Environmental Air Pollution

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WHAT DO WE KNOW?

Components of Environmental Air Pollution

The effects of air pollution on health have been recognized for many hundreds of years. In London, during December 1952, a particularly bad smog, which involved extreme elevations of both SO_2 and black smoke, was associated with more than 1,000 extra deaths during a 5-d period (1). The majority of the pollution responsible for smogs is derived from the domestic and industrial burning of fossil fuels. The introduction of legislation to reduce the burning of fossil fuels in Britain and elsewhere has meant that the make-up of environmental air pollution has changed considerably. However, the decline in fossil fuel-associated pollutants has been replaced by a steady increase in traffic-associated pollutants such as finer, respirable particulates, oxides of nitrogen (NOx), ozone (O_3), and volatile organic compounds (VOCs).

Health Effects of Environmental Air Pollution

Chamber studies into the effects of NO_2 suggest that patients with allergic asthma can develop some clinical effects when exposed to NO_2; however, the epidemiological evidence remains inconclusive (2). Indoors, NO_2 is a major pollutant, particularly in homes with gas stoves, where it has been associated with lower respiratory tract infections (3). However, findings are inconsistent and studies into the effects of NO_2 in combination with other pollutants might be of use (2).

Ozone has been found to reduce lung function, increase airway sensitivity, and cause pulmonary inflammatory changes. However, at ambient exposure levels of ozone it is not clear whether there is a significant health risk (4).

Many of the VOCs identified in traffic pollution are carcinogenic; however, as individual compounds the concentrations are low, although the effects of the combined cocktail remain a danger to long-term health.

Particle Problem

For particulate matter, monitored in many countries as PM_{10} (particles collected by a convention that has 50% efficiency for particles with an aerodynamic diameter of 10 μm), no safe threshold for exposure has been identified (5). This is in distinct contrast to those pollutants discussed above. PM_{10} consists of a mixture of particle components, including traffic- and combustion-derived carbon-centered ultrafine particles (less than 100 nm in diameter), secondary particles (nitrates and sulfates), wind-blown dust of geological origin, potentially containing endotoxin, and biological particles (e.g., spores, pollen) with their associated allergens.

A large variety of epidemiological studies have described the potential health effects of particulate air pollution in both adults and children. PM_{10} pollution episodes have been consistently associated with increased mortality, particularly resulting from cardiovascular causes (5, 6). The increase in cardiovascular deaths has been suggested to result from an increase in the risk of blood clotting (7). This hypothesis is supported by data from the MONICA study (8), in which there was a clear increase in plasma viscosity in both men and women during an air pollution episode in Ausburg in 1985.

Epidemiological reports of the effects of PM_{10} on morbidity are not as consistent as the clear link between PM_{10} and mortality. A study of children has shown that a 10-$\mu g/m^3$ increase in PM_{10} was associated with a 2.7% increase in the prevalence of peak expiratory flow (PEF) decrements of greater than 10% (9). Notably, this was not seen in a previous panel study in which the mean PEF had been used, indicating the importance of an appropriate or sensitive measure of the respiratory health indicator. In contrast, the PEACE project, involving 14 centers in Europe, has been unable to identify any consistent associations between day-to-day changes in PM_{10} and PEF or respiratory health in children with chronic respiratory symptoms (10). More studies are required to determine whether the association between extreme decrement in PEF and increased PM_{10} is a consequence of the sensitivity of the measured endpoint, identification of susceptible individuals, or a potential statistical artifact.

Several studies have also looked at the possible effects of air pollution on the prevalence of asthma or asthma symptoms. Using a cross-sectional study of children in southern Holland, it was found that those who lived within 100 m of a freeway reported significantly more cough, wheeze, runny nose, and doctor-diagnosed asthma than other children (11). In addition, the same study identified a significant association between truck traffic density and black smoke concentration and chronic respiratory symptoms. In Paris, a strong association between black smoke air pollution and doctors' house calls for asthma-related illness in children has also been identified (12). In contrast, in London, a time series analysis of daily numbers of doctor consultations for asthma in children found the strongest associations during pollution episodes involving NO_2, carbon monoxide, and SO_2 (13). For adults the strongest associations were with PM_{10}, indicating some differences in susceptibility between children and adults in this study group.

