

**EPA NW Research Center for Particulate Air Pollution and Health
Progress report: January 8, 2002**

1. Main hypotheses

The broad mission of the NW PM Center is to determine the health effects of PM in western states where sources of fine particles differ significantly from the urban eastern states. Distinct sources of PM studied by our Center are those from vegetative burning characterized by wood smoke in residential areas of Seattle and other NW cities and smoke from agricultural burning in eastern Washington, as well as wildfires throughout the West. The mobile sources, however, are similar. As early findings from the initial 1-2 years of study begin to be understood, the indications are that different urban aerosols having different mixes of source types will show differential health effects and differential potency. Vegetative burning and the resulting PM exposures are a distinctive source in NW airsheds that allow us to explore and further define the relationships among aerosol composition, inhaled dose, human receptor characteristics, and health effect.

2. Current research

Research to date is centered on three areas; epidemiology, exposure assessment and attendant health effects, and toxicology.

Epidemiology

The epidemiology project collaborated on a series of studies of the association between sudden cardiac arrest (SCA) and air pollution in Seattle. The initial study of this series was a case crossover analysis of fine particulate matter and SCA. A report of the findings in this study was published recently by the Health Effects Institute (Checkoway et al, 2000). An analysis of a larger cohort of SCA is completed and a manuscript is in progress. The larger data set allowed analysis of personal data on individuals. Although this second analysis also gave negative results, a positive association between PM and SCA was seen in smokers with heart disease (Sullivan et al, Submitted). Both analyses had only 24 hr PM data available. Future research using short-term (hourly) exposure data is warranted and continuous PM values are now available in Seattle for future studies, both from our Center monitoring and agency monitoring.

Exposure assessment and health effects:

To address these issues we have conducted a two-year series of panel studies in populations thought to be susceptible to the inhaled effects of PM air pollution. The four groups of subjects studied are: subjects 65 years of age and older with chronic obstructive pulmonary disease (COPD); subjects 65 years of age and older who are healthy; subjects

50 years of age and older who have cardiovascular disease; and children with asthma aged 6-12. We screened 129 subjects during years 1 and 2. Of these 107 were enrolled for at least one 12-day monitoring/health session: 34 adults with COPD, 30 healthy adults, 25 adults with heart disease, and 18 children with asthma. Approximately 60% of the subjects have re-enrolled for a second monitoring session in a different season.

Toxicology

The current toxicology project is a study of mechanisms of toxicity of PM using transgenic mouse strains. The objective of this project is to evaluate mechanisms of toxicity of PM using transgenic mouse models of cardiac susceptibility. The transgenic strain chosen is the apoprotein E (-/-) mouse. The apolipoprotein E deficient mouse is generated via a targeted disruption of the mouse Apo-E gene. The deficiency of Apo-E leads to a spontaneous hypercholesterolemia. The nonhypertensive animals form atherosclerotic lesions throughout the vasculature at 3 to 5 months of age which resemble, in part, human atherosclerotic lesions. Year 1 was devoted to acquiring instrumentation from Data Sciences International that allows monitoring of cardiac endpoints in free moving mice. After attempts to implant the telemetry device in the abdominal aorta were proven unsatisfactory due to poor viability, we changed our surgery to the left carotid artery. This has proven highly successful with viability in approximately 90% of the animals. During year 2 we have acquired the skills to perform laryngeal aspiration as a tool for lung exposure to particles using a published technique. Light microscopy of histological sections has confirmed good peripheral distribution of the particles including penetration into the interstitium. Heart rate decreased in both control and apoprotein E(-/-) mice exposed to Washington DC or St Louis PM dust samples (Luchtel et al, 2002). The transgenic mice appeared to have a greater reduction in heart rate but more experiments to verify this are ongoing.

