

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

PROGRESS REPORT : YEAR FOUR

THEME I: ASSESSING PARTICLE EXPOSURES FOR HEALTH EFFECTS STUDIES

Project Ia: Assessing Human Exposures to Particulate and Gaseous Air Pollutants

The analysis of the Baltimore, MD, Atlanta, GA, and Los Angeles, CA, studies has been completed. We are currently in the process of completing the analysis of the Boston, MA, and Steubenville, OH, exposure assessment studies). As part of our exposure studies, we have collected several thousand simultaneous outdoor, indoor, and personal particle and gas samples for several potentially sensitive subgroups, including senior citizens, children, and individuals with chronic obstructive pulmonary disease (COPD) or recent myocardial infarctions (MI). Data collection for the Steubenville and Atlanta studies were co-funded by the Center, while data collection for the remaining studies were supported by other agencies, such as HEI, EPRI, API and EPA (under a separate cooperative agreement).

The objectives of these exposure studies are the following: (1) estimate the contribution of particles of outdoor and indoor origin to personal PM_{2.5} exposures; (2) examine the potential for confounding by gaseous pollutants to affect epidemiological study results and; (3) investigate the ability of particles to penetrate from outdoor to indoor environments. To date, we have published several papers addressing these issues (Chang et al., 2000; Long et al., 2000; Sarnat et al., 2000; Sarnat et al., 2001; Sarnat et al., 2002).

Initial results suggest that the impact of outdoor PM on personal PM exposures varies by season, but does not vary by sensitive cohort (Brown, in preparation). The contribution of particles of outdoor origin was determined using sulfur (Sarnat et al., 2002). In addition, the impact of outdoor PM sources on the indoor environment may vary significantly by geographical location and season.

Indoor, outdoor and personal exposure data from the Steubenville exposure assessment study is currently being analyzed to confirm previous Center supported research on the confounding effect of gaseous pollutants (Sarnat et al., 2001). In addition, this analysis will focus on factors, such as home ventilation, that may induce heterogeneity among the observed pollutant associations (Ebelt, in preparation).

Project Ib: Quantifying Exposure Error and its Effect on Epidemiological Studies

We have continued our research examining the impact of exposure-related factors on risk estimates from time-series studies of PM₁₀ and hospital admissions. In a paper published last year, we used data from 14 cities located across the US to examine the relationship between air conditioning prevalence and the coefficient for the association between ambient PM₁₀ concentrations and cause-specific hospital admissions (Schwartz et al., 2002). In addition, we examined whether observed variability in the risk coefficients was specifically related to PM₁₀ emissions from mobile, combustion, and other sources. Results from these studies indicate that air-conditioning use explains a substantial amount of the variability in the risk coefficients from the different cities. Furthermore, PM₁₀ emissions from mobile and diesel sources were also found to be important determinants of the variability in the risk coefficients, particularly for CVD-related hospital admissions.

Recently we analyzed the same data to examine whether ventilation and source emission profiles explain season-specific risks of PM₁₀ on hospital admissions in each of these 14 cities. A manuscript is almost completed (Suh et al., in Preparation).

Future work will include the development and application of near-source and long-range atmospheric dispersion models to better quantify the relationship between emissions and concentrations of primary and secondary PM. The goal of this analysis will be to improve spatially resolved exposure estimates and reducing exposure misclassification.

Finally, using data from multi-pollutant exposure studies in Boston and Baltimore, simulations were conducted to assess the feasibility of health risks attributed to gases and particles (Schwartz, in preparation). Results provide evidence that the gaseous pollutants are unlikely confounders of PM health risk estimates for these locations.

