

**EPA CENTER FOR AMBIENT PARTICLE HEALTH EFFECTS
AT HARVARD SCHOOL OF PUBLIC HEALTH**

PROGRESS REPORT : YEAR ONE

Theme I: Assessing Exposures for Health Effect Studies

The primary focus of Theme I was to improve our ability to characterize air pollutant exposures for health effect studies. Research activities conducted under Theme I were originally proposed as three studies that were based on personal, indoor, and outdoor particulate and gas concentrations that were measured as part of our previous or current exposure studies. As such, research conducted as part of Theme I was intended to address six of the ten research priorities identified by the National Research Council.

NRC Research Topics 1, 5 and 7: Outdoor Measures vs. Actual Exposures for Particles, Particle Components, and Gaseous Co-Pollutants

Findings: The first of the three research projects was intended to examine the ability of outdoor particulate concentrations to estimate exposures for a community. Findings from recent studies conducted by a variety of researchers have found relatively strong associations between personal PM_{2.5}, and to a lesser degree PM₁₀, exposures and ambient concentrations over time. Although the strength of these associations varied substantially by individual, results from one of our recent studies of individuals with COPD (Rojas-Bracho et al., 2000) indicated that for certain individuals ambient PM_{2.5} concentrations are an appropriate surrogate for personal PM_{2.5} exposures. This observed inter-personal variability was attributed to variability in indoor PM_{2.5} concentrations, as the association between personal PM_{2.5} exposures and outdoor concentrations was strongly correlated with corresponding associations between outdoor and indoor PM_{2.5} concentrations. This finding suggested that indoor sources and indoor ventilation characteristics are important determinants of personal PM_{2.5} exposures and their relationship to outdoor levels.

We explored this issue further in our study of older adults conducted in Baltimore, MD (Sarnat et al., 2000; attached). Findings from this study confirmed that indoor ventilation was one of the key determinants of both personal PM_{2.5} exposures and their relationship to corresponding outdoor concentrations. Perhaps more significantly, findings also showed that personal-ambient associations for PM_{2.5} were (1) not individual-specific, (2) strong when windows were open indoors, and (3) weak when windows were closed indoors. The influence of ventilation was attributed to its combined effect on effective penetration efficiency and indoor particulate emissions, where in indoor environments with closed windows, the effective penetration efficiency of particles from outdoor to indoor environments was lower but the accumulation of particles from indoor sources was greater. These results suggest that ambient PM_{2.5} concentrations are appropriate surrogates of exposures to particles of ambient origin. They further suggest that the ability of ambient PM_{2.5} concentrations to act as a surrogate for personal exposures may vary by region of the country or season, as ventilation characteristics may differ by both parameters. This variability in the personal exposure-ambient concentration relationship for PM_{2.5} may have contributed to the observed variability in particle-related health risks in epidemiological studies.

These personal-ambient associations were unique to PM_{2.5} and were not observed for any of the other measured co-pollutants, including O₃, SO₂, NO₂, and PM_{2.5-10}. Personal exposures for these co-pollutants were not significantly associated with corresponding ambient concentrations, nor were they significantly related to corresponding personal exposures to total PM_{2.5} or PM_{2.5} of ambient origin. As a result, the potential for confounding appears to be limited, despite significant correlations that were observed among ambient pollutant concentrations. These findings provide the first evidence from an exposure study that the effects observed in the PM

epidemiological studies are probably not due to confounding by the measured co-pollutants. Strong correlations between the measured ambient co-pollutant concentrations and personal PM_{2.5} exposures, however, suggest that ambient co-pollutant concentrations may be acting as surrogates for exposures to PM_{2.5} or PM_{2.5} of ambient origin.

Plans: We are continuing to investigate the relationship between personal particulate exposures and corresponding ambient concentrations and the potential for confounding by gaseous pollutants in several multi-pollutant exposure studies of sensitive cohorts. These studies, which are being conducted in a variety of cities (Atlanta, GA, Boston, MA, Los Angeles, CA, and Steubenville, OH), represent a significant advance over our previous studies, since they allow us to assess concentrations of specific particulate components in addition to the more traditional PM_{2.5} or PM₁₀ measurements. For each of study participant, for example, we measure simultaneously the personal exposures and indoor and outdoor concentrations of PM_{2.5}, PM₁₀, and gaseous co-pollutants (ozone, sulfur dioxide, and nitrogen dioxide) as before. In addition, we are also measuring personal, indoor, and outdoor concentrations of important particulate constituents, sulfate (SO₄²⁻), nitrate (NO₃⁻), elemental carbon (EC), organic carbon (OC), and elements. These measurements are now possible due to the recent development of our multi-pollutant sampler, which allows simultaneous measurements to be made for varying combinations of PM_{2.5}, PM₁₀, SO₄²⁻, NO₃⁻, EC/OC, elements, O₃, SO₂, and NO₂ using a single sampling pump (Demokritou et al., 2000; attached).