3. Key investigators

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4. Major accomplishments

Epidemiology

We have constructed a model for use in referent selection in case-crossover epidemiologic studies and used it to evaluate associations between sudden cardiac arrest and PM in Seattle (Lumley et al, 2000). In this study of 362 cases there was no association between SCA and air pollution. The analysis, repeated in another, larger sample of SCA cases also was negative. In that study, we studied the association between the incidence of primary cardiac arrest and daily measures of fine particulate matter using a case-crossover study of 1206 cases of out-of-hospital cardiac arrest in individuals with (n=764) and without (n=442) clinically recognized heart disease in Seattle (Sullivan et al, Submitted). We compared particulate matter levels at index times with particulate matter levels from referent days matched on day of week within strata defined by month and year. The estimated relative risk at a lag of 1 day for an inter-quartile range (IQR) change in nephelometry ($0.54 \times 10^{-1} \text{ km}^{-1}$ [equivalent to $14 \mu\text{g}/\text{m}^3$ of $\text{PM}_{2.5}$]) was 0.93 [95% CI: 0.87-1.00]. Similar analyses of 0-day and 2-day lag periods demonstrated comparable results. Analysis of effect modification by individual-level variables did not reveal an increased risk in all cases with pre-existing cardiac disease (OR 0.95 [95% CI: 0.86 –1.03]); however, an unexpected association appeared in current smokers with pre-existing heart disease in the 2 day lagged analysis (OR 1.24 [95% CI: 1.03, 1.48]). This association was not present in the 0 day or 1 day lag analyses or in individuals' with other co-morbid diseases. Our study does not support a consistent association between an increase in fine PM and risk of primary cardiac arrest among persons with and without clinically recognized heart disease. The null results of this study may result from several factors, including the absence of analysis of short-term peak effect of PM. The positive association found in smokers with heart disease only at the longer latency period warrants further consideration.

Exposure assessment and health effects/dosimetry

We have conducted exposure assessment/health studies on 107 subjects in four host susceptibility classes (subjects over 65 years of age who are healthy, have cardiovascular disease or chronic respiratory disease, and children with asthma). Health measurements include lung function, pulse oximetry, heart rate variability, blood pressure, exhaled nitric

oxide (in the children with asthma), and diet. Exposure measurements include daily personal, indoor, and outdoor PM_{2.5}, PM_{1.0}, PM₁₀, CO, NO₂, SO₂, EC/OC, and urine. A special chamber was constructed weighing filters (Allen et al, 2001).

Exposure studies in Seattle have provided important contrasts to similar studies conducted in the eastern US. Findings from other EPA PM Center-supported studies indicate that most of the PM_{2.5} in northeastern US cities is secondary in origin and exhibits very little spatial variability. However, this is not the case in Seattle and other Pacific Northwest cities where PM_{2.5} is dominated by local, primary sources (Maykut et al, 2001, Kim et al, submitted). In Seattle, PM_{2.5} also exhibits modest, yet significant, spatial variability within a radius of 20 km. These spatial differences are associated with both proximity to major highways and the elevation of the monitoring location (Goswami et al, 2001). These same exposure studies have provided additional evidence of the impact of non-outdoor PM sources for both cohorts of healthy individuals and susceptible sub-populations. In Seattle, non-ambient PM_{2.5} sources contributed on average 49% of the total personal PM_{2.5} exposure (Liu and Allen, 2001; Sheppard, 2000). Subject age significantly influenced the fraction of non-ambient PM contributions to total personal exposures, with greater non-ambient PM contributions observed for children. In addition, particle effective penetration efficiencies vary substantially by residence type and exhibit significant inter- and intra-home variability (Larson et al, 2001). For a total of 30 homes monitored, the estimated mean effective penetration efficiency was $56 \pm 8\%$ and the hourly variations in the levels of indoor PM of outdoor origin could be well described by a non-equilibrium model.

We also are studying the application of both analytical and statistical methods to the source apportionment of PM_{2.5} exposure. Traditional applications have focused on outdoor particles, with very little attention to indoor and personal samples. We are currently analyzing a number of PM_{2.5} samples via XRF as a first step in assessing the sources of PM_{2.5} in various microenvironments. The fact that a majority of the PM_{2.5} in Seattle is primary in origin and rich in combustion-derived organic compounds, including wood smoke, poses additional challenges. To this end, we have developed a new assay for methoxyphenols, markers of lignin combustion, collected on Teflon filters (Simpson et al, 2001). This will enhance our ability to separate the influence of this source from other important combustion sources in our exposure assessments. It is also an important step in the validation of a urinary biomarker for wood smoke exposure.