Project Ic: Differentiating Health Effects of Particles from Outdoor and Indoor Sources

We have completed data collection for two field studies conducted in Atlanta and Steubenville, both of which have been co-sponsored by the Center. For the Atlanta study, multi-pollutant exposures and cardiovascular health status were measured repeatedly for two cohorts: individuals with COPD and recent MIs. For the Steubenville study, multi-pollutant exposures and cardiovascular health status were measured for elderly individuals living in government-subsidized housing complexes. The same health protocol was used for each of these studies, with data on heart rate, heart rate variability (HRV), blood pressure, oxygen saturation, and daily symptoms obtained for each participant on at least seven days. Twenty-four hour indoor, outdoor, and personal measurements of PM, ozone, carbon monoxide, nitrogen dioxide were also measured on each of the monitoring days. Data analysis from the Atlanta study is nearly complete, with a paper expected to be submitted to a peer-reviewed journal by the end of this year. Laboratory analysis of the ECG data from Steubenville data is currently ongoing, with data analysis expected to start early next year.

Our analysis of the toxic effects of indoor and outdoor particles using in vitro bioassays was published in *Environmental Health Perspectives* (Long et al., 2001). In this study, particle-induced pro-inflammatory responses were assessed using tumor necrosis factor (TNF) production in the macrophages. TNF production was significantly higher for indoor as compared to outdoor particles, both before and after normalization for endotoxin concentrations. Indoor and outdoor particle samples were also collected in 46 homes in Atlanta, GA, and will undergo a similar analysis to investigate the relative toxicity of indoor and outdoor particles.

THEME II: IDENTIFYING POPULATIONS SUSCEPTIBLE TO THE HEALTH EFFECTS OF PARTICULATE AIR POLLUTION

Project IIa: Examining Conditions which Predispose Towards an Acute Adverse Effects of Particulate Exposures

Several projects on susceptibility have already been completed, suggesting that individuals with cardiovascular disease and diabetes are at higher risk from exposure to PM. Among the published papers dealing with this issue are: (Bateson & Schwartz, 1999; Braga, 2000; Coull et al., 2001; Ha et al., 2001; Zanobetti & Schwartz, 2000). Currently, data from five clinical trials from the Joslin Diabetes Center and Beth Israel/Deaconess Medical Center are being prepared to investigate associations between PM and endothelial function and blood markers of inflammation among diabetics.

Furthermore, we have conducted mortality follow-ups of subjects whose potentially predisposing conditions were identified for use in hospital admissions data. These analyses will use the case-crossover approach. We have recently completed a methodological paper examining the potential for bias and confounding in that approach, and developed new statistical methods to address

these problems (Bateson & Saldiva, 2001; Bateson & Schwartz, 1999). The newly-developed methods estimate and subtract biases from health risk estimates. We have also conducted simulations showing our method has correct coverage probabilities (Bateson & Schwartz, in Review).

Project IIb: Assessing Life-Shortening Associated with Exposure to Particulate Matter

During the first two years of the PM Center grant the focus of this project dealt with harvesting. Currently, this project deals primarily with the development of statistical methods for investigating confounding, dose-response relationships and other particle health effects issues.

Harvesting: We have examined whether particles advance mortality by a few days (harvesting) or have a more profound impact on public health. We have published several papers on the harvesting effect. Two papers used a smoothing approach to examine the association of PM over time with daily deaths in Boston (Schwartz, 2000b) and Chicago (Schwartz, 2001). Hospital admissions were also examined in the Chicago paper. The main conclusions of our analyses were that particle effects on mortality and morbidity become stronger as averaging time increases, thus rejecting the harvesting hypothesis.

We also have developed a new methodology (smoothed distributed lag models) to investigate the relationship between pollution and daily deaths in Milan, Italy (Zanobetti et al., 2000). This paper confirmed that far from reduced effects, "harvesting resistant" estimates are higher by a factor of two. More recently, we extended the distributed lag approach to examine the potential harvesting effect in 10 European cities. As with our previous results, the findings from this study do not provide evidence to support a harvesting effect (Zanobetti et al., 2000).

Dose-response: To date, PM health effects studies suggest a no-threshold dose-response relationship. If in fact there are thresholds for the effects of particles on deaths or hospital admissions exist, however, estimated health effects may be overstated. We have therefore developed a new methodology that allows combining smoothed dose-response curves from multiple locations and demonstrated its effectiveness using simulation studies to examine this result. Subsequently, we applied this method to analyze daily deaths in 10 US cities. No deviation from linearity down to the lowest exposure concentrations was observed (Schwartz, 2000a). In addition, case-crossover studies have been developed and applied to examine the association between PM_{2.5} concentrations and hospital admission for MIs in Boston (a paper is currently in preparation) (Bateson & Schwartz, In Review).