Research Topics 2 and 8: Exposures of Susceptible Populations and Assessing Effects of Hazardous Particulate Components

Findings: We have conducted several studies of individuals with COPD living in Nashville, TN, and Boston, MA and of older adults living in Baltimore, MD (see above). Results from these studies show that personal exposures to particles may be lower or higher than corresponding outdoor concentrations, depending on the sampled cohort. In our study of individuals with COPD living in Nashville, for example, we found mean personal PM_{2.5} exposures to be lower than ambient concentrations and attributed these lower exposures to the cohort's low activity level (Bahadori et al., 1999). Similar results were found for our older adult cohort living in Baltimore. It is possible that lower personal exposures for our older adult cohort are also due to lower activity levels. These issues will be examined in a subsequent analyses. Results from Nashville and Baltimore, differ from those reported for our Boston cohort of individuals with COPD, for which median personal PM_{2.5} and PM₁₀ exposures were higher than corresponding outdoor concentrations. Findings for our Boston cohort were comparable to those observed for healthy individuals.

Plans: We are currently continuing our efforts to characterize personal multi-pollutant exposures and their relationship to corresponding ambient concentrations for different cohorts of sensitive individuals, including individuals with COPD, older adults, children, and individuals with cardiovascular disease (see above). These individuals will live in metropolitan areas characterized by different weather conditions (e.g., hot summers/mild winters and mild summers/harsh winters) to examine the effect of ventilation on observed personal-ambient associations. In total, we will characterize the multi-pollutant exposures for 158 sensitive individuals, including 45 with COPD, 25 with cardiovascular disease, 40 older adults, and 48 children.

In addition to these exposure measurements, we have expanded the scope of two of our studies to include cardiovascular health measurements, as proposed in the third research project of Theme I. In our Atlanta and Steubenville studies, for example, we measured the heart rate variability and ascertained the cardiovascular health status of each participant on each morning following his/her 24-h exposure monitoring period. We will use these data to examine the association between cardiovascular health and various particulate matter components, including (1) outdoor PM_{2.5} concentrations; (2) indoor source-related indoor PM_{2.5} concentrations; (3) outdoor source-related personal PM_{2.5}; and (4) indoor source-related personal PM_{2.5}. Data

collection has recently been completed in Atlanta, GA and is currently underway in Steubenville, OH.

NRC Research Topic 10: Analysis and Measurement

Plans: Data from the Atlanta exposure and health study will also be used to conduct research proposed in the second of Theme I's projects. We plan to use data collected in our Atlanta, GA multi-pollutant exposure and cardiovascular health study to determine the effect of exposure error on observed health effects in time-series morbidity and mortality studies. Data collection for our Atlanta study was recently completed, with sample analysis currently underway. The exposure error research will be conducted in conjunction with Paige Tolbert at the Emory University Rollins School of Public Health, who is the principal investigator for a time-series morbidity study that was conducted for similar time periods in Atlanta.

Theme II: Identifying Populations Susceptible to Health Effects of Particulate Air Pollution

Research being conducted under Theme Two will attempt to identify subpopulations who show increased susceptibility to respond to particulate air pollution, to identify the specific characteristics of ambient particles and/or copollutants responsible for effects observed in these susceptible populations, and to understand the pathways between particulate matter exposure and observed health effects in epidemiologic studies. As such, the research being conducted as part of Theme II is intended to address five of the research priorities identified by the national Research Council. Progress and future plans for each of these research priorities are described below.

NRC Research Topic 2 and 5: Biologically Important Constituents and Characteristics of Particulate Matter

Findings: We previously reported that daily mortality in six US cities was associated with PM_{2.5} but not with coarse particle mass. We have now used the elemental composition data for these same fine particles to estimate the association of source-specific fine particle mass with daily mortality (Laden et al, 2000). Using factor analysis we estimated fine particle mass concentrations from soil and crustal material, motor vehicles, coal combustion, and up to two additional factors in each city. In a combined analysis across the six cities, a 10 µg/m³ increase in PM_{2.5} from mobile sources was associated with a 3.4% increase (95% CI 1.7% to 5.3%) in total daily mortality. An equivalent increase in coal combustion PM_{2.5} was associated with an increase of 1.1% (95% CI 0.2% to 2.0%). There was no increase in daily mortality associated with soil or crustal source fine particles.