We have found that the temperature resolved fractions of particulate carbon collected on quartz filters can be useful in resolving source contributions to outdoor PM_{2.5} (Maykut et al, 2001). However, when attempting to extend this approach to indoor and personal samples, we have documented a significant positive sampling artifact associated with the adsorption of organic vapors onto the quartz filter medium (Claiborn et al, 2001). Fortunately, this artifact has been eliminated with the development of a new personal sampler that uses carbon impregnated, open cell foam as an upstream, compact denuder (Pang et al, submitted). We are currently collecting samples with this new method in order to more accurately quantify the true particulate organic carbon in indoor

and personal microenvironments and therefore to better resolve the source contributions to both indoor and personal PM_{2.5} samples.

Preliminary health effects findings are beginning to emerge; we submitted three abstracts to the American Thoracic Society annual meeting to be held in May 2002. One abstract described the associations between outdoor fine particles and exhaled nitric (eNO) samples collected from children with asthma who participated in our panel study (Koenig et al, Submitted). We used a linear mixed effects model with random intercept to test for within subject associations between eNO and PM_{2.5} values estimated from nephelometry measurements averaged from three community sites. In this pilot study we found a 10 ug/m³ increase in PM_{2.5} was associated with a 4.8 (2.26-7.38) ppb increase in eNO. These preliminary findings suggest that eNO may be an effective, noninvasive method for estimating lung inflammation in epidemiological studies of health effects of air pollution. Another abstract described changes in heart rate variability (HRV) in elderly subjects with cardiovascular disease (Sullivan et al, Submitted). Multivariate analysis using a linear mixed model with random intercepts that controlled for temperature, relative humidity, and medication use found that a 10 ug/m³ increase in outdoor fine PM lagged by 1 hour was associated with a 25% (-45%, 01%) decrease in the median of the log transformed HF power in those subjects with cardiovascular (CV) disease during the paced breathing sessions. We also found borderline significant effects of outdoor measured PM on HF HRV in the CV group at 4 hours with a 34% decrease (-58%-0.1) and at 24 hours (30% decrease (-55%, 9%). Neither healthy subjects nor those with lung disease showed this effect. The finding of a decline in HF power with an increase in outdoor levels of fine PM within 1 hour prior to HRV measures suggests that fine PM may have a rapid onset of effect on cardiac autonomic modulation in susceptible subgroups. We also saw a suggestion of an association between lung function and PM only in healthy elderly subjects, finding that warrants further analysis (Trenga et al, Submitted).

We have identified a potential biomarker of exposure to wood smoke measured in urine and are currently conducting studies to validate it including data collection in communities in the West impacted by smoke from wildland forest fires or agricultural burning (Dills et al, 2001; Simpson et al, 2001). Aerosol number-size distribution is being monitored daily at a central site. The size distribution includes the size range from 20 nm to 10 mm diameter covering the Aitken, accumulation and coarse modes. The results of principle component analysis of the first three months of data show identifiable subsets of the size distribution that are related to either sources or a combination of sources and wind direction. A pilot study of exposures, lung function, and urinary biomarkers was conducted during the summer of 2001 in two communities exposed to wildfire smoke. Nine subjects were studied. Data analysis is underway.

Toxicology

For toxicology studies, we have developed a PM exposure protocol using a transgenic mouse model for human cardiovascular disease (apoprotein E -/-). An initial series of experiments compared the responses of the apoE (-/-) strain with normal C57/BL6 mice. Physiological monitoring of cardiovascular function was done using

radio-telemetry (Luchtelet al, Submitted). A catheter (connected to a radio transmitter) was surgically implanted into a carotid artery to monitor heart rate and blood pressure. Individual mice were exposed to 125 µg of SRM #1649 (Washington, DC. urban dust) in 50 µl saline by oropharyngeal aspiration. A 24-hr daily measurement consisted of the average of 10 second recordings taken every 5 minutes. Each animal served as its own control. Heart rate was reduced after exposure to PM in apoE^{-/-} mice. ApoE^{-/-} animals showed more individual variability but overall, notable differences were not found in the responses of normal C57/BL6vs.ApoE^{-/-} animals. This may be due to the relatively young age (9-12 wks) of the animals used. Experiments now are being conducted with aged ApoE^{-/-} mice.

In summary, in the first two years, we have documented the relationships among personal, indoor and outdoor measurements of PM for susceptible subjects. We also see a high correlation between the outdoor PM monitors in residential areas and the fixed PM monitors placed by the air agency. These findings suggest that epidemiologic studies that use fixed site monitors are valid. Preliminary data suggest that outdoor PM in Seattle 1) may be associated with decrease in HRV in panel subjects with cardiac disease, 2) may be associated with increases in exhaled NO (a marker of airway inflammation) in children with asthma, and 3) may be associated with decrements in lung function in healthy subjects over the age of 65. In the next several months we plan to test associations between indoor and personal PM and various health indicators.