Co-pollutant effects: We have investigated the confounding effect of gaseous co-pollutants for both morbidity and mortality. We have developed a hierarchical model to assess confounding, and applied it to examine the association between PM₁₀ and daily deaths (Schwartz, 2000a). The results of this analysis suggested that PM-related associations were not confounded by gaseous air pollutants. Further work has shown that the two-stage hierarchical modeling approach is more resistant to measurement error in the pollutants and confirmed that there is no association of gaseous co-pollutants with mortality in ten U.S. cities (Schwartz & Coull, in Press).

Statistical methods: We have demonstrated that it is possible to control for season and analyze mortality and morbidity using the case crossover approach. Last year, we showed that potential selection bias in applying the case crossover approach exists, which can be estimated and corrected (Bateson & Saldiva, 2001). Using this approach, we have re-investigated the association between PM₁₀ and daily deaths in 10 US cities.

Over the last six months the validity of using Generalized Additive Models to assess PM health outcomes has been under examination. Center investigators have spent a great deal of time addressing this issue. Towards this end, we have re-analyzed our 10 city mortality study, the Six City time series study, the Six City Source Apportionment Study, our Hospital Admissions studies, and the long term distributed lag models from the APHEA study. In addition to re-analyzing these

data using different convergence criteria and natural splines, we have developed alternative approaches including the penalized spline method.

Project IIc: Investigating Chronic Effects of Exposure to Particulate Matter

We have followed up the Six Cities Study cohort in an effort to assess the cumulative effect of long-term exposures on the incidence of lung cancer, nonmalignant respiratory disease, cardiovascular disease, and cause-specific mortality. More specifically, vital status was determined for the 8111 participants in the Harvard Six Cities adult cohort for an additional nine years of follow-up (1990-1998). We identified 1430 additional deaths bringing the total to 2737 deaths. Survival analyses of all-cause mortality shows that life expectancy continues to be reduced in the more polluted cities, with the survival relative ranking being the same as that observed in the original study. During the follow up-period, 1990-1998, air pollution levels decreased in two of the cities, while they remained about the same in the other four. Accordingly, the relative risk from mortality decreased in these same two cities as compared to the other four. This project has been completed; however, elemental carbon data may be provided by EPA, which will make it possible to relate morbidity and mortality outcomes to tracers of traffic and power plant emissions. A paper is under preparation by Laden et al., and an abstract was presented at the 2002 ISEE meeting.

We have completed an analysis of the effects of control of particulate air pollution on mortality in Dublin, Ireland (Clancy et al., 2002). Because of high particulate (Black Smoke) levels, the Irish government banned the sale of coal within the city of Dublin as of September 1990. We showed that mean Black Smoke concentrations dropped by 36 g/m³ following the ban. After adjusting for the age distribution of the population, weather, influenza epidemics, and background mortality in the rest of Ireland, Dublin total mortality rates dropped by 6%, respiratory mortality dropped by 16%, and cardiovascular mortality by 10%. This analysis is being extended to other Irish cities that subsequently banned coal sales.

Future efforts include the assessment of the effects of chronic air pollution exposures (using ambient measurements and GIS) on the incidence of disease among participants in ongoing chronic disease studies based on national samples. During the past year, we have added two new investigators who are currently exploring different modeling approaches to assess chronic exposures. To date, the results are very encouraging and it is anticipated that these efforts will be continued over the next two years. There are no plans for the collection of health data, since this project will focus exclusively on exposure assessment.