Plans: We propose to characterize particle exposures of children previously examined in the Twenty Four and Five Cities studies by analyses of archived filter samples. Based on hypothesized mechanisms responsible for adverse effects, these archived samples would be analyzed for elemental composition by x-ray fluorescence with particular attention to concentrations of metals (Fe, Ni, Cu, Mn, Mg, Vn, Se). The respiratory health status of the participants in these studies has been collected and previously analyzed compared to fine particle and gaseous pollutants. As in the completed daily mortality study described above, we will examine element specific associations as well as estimating associations with source-specific components of the fine particle mass.

NRC Research Topic 10: Methods for Statistical Analysis of Epidemiologic Studies

Findings: The epidemiologic studies of the effects of acute PM exposures on daily mortality and daily hospital admissions have been based on traditional time-series regression applied to single cities. The strength of these analyses has been the consistency of the results across cities. Composite estimates of effects across cities have been generated. Single city analyses have low power to assess confounding and effect modification. We have developed and applied new

methods for combining results across multiple cities to assess confounding, effect modification, lag structures, and the shape of the dose response function.

These multi-city approaches have been applied to existing daily mortality and hospital admissions databases to assess confounding by gaseous co-pollutants (Schwartz, 2000) and effect modification (Schwartz, 2000; Zanobetti and Schwartz, 2000). These results are described in more detail below.

Assessing PM effects requires consideration of lag structures over multiple days. Estimation of distributed lag models was previously only feasible using ordinary linear methods. Zanobetti and colleagues (2000) have developed methods for estimating distributed lag models within the preferred generalized additive models.

We applied these distributed lag methods to daily mortality time series in ten cities, and estimated the net effect of PM₁₀ on daily cause-specific mortality up to seven days after exposure and the shape of the lag structure (Braga et al, 2000). A 10 $\mu\text{g}/\text{m}^3$ increase in seven-day exposure to PM₁₀ was associated with a 2.7% (95% CI 1.6% to 3.8%) increase in pneumonia deaths, a 1.7% (95% CI 0.1% to 3.3%) increase in chronic obstructive pulmonary disease deaths, and a 0.6% (0.2% to 1.0%) increase in cardiovascular deaths. Respiratory deaths were more affected by PM₁₀ exposure over several days prior, while cardiovascular deaths were more affected by PM₁₀ exposure on the same day.

We applied nonparametric smoothing methods to assess the shape of the PM₁₀ exposure response with daily mortality in ten cities (Schwartz and Zanobetti, 2000). These city-specific exposure response functions were then combined across all cities. The combined exposure response function was very close to linear, and showed no indication of a threshold down to the lowest levels observed in the analysis.

Plans: These combined multi-city methods are being applied to other health outcome data and other cities.

NRC Research Topic 7: Combined Effects of Particulate Matter and Gaseous Co-Pollutants

Findings: Previous city-specific analyses have assessed confounding of the PM associations by gaseous pollutants using traditional regression methods. We have applied newly developed multi-city analytic approaches to use the additional information in multiple cities with varying compositions of the air pollution mixture to address this issue.

We examined the association of daily deaths and ambient particles in ten US cities with daily measurements of PM₁₀, SO₂, O₃, and CO (Schwartz, 2000). To assess confounding of the particle and daily mortality associations, city- and season-specific PM₁₀ effect estimates were regressed against the regression coefficients of PM₁₀ against each of the gaseous pollutants. Controlling for the gaseous pollutants by this method did not substantially or significantly change the estimated daily mortality effects of PM₁₀ in these cities.

Plans: The second stage analytic methods to assess the effects of copollutants are being applied to hospital admissions data and to other cities.

NRC Research Topic 8: Susceptible Subpopulations

Findings: Using combined analyses of daily hospital admissions and mortality data, we have examined differences in response to PM exposure by sex, race, and socioeconomic status. We are identifying pre-existing medical conditions that increase risk for response to PM exposures. We are assessing how much of the observed increase in daily mortality is due to small advances in the date of death among seriously ill subjects (harvesting).

