Final Technical Report

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Center Name: Southern California Particle Center and Supersite (SCPCS)
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Title: Controlled Human Exposure Studies with Concentrated PM
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RFA: Airborne Particulate Matter (PM) Centers (1999)
Research Category: Particulate Matter

Topic C: Studies of the Effects of Varying Spatial and Temporal Patterns of Ambient Particulate Matter (PM) and Co-pollutants and Resulting Health Effects with Emphasis on the Role of Atmospheric Chemistry

Objective(s) of the Research Project: The objectives of this project were as follows:

1. Perform controlled exposures of human volunteers to typical Southern California urban ambient atmospheres polluted by PM, using ambient particle concentrators. The exposures were designed to represent realistic combinations of relatively high PM concentrations and vulnerable people. The different exposure projects addressed the three key PM size ranges (fine [F], coarse [C], and ultrafine [UF]) in a metropolitan location with heavy primary PM pollution and secondary photochemical PM pollution. The volunteer subjects included healthy adults (under age 50), asthmatic adults, healthy elderly adults, and elderly adults with chronic obstructive pulmonary disease (COPD).

2. Measure short-term health effects of the above exposures, using the most sensitive practical (i.e., relatively noninvasive) measures of cardiopulmonary health and systemic inflammation. The acute biological endpoints to be measured were selected for relevance to recent epidemiological studies and included symptom inventories, clinical respiratory function (e.g., forced expiratory spirometry, pulse oximetry), airway inflammation (as inferred from cytology and biochemistry of induced sputum), systemic inflammation, and hemostasis (as inferred from biochemistry of peripheral blood), and cardiac rhythm alterations documented from continuous ambulatory electrocardiograms (ECG).

These clinical efforts were among the first in the country to apply concentrator technology capable of concentrating different PM modes. The School of Engineering of the University of Southern California provided significant environmental monitoring and concentrator support during the studies. All exposures were performed at the base laboratory location (Downey, CA), which is heavily influenced by local and regional primary motor-vehicle pollution, as well as with some emissions from stationary sources and ships. Thus, we were able to focus and study

intensively the health effects of ambient PM at one dedicated and characterized impacted location.

The Southern California Particle Center and Supersite (SCPCS)-supported studies (in combination with immediately preceding and concurrent efforts primarily funded by the U.S. Environmental Protection Agency (EPA) through other grants) yielded the health effects investigations and publications summarized in Table 1. These efforts were complementary and shared important components so that comparisons and understanding of the results could be efficiently derived. Each study was approved by the local institutional review board and each subject provided signed informed consent prior to his/her participation. All studies followed essentially the same experimental protocol, involving 2 hours of exposure to the scheduled PM mode and control (filtered air alone) in a single-person exposure chamber (a modified body plethysmograph interfaced to the appropriate particle concentrator). Moderate ergometer exercise was performed for 15 min of each half hour. Holter ECG was continuously recorded for about 24 hr, beginning about 1 hr before the experimental exposure. Most measures of health status were ascertained just before and immediately after the exposure period, again 4 hr after exposure ended, and again on the following morning (about 22 hr after exposure ended). Sputum induction to assess airway inflammation was performed only on the morning following each exposure.

Table 1. Summary of PM Concentrator/Human Exposure Studies Associated with the SCPCS

Atmosphere, Mean Concentration	**Subjects**	**Primary Sponsor**
$PM_{2.5,}$ 174 $\mu g/m^3$	12 healthy + 12 asthmatic adults	Health Effects Institute
$PM_{2.5}$, 194 $\mu g/m^3$	6 healthy elderly + 13 elderly with COPD	SCPCS
$PM_{2.5}$, 203 $\mu g/m^3$ + NO_2, 0.4 ppm	6 healthy elderly + 18 elderly with COPD	EPA-STAR
$PM_{10-2.5}$, 157 $\mu g/m^3$	4 healthy + 12 asthmatic adults	SCPCS
$PM_{0.1}$, 145,000 particles/ml	17 healthy + 14 asthmatic adults	SCPCS

Summary of Findings:

Healthy and Asthmatic Adults Exposed to Fine Particles ($PM_{2.5}$)

A two-hour exposure to F was associated with mixed exposure-related unfavorable effects. This might be expected given the short duration, moderate PM exposure concentration (25–50% of normal levels for that neighborhood) and small group sizes. We were able to detect differences by exposure group in some acute cardiovascular, circulatory and central airways responses.

