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Particulate Air Pollution and Increased Mortality: Biological Plausibility for Causal Relationship

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INTRODUCTION

Recently, a number of epidemiological studies have concluded that ambient particulate exposure is associated with increased mortality and morbidity at PM concentrations well below those previously thought to affect human health. These studies have been conducted in several different geographical locations and have involved a range of populations. While the consistency of the findings and the presence of an apparent concentration response relationship provide a strong argument for causality, epidemiological studies can only conclude this based upon inference from statistical associations.

The biological plausibility of a causal relationship between low concentrations of PM and daily mortality and morbidity rates is neither intuitively obvious nor expected based on past experimental studies on the toxicity of inhaled particles. Chronic toxicity from inhaled, poorly soluble particles has been observed based on the slow accumulation of large lung burdens of particles, not on small daily fluctuations in PM levels. Acute toxicity from inhaled particles is associated mainly with acidic particles and is observed at much higher concentrations than those observed in the epidemiology studies reporting an association between PM concentrations and morbidity/mortality.

To approach the difficult problem of determining if the association between PM concentrations and daily morbidity and mortality is biologically plausible and causal, one must consider 1) the chemical and physical characteristics of the particles in the inhaled atmospheres, 2) the characteristics of the morbidity/mortality observed and the people who are affected, and 3) potential mechanisms that might link the two.

Chemical and Physical Characteristics of Particles in Inhaled Atmospheres

The PM_{10} standard is the only national ambient air quality standard that is not chemical-specific. The chemical composition of a particle will greatly affect its toxicity and must be considered in determining if the association between atmospheric PM concentrations and increases in morbidity/ mortality is causal. For example, alpha-quartz particles are more toxic than TiO_2 particles;[1] acid sulfate aerosols are more likely to cause acute adverse health effects than are neutral sulfate aerosols.[2] Size is also important in defining the toxicity of particles. Recent studies indicate that ultrafine particles ($PM_{2.5}$, especially particles < 0.1 μm) are more toxic than larger inhalable particles.[1,3] The ultrafine particles have a greater number and surface area per unit mass than larger particles, which may account, in part, for their greater toxicity. Fine particles may also have a different chemical composition than coarse particles, because their source is often combustion processes. A study of the chemical composition of $PM_{2.5}$ particles versus PM_{10} particles in Los Angeles indicated that nitrates, sulfates, ammonium and organic and elemental carbon were the most abundant species in the $PM_{2.5}$ fraction while the coarser particles contained soil-related species, such as aluminum, silicon, calcium, and iron.[4]

In some epidemiology studies, the investigators attempted to determine what chemical form of particles had the strongest association with health effects. In the Harvard 6-cities study,[5] the excess mortality was most strongly associated with the fine particles, including sulfates. However, in a study of air pollution in St. Louis and eastern Tennessee by the same authors,[6] the strongest association of particulate pollution with daily mortality rates was PM_{10}, with progressively weaker associations with $PM_{2.5}$, sulfate and aerosol acidity. This is the opposite of what one would expect if aerosol acidity were the cause of increased mortality as has been suggested.[7] The investigators state, however, that the low daily death counts, the short study period, and the large geographic areas considered in the St. Louis/Eastern Tennessee study limit the statistical power of the study such that they could not conclude that the acidity of the aerosol was not associated with mortality.

If the chemical and physical forms of the PM are important in determining the adverse health effects induced by PM, one would expect different concentration response curves to be observed in different epidemiology studies, depending on the type of aerosol present in the atmospheres. Such was reported to be the case by Spurney[8] in his analysis of the epidemiology studies conducted in Utah, St. Louis, Philadelphia, and Detroit, with the atmospheres in Utah and St. Louis being more toxic than those in Philadelphia, and Detroit. The different slopes of the concentration response curves for the different cities could be due to several factors, including differences in physicochemical properties and resultant potency of the PM in the different cities.

Characteristics of Observed Morbidity and Mortality

In general, the health effects that have been reported to be associated with particulate pollutants are cardiopulmonary in nature. They include all malignant neoplasms, decreased pulmonary function, asthma, lung cancer, cardiopulmonary disease, cough, shortness of breath, wheezing, hospitalization rates, chronic obstructive pulmonary disease (COPD) and restricted activity due to illness. Schwartz[9] compared causes of death in the Philadelphia epidemiology study with the causes of death in the London smog of 1952, and found similar patterns. On high PM pollution days (average = 141 $\mu g/m^3$), there was a disproportionate increase in deaths from COPD, pneumonia, heart disease, and stroke. Thus, the characteristics of adverse health effects on high particle pollution days are mainly cardiopulmonary in nature and are the types of effects that can be considered plausibly related to airborne toxicants.