In the four largest US cities with daily PM10 measurements (Chicago, Detroit, Minneapolis-St. Paul, and Pittsburgh), Zanobetti and Schwartz (2000) the estimated effect of PM10 on daily mortality was one-third larger in women compared to men. However, they found little evidence for effect modification by race or by socioeconomic indicators.

In the previously cited analysis of ten US cities, Schwartz (2000) found that socioeconomic differences between the cities did not explain the observed differences in the city-specific PM10 associations with daily mortality. As in previous studies, The increase in deaths out of hospital 0.89% (95% CI 0.67% to 1.10%) per 10 $\mu\text{g}/\text{m}^3$ PM10 was substantially greater than the increase in deaths in hospital (0.49%, 95% CI 0.31% to 0.68%).

Zanobetti and Schwartz (2000) tested whether previous admissions or secondary diagnoses for respiratory illness increased the risk of cardiovascular hospital admission associated with ambient PM10 exposure. Based on Detroit hospitalizations of the elderly, they found that a concurrent or previous hospitalization for a respiratory infection more than doubled the risk of a particulate air pollution associated admission for cardiovascular disease. A previous admission for chronic obstructive pulmonary disease was also associated with increased risk of a PM10 associated cardiovascular admission.

Braga et al (2000) assessed confounding of the air pollution-daily mortality associations by respiratory epidemics in five US cities. Respiratory epidemic periods were identified by excess pneumonia hospital admissions in each city. Controlling for the respiratory epidemics only slightly reduced the estimated effect of PM10 on daily mortality. The combined effect estimate across the five cities adjusted for respiratory epidemics was 0.85% (95% CI 0.60% to 1.10%) for each 10 $\mu\text{g}/\text{m}^3$ PM10, showing that the observed associations were not confounded by respiratory epidemics.

Schwartz (2000) examined harvesting in a time series analysis of PM10 and daily mortality and hospital admissions in Chicago. To assess the net effect of PM10 exposures without any harvesting effects. Associations were estimated with successively larger time windows between 15 and 60 days. If only the most susceptible were having their date of death advanced by a few days, then by considering longer averaging times, any short-term deaths or admissions due to harvesting would not be counted. If harvesting were important, then the estimated associations should decrease in magnitude as the time windows increased. In contrast, the estimated effect of PM10 on daily mortality increases with window size. There was no change in deaths of patients in hospital, while the estimated effect of PM10 on deaths of subjects out of hospital increased more than three-fold. This suggests that particle exposures are increasing the risk of sudden death in subjects with apparently good health but underlying heart disease.

Plans: Current work will take assess response to particulate exposure among well-characterized patients in existing follow-up studies. Data collection is currently underway to assess particulate response among adult participants in the Six Cities study through continued follow-up. In addition data is being collected to assess markers of inflammatory response following particulate matter exposure among participants in the normative aging study.

Theme III: Biological Mechanisms/Dosimetry

Theme III focuses upon mechanisms of cardiac vulnerability as a result of air pollution exposure. In this theme, there are 3 projects which specifically address 5 of the NRC research priorities. In the first project (IIIa), we seek to define biological mechanisms that may contribute to adverse outcomes on a substrate of coronary heart disease. In addition, we are exploring mechanisms from the viewpoint of pollution with studies defining particle composition, size, and the contributions of gaseous pollutants. In the second project (IIIb), we are determining in situ particle doses during inhalation of concentrated ambient particles (CAPs) using online measurements of particle number and size in the inhaled and exhaled air. Project IIIc is a human panel study investigating air pollution levels on blood viscosity and other clotting parameters using the

normative aging study population. Significant progress has been made in projects IIIa and IIIb. Project IIIc had a slow start due to the relocation of the normative aging study investigators.

NRC Research Topics 5, 8, and 9: Assessing Hazardous Particulate Matter Components in Susceptible Population and Defining Mechanisms of Biological Response.

Progress/Findings: Project IIIa has had progress on all fronts. From the pollution mechanism viewpoint, we have concentrated on particle composition. However, hardware and facilities have been worked on to both develop and implement a coarse ambient particle concentrator. Although there has been progress in this area, we have not yet done any exposures with this concentrator. Similarly, we have not pursued the gaseous pollutant issue in the first year with the coronary disease models. A large number of studies were conducted in our laboratory using CAPs and ozone exposures at 0.3 PPM levels using mice. These were not center supported studies, but their results contributed to our decision making process as to where to place our efforts. The mice studies did not yield impressive results. Statistically significant, but biologically minute changes in pulmonary parameters were found. Therefore, we did not choose to make exposures to CAPs and gaseous pollutants a first year priority.