The vast array of epidemiological data is confusing, but in general it indicates that although PM_{10} induces inflammatory responses of the airways resulting in decrements in pulmonary function and exacerbation of preexisting inflammation, it is not a primary cause of asthma (14). Although additive or synergistic effects with other pollutants are difficult to discount, modern epidemiological approaches do allow interactions to be described. Such interactions have been detected, for example, with ozone, but in general the particle effect is greater than any interaction term, and adverse health effects of PM_{10} occur at levels currently existing in our cities. Most of the epidemiological studies conducted to data deal with the acute effects of identifiable pollution episodes; little is known about the potential chronic effects of PM_{10} or other pollutants.

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Hypothesized Mechanisms behind the Adverse Health Effects of PM_{10}

Several hypotheses that have been proposed to explain the proinflammatory effects of PM_{10} suggest that the metal components (15, 16) and/or the ultrafine fraction (7, 17) of PM_{10} are important. Both hypotheses propose a role for oxidative stress and induction of cytokine expression by epithelial and macrophage cells, which lead to inflammation (Figures 1 and 2).

The original suggestion that ultrafine particles may play a role in the health effects of PM_{10} was derived from a study by Ferin and coworkers (18). This study demonstrated that for an equal mass dose, ultrafine titanium dioxide (25-nm diameter) induced more inflammation and resulted in greater interstitialization than respirable but nonultrafine titanium dioxide (200-nm diameter). On exposure to epithelial cells, ultrafine particles have been shown to induce oxidative stress (19) and to stimulate production of the cytokine interleukin-8 (IL-8) (20). Instillation of ultrafine carbon black into the rat lung stimulates influx of neutrophils into the air spaces, indicative of inflammation (21). Epidemiological data suggest that, in adults (22) and children (23) with a history of asthma, there is a stronger association between PEF and the number of ultrafine particles than with PM_{10}. Hence, limited support for the importance of ultrafine particles in the proinflammatory effects of PM_{10} has been provided by *in vitro*, *in vivo*, and epidemiological data.

There is also considerable support for the importance of metals in the proinflammatory effects of PM_{10}. Transition metals are known to redox-cycle by Fenton chemistry, generating hydroxyl radicals capable of inducing oxidative stress and damage within biological systems. For example, iron has been implicated in the free radical activity of PM_{10} (15). Many studies have used residual oil fly ash (ROFA), a transition metal-rich particulate emitted by power plants that burn heavy oil. In one study ROFA was reported to induce the expression of proinflammatory cytokines such as IL-8, IL-6, and tumor necrosis factor α (TNF-α) in a normal human bronchial epithelial cell line (16). In the same study, pretreatment with the metal chelator deferoxamine inhibited the induction of cytokine expression.

There is considerable overlap between the ultrafine and transition metals hypothesis with regard to the mechanisms suggested to be responsible for their proinflammatory effects. For example, as mentioned previously, both stimulate the expression of proinflammatory cytokines. In addition, ROFA (24), and PM_{10} (25) all increase the activation and nuclear translocation of the transcription factor nuclear factor κB (NF-κB). NF-κB is known to upregulate the transcription of genes encoding many proinflammatory molecules such as TNF-α and IL-8 (26), hence its activation may be focal to the induction of inflammation by PM_{10}.

Several studies have also considered the allergen (e.g., latex) or endotoxin content of PM_{10} with respect to their effects on health (27). Endotoxin has a vast array of biological effects including upregulation of IL-8 expression by alveolar and bronchial epithelial cells. However, much of the data on the role of endotoxin in the biological effects of PM_{10} used endotoxin inhibitors with inadequate specificity. For example, polymyxin B is an inhibitor of protein kinase C, a potential component of the intracellular pathway involved in the expression of cytokine genes.

WHAT DO WE NEED TO KNOW?

Susceptibility to PM_{10}-induced Disease

It is clear from epidemiological studies that the effect of PM_{10} on normal healthy individuals is minimal, but that there are clearly individuals who are more at risk. However, the factors that make an individual more vulnerable or susceptible remain speculative and can be subdivided into groups on the basis of the classic toxicological paradigm of exposure: dose and response.

Susceptibility to exposure. Differences in susceptibility to PM_{10} may be the extent of exposure. An obvious example includes children living close to freeways. Obviously those individuals who live within a city will have a greater exposure to PM_{10} than those living in rural areas. The components of the PM_{10} in these two extremes may be different in that the city-derived PM_{10} will be dominated by traffic-derived particles. In addition, individuals who smoke, and those who live with them, will be exposed to far greater numbers of ultrafine particles and other components of environmental tobacco smoke than nonsmokers, and hence this could be a factor in increased susceptibility to PM_{10}. Maternal smoking has been found to double the risk of sudden infant death syndrome (28), indicating that exposure to environmental tobacco smoke is clearly a factor in infant mortality.