It is also of interest to know the types of people affected. The cohorts in the pertinent epidemiology studies included general populations (6-cities studies), members of a religious group that refrains from smoking and drinking alcohol (California), smokers (Salt Lake City) and working age adults plus the elderly (Helsinki). However, the persons whose deaths might have been associated with particulate exposures are not well described; it is not known if they had previously existing health conditions, such as cardiopulmonary disease or other debilitating conditions, that might make them more susceptible to particulate pollutants than healthy persons. Such a situation might result in an increased daily mortality rate on days with higher PM_{10}, followed by a decreased daily mortality rate so that the average mortality rate over a longer time period would not be affected. Thurston et al.[10] analyzed the 1958-1972 winter mortality-pollution records for London and found that the log of acid aerosol concentrations was more strongly associated with total mortality than was either SO_2 or British Smoke. The authors pointed out that the logarithmic nature of the exposure portion of the acid-mortality relationship suggested a saturation model of the pollutant effects, possibly due to harvesting of a susceptible subpopulation. The investigators also noted that mortality effects usually followed pollution in time in their mortality-pollution cross-correlation analyses, suggesting a causal relationship.

Research data on the relative effect of particle exposures in persons with pre-existing pulmonary disease compared to healthy persons do not give a clear picture. Pope and Kanner[11] reported an approximate 2% decline in FEV_1 in smokers with mild to moderate COPD with an increase in PM_{10} of 100 $\mu g/m^3$ in Salt Lake City. However, persons with severe COPD (average FEV_1 equal to 50% of predicted) had no further reduction in pulmonary function upon acute (2 h) exposure to 90 $\mu g/m^3$ H_2SO_4 in clinical studies.[12] Exercising asthmatics experienced mild bronchoconstriction following the same exposures. In an elastase-induced rat model of emphysema, Mauderly et al.[13] found that exposure to diesel exhaust, which contains ultrafine soot particles, resulted in less particle deposition in the emphysematous rats than in normal rats, thus sparing the emphysematous rats in the health effects induced by the particles.

Potential Mechanisms of Causality Between Low Levels of Particulate Pollution and Adverse Health Effects

The potential mechanisms by which PM can cause adverse health effects have been described earlier in this chapter. The mechanisms can be generally summarized as health effects due to accumulation of particles in the lung, impaired respiratory function, or impaired pulmonary defense mechanisms. Most studies have been directed toward determining the toxicity of single compounds. It is also essential to consider possible interactive mechanisms that will influence the health effects induced by air particulates.

Toxicity Resulting from Accumulation of Particles in the Lung. The accumulation of large lung burdens of poorly soluble particles can lead to decreased clearance of subsequently inhaled particles and an enhanced rate of accumulation of particles in the lung.[14] Large lung burdens of particles of even relatively low inherent toxicity have been shown to induce lung cancer in animal models.[15] How much exposure to particles is required to accumulate enough particles to impair clearance of subsequently inhaled particles? Rats exposed to 0.35 mg/m^3 diesel soot (ultrafine carbon particles) for 24 mo did not accumulate enough particles to induce pulmonary inflammation (as measured by both histopathology and analysis of bronchoalveolar lavage fluid) or to impair particle clearance, but rats exposed to 3.5 mg/m^3 for the same length of time did. Rats that inhaled carbon particles at the 8-h time-weighted concentration of 10 mg/m^3 limit recommended for occupational exposures by the ACGIH 5 days a week for 12 weeks accumulated enough particles to induce an inflammatory response by 6 weeks.[16]

The toxicity resulting from accumulation of large burdens of particles in the lung does not provide a plausible biological basis for the observed association between PM concentrations and daily mortality and morbidity rates except in special cases. In the Harvard 6-cities study, an association was found between daily mortality rates and particulate pollutant levels in the different cities, some rural communities and some industrialized cities. Because the ranking of the cities in terms of air-pollution levels did not change during the study period, it is not possible to distinguish between effects due to historical exposures and those due to recent exposures. Therefore, the elevation in daily mortality rates in industrialized cities such as Steubenville compared to less industrialized cities such as Topeka or Portage may be based on accumulated exposures to higher pollutant levels in Steubenville. This does not explain however, the association between daily mortality rates and particulate pollution within the city of Steubenville itself.[17]