From the viewpoint of biological mechanisms, we have continued to make progress with coronary artery models as well as studies to define autonomic mechanisms in relationship to particle composition. We have carried out thoracic surgery for placement of balloon occluders on four canines. Exposures and analyses of these animals are in progress. We expect to combine these data with that previously collected in order to assess particle compositional issues.

We have also developed a rat model of myocardial infarction. We have produced infarctions in the distribution of the left anterior descending coronary artery by occluding this vessel. The rats recover within a day and then are exposed while their infarction is at the most vulnerable point. This model will permit higher throughput of experiments in order to assess both particle compositional issues as well as biologic mechanisms. We have developed this model using Residual Oil Fly Ash (ROFA), but have also used it with exposure to CAPs. In this model, both ROFA and CAPs significantly increase the heart rate and increase the rate of premature ventricular contractions and other serious arrhythmia. Interestingly, in these outcomes, the changes with CAPs are greater than that of ROFA. These changes are not only statistically significant, but also very significant biologically because they model an outcome, which is observed in epidemiologic studies. In addition, they point to a sympathetic nervous system mechanism as a potential basis for the effects seen. In the CAPs studies, there is no apparent relationship with overall mass. Compositional studies are in progress.

We have completed studies of particle compositional assessment and the relationship to cardiac autonomic nervous system changes in normal dogs. The enclosed manuscript details these studies. We find an activation of both the sympathetic and parasympathetic nervous system with CAPs exposure in dogs. The parasympathetic activation is in part pulmonary based, but even when controlling for the respiratory effect there is still a decrease in heart rate in normal dogs not explained by the respiratory effect. At the same time, heart rate variability changes indicate a concomitant increase in sympathetic activation. When related to the various factors making up the composition of ambient fine particulate, the observed cardiac changes relate best to traffic factors. Other factors appear to have little influence on the observed results.

Although cardiac effects mediated by the autonomic nervous system appear to be very important mechanisms, the role of blood constituents as mediators of cardiac effects is an equally viable hypothesis. We assessed hematological and coagulation factors before and after CAPs or sham exposures of canines. These studies are detailed in the enclosed manuscript, Clark et al, 2000. Increased total peripheral white blood cell (WBC) counts, circulating neutrophils, and circulating lymphocytes were associated with increases in the aluminum (Al)/silicon (Si) factor. Increased circulating neutrophils were associated with the vanadium (V)/nickel (Ni) factor. Significant decreases in red blood cell counts and hemoglobin levels were correlated with the sulfur (S)

factor. Variation in fibrinogen and platelets were not significantly associated with any factor. Hematological parameters were not associated with increases in total CAPs mass concentration. These data suggest that CAPs inhalation is associated with subtle alterations in systemic cell profiles and specific components of CAPs may be responsible for these biological responses.

Plans: In the coming year, we expect to implement the coarse particle concentrator and carry out exposures using the rat model of cardiac ischemia. In these studies, we will directly compare the responses to coarse and fine particle fractions on the same days. We will measure heart rate, heart rate variability, and frequency of arrhythmia. Also in the coming year, we will continue our studies assessing ischemic responses of the canine in relationship to concentrated fine particles using surgical and pharmacologic approaches to define autonomic and inflammatory mechanisms. We will also use the rat model of myocardial infarction to determine if the arrhythmias seen in the most vulnerable periods after infarction are influenced by CAPs via autonomic or inflammatory mechanisms.

NRC Research Topic 6: Dosimetry

Progress/Findings: We have also made progress on Project IIIb. In this project we have developed the capability to assess deposition of CAPs in awake dogs. These studies focus upon using ambient particles to assess deposition in relationship to particle size, mass, and number. Hardware needed to be designed and implemented specifically for these studies. In addition, a number of modifications in existing equipment were needed to adapt these for use with the ambient particle concentrator. These have all been completed, and tested. Deposition studies have been carried out on one pair of dogs. These went well and data analysis is in progress. We expect to present our initial findings in this area at the advisory council meeting.

Plans: In the coming year, we expect to place considerable emphasis on our deposition studies. We expect to use the fine concentrator and define deposition of particles under a number of different atmospheric, seasonal, and weather pattern conditions. The relationship of mass, particle size, and compositional factors will be studied in relationship to deposition of ambient particles. In addition, we expect to be able to use our collected data in relationship to deposition models developed in our laboratory.