Susceptibility to increased dose. For any individual exposed to a cloud of particles the dose will be a function of the deposited mass and the efficiency of clearance by the mucociliary

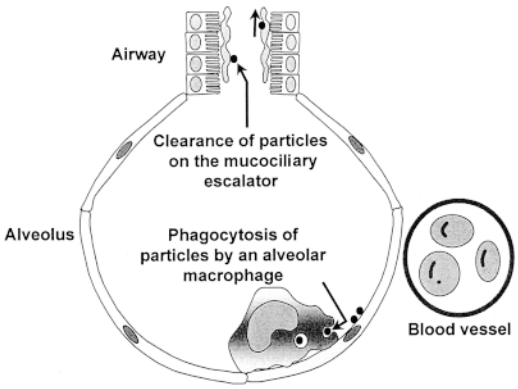

Figure 1. Phagocytosis and clearance of particles deposited in the alveolar sacs and airways of the lung.

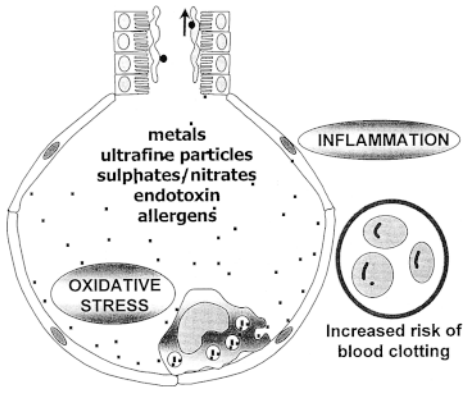

Figure 2. Exposure of the lung to PM_{10} and its various components leads to oxidative stress within the various lung cells and an activation of gene expression resulting in the production of various pro-inflammatory mediators such as cytokine. The escalating inflammation in susceptible individuals may exacerbate any preexisting pulmonary or cardiovascular disease.

escalator and by macrophages. Deposition is a function of several complex factors including depth and frequency of breathing as well as the size and anatomy of the airways (29). Differences in macrophage clearance can also be anticipated but have not been extensively studied. Macrophage function in infants is immature with respect to bacterial ingestion/killing and the production of reactive oxygen species (30); therefore, clearance of environmental particles from the infant lung may be reduced compared with adults. Any factors that tend to increase the effective dose to the target tissues—the epithelium and interstitium—could contribute to susceptibility.

Susceptibility to response: Those with a preexisting disease such as an inflammatory lung disease (e.g., asthma and cystic fibrosis) or infection may be more susceptible than healthy individuals. The pulmonary epithelium or leukocytes in these compromised people may be "primed" to produce an exaggerated proinflammatory response on exposure to PM_{10}, which may be sufficient to induce an exacerbation of the preexisting disease (Figure 2). Evidence for such a susceptible group comes from epidemiological mortality data (5, 6). The link between PM_{10} exposure and increased death from cardiovascular disease remains more problematic at a mechanistic level. However, such patients may have increased systemic procoagulant, such as fibrinogen or factor VII, which may be increased by PM_{10} exposure, triggering a heart attack or stroke (7). Studies initially in dogs (31) and now in humans (32) have also shown that there is a change in heart rate variability during high particulate air pollution, and this could also be a factor leading to heart attacks. Susceptibility to response may also involve as yet unidentified genetic factors.

Children. Children could be a susceptible group for any of the three reasons given above. For example, because of the differences in size and maturity of the respiratory system, the deposition and clearance of particles may differ from adults and this could result in increased or decreased inflammation and hence disease.

Computer models that predict regional particle deposition in the human lung suggest that total and specifically alveolar deposition of ultrafine (50-nm diameter) and fine particles (200-nm diameter) differ with age, reaching a peak at 1 yr of age (29). Confirmation of difference in the actual deposition of PM_{10} components in infants versus adults requires physical confirmation. With respect to particle clearance, functions such as ingestion or killing of bacteria and the production of reactive oxygen species are known to be immature in infant macrophages (30). Hence, particle deposition may be enhanced and the clearance of particulate matter may be impaired, resulting in an increase in particulate dose. Studies investigating these problems have yet to be conducted. However, because infants are obligate nose breathers, removal of particulate matter (coarse rather than ultrafine particles) from the upper airways is possible.