Acute Toxicity. Recently it has been observed that certain types of particles are acutely toxic to the lung at low exposure concentrations. A half hour exposure of rats to freshly generated ultrafine polytetrafluoroethylene particles at a concentration of 64 $\mu g/m^3$ resulted in pulmonary inflammation and death.[18] In a study of the toxicity of fresh versus aged fumes from thermal degradation of polymers, Warheit et al.[19] reported 100% mortality in rats exposed for 0.5 h to 200 $\mu g/m^3$ of fresh ultrafine (0.05 μm) aerosol; mortality decreased to 20% if the aerosols were aged for 5 min. Analysis of bronchoalveolar lavage fluid and histopathology indicated that the rats died of severe lung injury. The significance of the highly toxic fresh aerosols for environmental exposures is questionable, because of the rapid loss of toxicity of the aerosols with time and the lack of information on the amount of such aerosols in the environment.

Impaired Respiratory Function. As described earlier in this chapter, acidic sulfate particles may lead to impaired pulmonary function but at concentrations in the mg/m^3 range, well above peak ambient levels of 50-75 $\mu g/m^3$.[20] An exception to this statement is the work of Amdur[21] and Amdur and Chen[22] in which single exposure of guinea pigs to 100 $\mu g/m^3$ of H_2SO_4 increased airway

resistance and daily, 3-h exposures of guinea pigs to 20 $\mu g/m^3$ of metal particles coated with H_2SO_4 resulted in a reduced vital capacity. In humans, however, inhalation of 1 mg/m^3 H_2SO_4 aerosol for 3 h did not cause any influx of inflammatory cells into the lung based on analysis of bronchoalveolar lavage fluid obtained 18 h after the exposures.[23] Of interest is the finding that hyper-responsive airways develop after exposure of healthy rabbits to as little as 75 $\mu g/m^3$ H_2SO_4 for a 3 h exposure.[24]

Impaired Pulmonary Defense Mechanisms. Sulfuric acid is known to slow mucociliary clearance in rabbits during the first few weeks of exposure to 250 $\mu g/m^3$ H_2SO_4, for 1 h/day, 5 days/week for 12 mo.[25] Repeated exposures to 250 $\mu g/m^3$ H_2SO_4 also causes hypertrophy and hyperplasia of epithelial secretory cells and a shift toward synthesis of a more viscous mucus. The increased secretory cells and excess mucus production are characteristic of human chronic bronchitis. Alveolar macrophages from rabbits exposed to H_2SO_4 aerosol at 75 $\mu g/m^3$ for 2 h/day for 3 days had a reduced ability to produce reactive oxygen compounds and tumor necrosis factor.[26]

Synergistic Effects. An area in which there is very little information is the potential interactive effects of air pollutants. The potential significance of mixtures is illustrated by the studies of Amdur and Chen,[22] in which it was shown that coating H_2SO_4 on a metal particle (ZnO) greatly increased the response of guinea pigs to inhaled H_2SO_4. A 1 hour exposure to 20 $\mu g/m^3$ H_2SO_4 coated on the ultrafine metallic particles increased bronchial reactivity in guinea pigs; a 10-fold higher concentration of H_2SO_4 alone was required to produce the same response. However, such synergistic effects were not observed by Anderson et al.,[27] who studied the effects on 15 healthy and 15 asthmatic volunteers of 1-h exposures to 100 $\mu g/m^3$ H_2SO_4 (0.5 μm) or 250 $\mu g/m^3$ carbon black (0.5 μm) separately or with the H_2SO_4 coated on the particles. The exposures did not result in changes in symptoms or pulmonary function, except for an equivocal response in one person.

Conclusions

Having considered the characteristics of the particulate exposure atmospheres and the types of morbidity and mortality associated with the polluted atmospheres, what can be concluded about the biological plausibility of the association that has been observed? It is clear that the health effects associated with the elevated particulate pollutant levels are cardiopulmonary in nature and it is biologically plausible to relate such effects to inhaled toxicant particles. Therefore, the response portion of the concentration response curve seems plausible if one accepts the temporal relationships modeled in the epidemiological studies. The concentration of particulate matter that is associated with such responses, however, is lower than would be expected based on animal and human clinical studies in response to single particulate pollutants. This is true even when one considers that there is evidence that the people who make up the excess mortality population may be susceptible subpopulations. Moreover, it is not clear what portion of the inhalable particulate matter constitutes the delivered dose that is associated with the observed morbidity or mortality. There is evidence from both animal toxicology data and epidemiology data that ultrafine acid aerosols may be of greater health significance than the rest of the mass. Finally, the potential for interactive effects between PM of different types and PM and other air pollutants has only begun to be explored.

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