5. Expected Accomplishments

Epidemiology

Plans are underway to evaluate the effect of acute exposure to PM on the occurrence of myocardial infarction in a very large population-based study of M.I. onset in Seattle. An increase in M.I. incidence was associated with PM_{2.5} exposures measured 2 hours prior to the event in a small-scale study in Boston (Peters et al, 2001). This Seattle analysis will permit us to test the robustness and generalizability of that finding.

We also are beginning a new epidemiologic study of the potential chronic effects of PM exposure by evaluating the effect of long-term exposure to fine particulate matter air pollution and other pollutants on the incidence of cardiovascular events in a large multi-city cohort (Women's Health Initiative). This will be an observational study of 93,000 women aged 50-79 years from 40 centers in the US. The analysis will adjust for potential confounders and assess effect modifiers. Assessment of effect modification by subject characteristics may provide insight into susceptibility to, or mechanisms of, PM health effects. This study will complement two other cohorts being studied for long term PM effects, the 6-city study and the American Cancer Study.

Panel studies

Exposure assessment

Our extensive 2-year indoor, outdoor, and personal PM_{2.5} data will be used not only to assess personal exposure to our panel subjects from outdoor PM and its constituents but also to construct models that predict community-wide exposure to PM_{2.5} in the Seattle airshed (and perhaps more generally). We have started modeling and characterizing key factors influencing the relationship of central site, outdoor, indoor, and personal measurements of PM and co-pollutants. We plan to develop models for predicting personal PM exposures and apply the exposure models to the concurrent health effects study to reach unbiased estimation of the effects. Results from the two years of monitoring work and four subpopulations should provide extremely valuable information on the relationships of personal PM and co-pollutant exposure to ambient PM and co-pollutant levels. We expect that the Year 2 measurements in particular will provide more comprehensive understanding of PM exposures due to the dry cold winter with several PM episodes. These results will enhance our knowledge on key factors influencing exposures of sensitive subpopulations to PM and the spatial and temporal variation and components of these exposures.

Plans for the future include at least one more year of intensive exposure assessment and health measurements in individuals exposed to wildfire smoke and also monitoring and health measurements in areas associated with exposure to smoke from agricultural burning.

We will work with the other PM centers to compare our results with those from other similar studies and to share data sets to validate models. Progress continues in our quest to find molecular tracers of biomass burning in urine samples. To date our emphasis has been on methoxyphenol structures that are known products of the pyrolysis of lignin. This project requires analysis of vapor phase methoxyphenols from personal PM filter samples and comparisons with urinalysis assays from the same subject and time period. Samples from the two wildland fire episodes we monitored will be useful in establishing dose-response curves.

Regarding aerosol size and distribution and dosimetry, during year 3 we will continue to collect and analyze the size distribution data at Beacon Hill. An additional size monitor will be operated at a site 15km north of Beacon Hill in a location that is minimally impacted by local residential, industrial or mobile sources to compare this slightly aged aerosol to that at the more central site. Additionally, measurement of the hygroscopic properties of the aerosol, ie., the change in size of the particles at high humidity, will be made at the second site as a preliminary step to modeling pulmonary deposition.

Modeling of the sources and transport of the aerosol using the MM5 (mesoscale model) to predict wind and other meteorological fields will be started in June of 2001. We will use the CMAQ code in Models 3 developed by EPA to predict the modal aerosol fields in time and space in the Puget Sound region. The source inventory will be based on work done by Region 10 EPA and Washington State Department of Ecology. The size distribution data we are collecting will be used to validate and correct the processes in the model. The ground work for this effort has been done in close cooperation with the

members of the Northwest Regional Modeling Consortium. The required computer facilities have been identified within the Atmospheric Sciences Department at the University of Washington.