One major omission in our current data is the relationship between indoor and outdoor air pollution. While the average adult spends the greatest proportion of his/her time indoors ($> 90\%$), the proportion may be even higher in the very young. Because the regional monitors of the Automated Urban Network in the United Kingdom, for example, record only outdoor air quality, it is easy to see how localized indoor particle changes could have an impact on health, which would be masked by using the regional monitors. Questions have been raised regarding the variation between PM_{10} levels at the curbside, specifically at child level, compared with those measured at monitoring stations, which are often situated away from the roadside. Roadside monitoring stations have been established in several cities including London and Glasgow and it is anticipated that these stations will provide useful information in this respect.

Proinflammatory Effects of PM_{10}

To assess useful treatment modalities for avoiding exacerbations of respiratory or cardiovascular disease during a pollution episode, it is important to elucidate the mechanism by which PM_{10} induces pulmonary inflammation. This will require identification of the components of PM_{10} that are responsible for its proinflammatory effects and this may then help to shape legislation controlling emissions. The role of ultrafine particles and metals in the health effects of PM_{10} needs to be studied further to elucidate whether they are both important, or in fact whether they could have additive or even synergistic effects when in combination with each other and other components of PM_{10}

HOW CAN WE ACHIEVE THIS?

Susceptibility to PM_{10}-induced Disease

First, clear identification of the individuals who are most susceptible to elevations of PM_{10} would allow formulation of improved hypotheses concerning the mechanism by which PM_{10} induces health effects and what factors are likely to make an individual susceptible. Obviously this requires further epidemiological studies that compare normal and potentially vulnerable people. A vulnerable group could conceivably consist of children or a subgroup such as children with asthma. Such studies would require the use of several sensitive end points. For example, as mentioned previously, significant effects of PM_{10} on PEF could be determined only for extreme decrements rather than mean decrements (6), consistent with the hypothesis that there is a susceptible subpopulation. The most appropriate end point for detection of early inflammatory changes in the airways is bronchoalveolar lavage (BAL) sampled opportunistically during anesthesia (33).

If susceptibility is a factor of dose, then comparison between locations that differ in their mean annual PM_{10} levels will be required. Obviously, control of dose can be easily achieved in chamber and in *in vitro* studies, but such techniques can reveal only short-term effects.

At present most laboratory investigations into the proinflammatory effects of PM_{10} use models involving healthy animals or pulmonary cells. Several laboratories are now developing models that attempt to mimic susceptible groups. Models include either animals or cells pretreated with oxidants, cytokines, or endotoxin, or infected with viruses. In this manner, the relative importance of preexisting oxidative stress and/or inflammation or infection can be examined.

Proinflammatory Effects of PM_{10}

To assess the relative importance of PM_{10} components in relation to their health effects, a more detailed analysis of the individual components such as ultrafine particle number and metal concentrations will be required. The information gained from such studies can then be used in future epidemiological tests. For example, the evolving database on the toxicological effects of ultrafine particles has resulted in their measurement in many ongoing studies, and they are now being related to adverse health effects. In addition, the PM_{10} collected during an epidemiology study can be used in a variety of biological tests either *in vivo* or *in vitro*, thus allowing comparison of PM_{10} samples with known compositions. Comparison of PM_{10} samples collected from different sites, for example, sites with high and low ambient air metal levels, together with the respective epidemiology plus the biological effects of the PM_{10}, will allow

a detailed investigation into the relative importance of the components of PM_{10}.

Because of the complex nature of PM_{10} many studies have used model components or surrogates such as ultrafine carbon black, solutions of metals, or direct treatment with endotoxin. Experimental use of defined mixtures of such model components will allow investigation of their potential additive or synergistic properties.

Future *in vivo* and *in vitro* experimentation will be important. The rat instillation and inhalation models remain sensitive tools with which to investigate the proinflammatory effects of particulates. These models may now be extended to investigate susceptibility, with transgenic animals having the potential to elucidate the importance of various genes in the response to PM_{10}.

To date, various *in vitro* models have been used, including macrophage and epithelial primary cells and cell lines. Good indicators of proinflammatory effects include upregulation of the expression of cytokines as well as activation of the transcription factor NF-κB. Again, these systems will require development for study of the responses of a susceptible model, with transient and stable gene transfection models providing hope for a real advance. Further investigations into the mechanism of NF-κB activation in relation to the proinflammatory effects of particulate matter are also ongoing. Greater understanding of the mechanism of biological activity of PM_{10} *in vitro* and in animal models will allow identification of suitable end points for measurement in children for both mechanistic and epidemiological studies including perspective investigations.

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