Conventional lung function tests and routine hematologic measurements did not show statistically significant ($P < 0.05$) changes in either healthy or asthmatic subject groups after F

exposure, relative to filtered-air control conditions. PM-related decreases of columnar epithelial cells were observed in the sputum of subjects from both groups, and this finding was statistically significant. Both respiratory rate and volume decreased in the exposed group, but respiratory symptoms were not significantly altered. Ventilation differences were corroborated by significant differences in average heart rate recorded during exposure. Both groups showed slight changes in certain mediators of blood coagulation and systemic inflammation, i.e., soluble intercellular adhesion molecule-1, interleukin-6, and factor VII. Symptoms related to cardiac function increased slightly with PM exposure. Heart rate variability data suggested a slight increase in parasympathetic influence on the heart during or after PM exposure, while sympathetic influence was unchanged or slightly decreased

Individual exposure concentrations varied by a factor of 2 in terms of total PM mass, and by larger factors when exposure to specific components was assessed, e.g., nitrate, sulfate, elemental carbon, iron. To explore effects of individual variation on results, numerous exposure-response relationships (i.e., correlations of individual change in a health endpoint with individual difference in a specific atmospheric component between PM and control studies) were calculated. Most were non-significant, as expected given the relatively low statistical power available from a small subject group. Among the exposure variables tested, sulfate showed the largest number of statistically significant relationships with health endpoints. Increasing sulfate concentration was associated with decreasing respiratory rate and minute volume during exposure, and decreased forced expiratory function post-exposure, although the overall difference in respiratory function between exposure and control was non-significant. The ratio of parasympathetic to sympathetic influence on heart rate, in addition to its significant overall difference between exposure and control, showed a significant relationship to exposure PM mass concentration.

Elderly Subjects With and Without COPD Exposed to Fine Particles ($PM_{2.5}$)

In the studies of elderly volunteers, we deliberately recruited an excess of individuals with COPD compared to those in good health. We expected that those with COPD would be more likely to show unfavorable effects, but also would show greater variance in their responses, thus requiring larger numbers to improve statistical power. This expectation was not realized: if anything, the healthy subgroup showed more evidence of exposure effects. We found no significant changes in symptom reports, lung function, or assays of induced sputum after F exposure, relative to control. Modest but statistically significant oxyhemoglobin desaturation (as measured by fingertip pulse oximetry) was observed immediately after and 4 hr after exposure. The mean loss of oxygen saturation was significantly larger in healthy relative to COPD subjects. Individual oxyhemoglobin saturation changes were significantly related to individual exposure mass concentrations, but in the counter-intuitive direction: the subjects with higher exposure concentrations tended to have less negative changes in saturation. Peripheral blood basophils increased after exposure in healthy but not in COPD subjects. Both groups showed slight increases in red cell counts 1 day after filtered air exposure, but not after F exposure. Heart rate variability between 4 and 24 hr after F exposure was significantly decreased in healthy subjects; this finding was not observed in COPD subjects. The incidence of supraventricular and ventricular ectopic heartbeats varied between F and filtered air studies. Supraventricular ectopic incidence was low in healthy subjects in filtered air, and doubled in fine particle exposures. The

supraventricular and ventricular ectopic incidences were higher overall in COPD subjects, but decreased in F exposures. The overall pattern of statistically significant findings was highly discordant between these elderly subjects and the younger adults studied earlier.

Separate and Combined Exposures to Fine Particles and Nitrogen Dioxide in Elderly Subjects With and Without COPD

This extension of the above study determined whether a gaseous pollutant that commonly accompanies primary particulate pollution—NO_2—would appreciably enhance unfavorable effects of particulate exposure. Most respiratory responses were again non-significant in exposures to F and NO_2, separately or combined. However, the maximal mid-expiratory flow, a measure influenced by peripheral airway patency, showed a small but statistically significant decline in healthy subjects exposed to F, whether or not NO_2 was present. F exposures were again associated with a small significant decline in arterial oxygen saturation, more pronounced in healthy than in COPD subjects. This response was not significantly affected by NO_2. Also, F exposures were associated with decreased percentages of columnar epithelial cells in induced sputum. Thus, it appeared that F was the primary pollutant causing acute health effects in this setting.

Healthy and Asthmatic Adults Exposed to Coarse Particles ($PM_{10-2.5}$)

The results of C exposure suggest that the responses are primarily systemic in nature, rather than localized to the respiratory tract. Small but statistically significant increases in heart rate and decreases in heart rate variability were observed, consistent with the decrease in heart rate variability observed in elderly adults exposed to F in the previous study, suggesting altered cardiac autonomic function. Those changes were larger in healthy than in asthmatic subjects. There were no significant changes in the incidence of ectopic heartbeats or exhaled nitric oxide between PM and filtered-air exposures. Relative to filtered-air exposures, C exposures did not elicit significant changes in respiratory function measurements, symptom reports, arterial oxygen saturation, or measures of airway inflammation. In addition to induced-sputum assays, a new tool to evaluate airway inflammation was made available by SCPCS support and initiated during this study, the exhaled nitric oxide (NOe) analysis.

