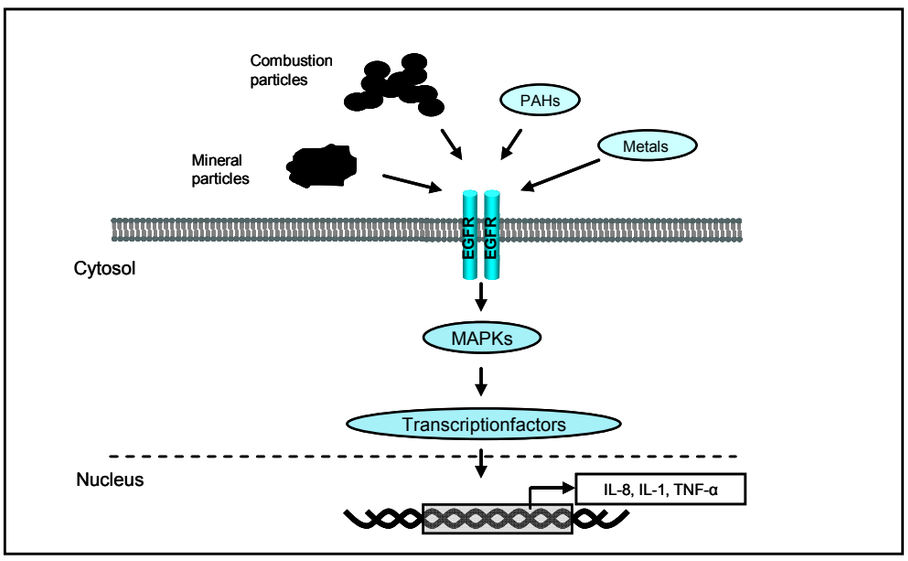

Fig. 3. Schematic figure of signalling pathways activated by particles from various sources and their components. Arrows do not necessarily indicate direct activation, but may mask involvement of other molecules, receptors etc. See text for specification of the involved MAPK and transcription factors.

5. Relationship between different types of particles and components with respect to pro-inflammatory responses

Identifying constituents and fractions of PM that play a critical role in eliciting health effects could provide more cost-efficient abatement strategies for the improvement of air quality. Given the relative similarity of risk estimates in epidemiological studies it is conceivable that particles of different composition might trigger similar cellular inflammatory reactions. Such a common response may be elicited through the activation of the same signalling pathways. One such pathway is the EGFR/ MAPK pathway. The activation of this pathway has been detected in bronchial epithelium of human volunteers after diesel exhaust exposure

(Pourazar et al., 2008). Similarly, this pathway has been reported to be activated after exposure of lung cells to particles or commonly occurring components of particles, including a mineral particle, a carbonaceous particle, metals and a nitro-PAH (Ovrevik et al., personal communication). The results indicate a coherence of responses of lung cells and humans exposed to particles. This mode of action is depicted in figure 3. Just how particles and their components might activate the EGFR, still needs to be elucidated.

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