Health effects

Associations between the many health endpoints measured in the panels and the many exposure metrics await final validation of the exposure data. During the past 2 years, our measures of HRV were short term, usually about 15 minutes. HRV data are not being collected using 24- or 48- hour Holter monitoring. We plan to compare the two protocols for use in air pollution research. Other new health endpoints being evaluated for their usefulness are breath condensate as a measurement of airway inflammation and daily intake of fruits and vegetables as well as omega3 fatty acids. Breath condensate is being collected in the field from panel subjects using a condensing device (Respiratory Research). Subjects are asked to breath on a mouth piece for 10 minutes into a tube cooled by an aluminum sleeve. The collected condensate is later analyzed by ELISA. Currently we are assaying for 8-isoprostane, a known marker of airway inflammation. The role of diet as a modifier of air pollution-induced effects is an area of considerable interest. We have published results of the positive effects of dietary antioxidant supplements on the response to ozone exposure in a controlled laboratory setting in adult subjects with asthma (Trenga et al, 2001). We collected three-day food records on many of our 107 panel subjects and will evaluate dietary antioxidant intake as a modifier of PM effects.

Toxicology

Animal

Currently we are evaluating various protocols for collection of sufficient PM at a speciation site in Seattle for toxicological exposures. This will allow exposure of the transgenic mice to a well-characterized western PM. Seattle PM available for toxicologic studies include samples taken from several well characterized microenvironments; central site (co-located with the speciation site), and inside subject residences, immediately outside subject residences, and personal samples from panel studies with various host susceptibility factors. This work will be done in collaboration with the source apportionment activities that will trace major outdoor sources (eg. woodsmoke, mobile) through various microenvironments along the exposure pathway.

During Years 3-5 we plan using the susceptible mouse model to study the toxicologic effects of well characterized PM from Seattle monitoring sites. In addition to the cardiovascular physiologic endpoints derived from the implanted transmitters, we will initiate microarray analyses directed at identifying changes in gene expression associated with PM exposures. This microarray research will be supported in part by the newly funded Toxicogenomics Center at UW.

Human

In an effort to better understand the health effects of the gaseous pollutants, we conducted laboratory exposures to 0.30 ppm NO₂ in a group of ten healthy adults over 65

years of age recruited from our pool of panel study subjects. Subjects were exposed by mouthpiece to air or NO₂ for 30 minutes at rest. The health endpoints measured were the same as measured in the panel studies. No NO₂-associated changes were seen in eNO, lung function, pulse oximetry, or symptoms. However both systolic and diastolic blood pressure increased after NO₂ exposure compared with air exposure. The blood pressure increases were not significant (p = 0.06) for systolic blood pressure (average increase 10 mmHg) (Wang, 2001).

We are developing a facility and protocol for controlled diesel exposures to human subjects. Specific aims of this project are several: 1) to evaluate whether there is a dose-effect relationship between diesel exposure and exacerbation of asthma; 2) are these effects associated with diesel exposures at levels near to those occurring in ambient and occupational environments; 3) does the apparent adjuvant effects of diesel exhaust (DE) exposures on allergic responses occur at ambient levels of DE; 4) is the activation of Th2 lymphocytes the mechanism for the augmentation of allergic effects; and 5) are apparent inflammatory effects of DE in the lung mediated through the generation of reactive oxygen species.

6. Centers versus Individual grants

A specific example of how the Center has allowed us to ask questions that would not be possible as individual investigators:

Our panel study of susceptible subjects requires expertise in aerosol measurement and exposure science. Exposure science is a relatively new discipline that has its own methods and models that are unrelated to traditional ambient aerosol science. Investigators in both disciplines are working together to better understand the sources and dynamics of particles as they move from their emission point, through selected microenvironments, to their uptake and passage through the human body. However, even this level of coordination is not sufficient to begin to answer the questions at hand. Our Center medical professionals not only select susceptible subjects for these exposure studies, but also guide the protocols to assess acute respiratory and cardiac effects. These professionals are, in turn, guided by ongoing toxicological studies involving cardiac effects in susceptible animal models. Center collaboration has closed this loop: the exposure group is collecting size resolved particle samples in microenvironments representative of our panel studies for use in the toxicological experiments. This is an outcome of discussions catalyzed by our weekly science meetings that will refine our understanding of the sources, exposures and effects of Northwest particles. Common to all of the above efforts is Center resources in data management and statistical design/analysis. Without this active component, not only would the information we obtain be less accessible to other investigators, but also the ongoing participation of this group provides them with unique perspectives as they continue to analyze epidemiological information for relevant air quality/health associations.

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