Healthy and Asthmatic Adults Exposed to Ultrafine Particles ($PM_{0.1}$)

Relative to control exposures, UF particle exposures were associated with small but statistically significant disturbances of arterial oxygen saturation, forced expiratory flow rates (observed the day after exposure but not immediately after exposure), and low-frequency (sympathetic) heart rate variability. These responses were not significantly different in healthy and asthmatic subjects. Exhaled nitric oxide increased after UF particle exposure in healthy subjects, possibly suggesting airway inflammation, but decreased (from a higher baseline level) in asthmatic subjects, possibly suggesting improvement in preexisting airway inflammation. There were no significant differences in sputum cell counts between UF exposures and controls. Between individuals, decreased low-frequency heart rate variability correlated significantly with increased particle count in the exposure. Also, symptom score increases during and immediately after exposure showed a significant positive correlation with particle count. These associations were

not significantly different in healthy and asthmatic subjects. Blood and sputum biochemistry data are available for only the initial 15 of 31 subjects. (The remaining biochemical analytical results are pending and are being kindly donated to this project by EPA laboratories.) The available blood data suggest that UF exposures did not affect blood coagulation properties or systemic inflammation, although the complete dataset could reveal statistically significant changes.

Discussion

More than 100 individual exposures to one or another size fraction of ambient particulate matter, typically concentrated to 8–10 times the usual ambient level, were conducted in this project. This experience is unique and demonstrates the overall feasibility and safety of clinical PM exposure studies using concentrator methodology. No major or clinically significant unfavorable responses have been observed in the exposures with the three major PM size fractions. This contrasts with the clinical experiences with ozone and sulfur dioxide, the pollutants from which the 2-hr, intermittent exercise investigative protocol was originally developed. For both gaseous pollutants, clinically obvious individual respiratory responses, as well as consistent patterns of statistically significant physiologic and symptom changes, can be observed at exposure concentrations within or modestly above the ambient range. Both here and in other laboratories performing human exposure studies with concentrated ambient particles (CAPs), statistically significant effects have been found in small groups of subjects, but the effects have been generally modest, and inconsistent across different studies. One reasonably consistent factor is that PM effects show up primarily in the cardiovascular rather than the respiratory system; cardiovascular effects are also found to be the most consistent outcomes in epidemiologic studies of PM. Thus, the concentrator studies have provided a basis for supporting evidence for systemic inflammation and cardiovascular effects frequently observed in epidemiological associations with PM. The PM concentrator studies in this project have generally not provided clear evidence for direct acute respiratory effects, although others have reported mild lung inflammation from bronchoalveolar lavage.

It is necessary to consider the limitations of the controlled-exposure studies described here and epidemiologic studies that might contribute to this lack of coherence. On the epidemiologic side, one possibly important limitation is lack of attention to weather factors, other than temperature, that might contribute both to PM pollution and to cardiovascular stress. In laboratory-based exposure studies, small samples are an obvious inherent limitation, exacerbated by lack of uniform exposure and standard monitoring techniques, which makes it difficult to pool data across multiple studies. Another issue is the limited ability to control intercurrent ambient exposures (much more of problem with PM than with ozone or sulfur dioxide). A typical subject's inhaled dose of ambient particles might be increased by no more than a factor of 2 on an experimental PM exposure day, and reduced by no more than 10% on a filtered-air control day. Still another challenge is the combination of secondary stresses (confinement, noise, lack of precise temperature control) inherent in particle-concentrator-based exposure protocols, which might mask subtle responses to PM. Regarding motor-vehicle-derived PM, it may be possible to bridge some remaining gaps in understanding through controlled exposures while riding in heavy traffic, contrasting the responses to unaltered on-road pollution and to pollution with PM

carefully filtered out. Such a study, drawing upon the experience gained in this project, is now in progress.

Conclusions

The body of evidence concerning acute effects of ambient PM inhalation has been considerably expanded by this project and by concurrent work with ambient particle concentrators in other laboratories. However, the extent to which PM contributes to increased morbidity and mortality on high-pollution days, the specific components of PM that present the greatest health risk, and the physiological/biochemical mechanisms by which they act, are still incompletely understood. The most consistent observation from this project and similar studies thus far is that circulatory effects are more likely expressed than respiratory effects, despite the fact that the respiratory system is most directly exposed to PM and other inhaled toxicants.

Supplemental Keywords: NA

Relevant Web Sites: http://www.scpcs.ucla.edu