Project IIId: Determining the Effects of Particle Characteristics on Respiratory Health of Children

The main objective of this project is to examine the effects of particle composition on the respiratory health of children using PM samples collected as part of the Harvard 24-Cities study. The chemical analysis and data processing of the 24-Cities samples has been completed. Currently, the statistical analysis, of the exposure and health data is being conducted. Preliminary results of this analysis presented in the 2003 SAC meeting, showed no association between air pollution-caused respiratory effects and elemental carbon concentrations. Upon the completion of the above analysis, we will conduct a collaborative inter-center assessment of the effects of chronic particulate exposures on respiratory health of children. The Harvard 24-Cities Study assessed respiratory health and particle exposures of 13,364 fourth and fifth grade school children in the United States and Canada between 1988 and 1991. The University of Southern California Children's Health Study has similarly assessed respiratory health and particle exposures of approximately 4000 fourth and fifth grade school children in twelve communities in Southern California. The Harvard study was designed to assess effects of power plant particles, while the Southern California Study focuses on effects from mobile source particles. The Harvard Study includes one Southern California community (Simi Valley) and two other California sites (Monterey and Livermore). We expect that pooling these studies will greatly improve our ability to

assess the relative contribution of power plant versus mobile source particles on respiratory health of children.

THEME III: BIOLOGICAL MECHANISMS AND DOSIMETRY

The aims of this theme are:

To investigate role of inhaled concentrated particles in increasing arrhythmia using an animal model of myocardial infarction (FY 02) (Project III.a) Establish links between synergistic inflammatory, autonomic and vascular endothelial responses and relate them to adverse outcomes in the models of myocardial ischemia and infarction (FY 03) (Project III.a).

To assess the role of gaseous co-pollutants as potential synergists for the particle response in rodent model of myocardial infarction (FY 04) (Project III.a).

To define the role of PM constituents and gaseous co-pollutants in mediating cardiopulmonary injury in healthy humans and animals.- (Revised from "Establish the components of ambient particles responsible for inflammation and autonomic system response") (FY 04) (Project III.a). Significant progress, which is outlined below, has been made toward all of these tasks and aims.

Project IIIa: Differentiating the Roles of Particle Size, Particle Composition and Gaseous Co-Pollutants on Cardiac Ischemia.

The main aim of this project is to investigate the effects of concomitant gaseous co-pollutants, particle size, and particle composition. To date, a large number of animal exposure studies have been completed. These studies have been totally or partially funded by the Center.

We have examined whether short term exposures to Concentrated Ambient Particles (CAPs) can cause pulmonary inflammation in normal rats and rats with chronic bronchitis (Saldiva et al., 2002); Four groups of animals were studied: (i) air-treated, filtered air-exposed (air-sham); (ii) SO₂-treated (chronic bronchitis (CB)), filtered air exposed (CB-sham); (iii) air-treated, CAPs-exposed (air-CAPs); and (iv) SO₂-treated, CAPs exposed (CB-CAPs). Pulmonary inflammation was assessed by bronchoalveolar lavage (BAL) and by measuring the numerical density of neutrophils (Nn) in the alveolar walls in the centri-acinar and in the peripheral segments of the pulmonary acinus. CAPs induced a significant increase in BAL neutrophils and in Nn in the lung tissue. Greater Nn was observed in the central compared to peripheral regions of the lung. A significant, dose-dependent association was found between V and Br concentrations and both BAL neutrophils and Nn. BAL neutrophils and protein were also correlated with Pb, SO₄²⁻, Si, organic carbon, and elemental carbon concentrations. Results demonstrate that short-term exposures to CAPs from Boston induce a significant inflammatory reaction in rat lungs, which depends on particle composition.

For the same animals we examined whether short term CAPs exposures altered the morphology of small pulmonary arteries (Batalha et al., 2002). Histologic slides were prepared from random sections of lung lobes and coded for blinded analysis. The lumen/wall area ratio (L/W) was determined morphometrically on transverse sections of small pulmonary arteries. When all animal data (normal and CB) were analyzed together, the L/W ratios decreased as concentrations of fine particle mass, silicon, lead, sulfate, elemental carbon and organic carbon increased. In separate univariate analyses, the association for sulfate was significant only in normal rats, whereas silicon was significantly associated in both CB and normal rats. In multivariate analyses including all particle factors, the association with silicon remained significant. Our results indicate that short-term CAPs exposures (median 182.7, range 73.5-733.0 µg/m³) can induce vasoconstriction of small pulmonary arteries in normal and CB rats. This effect was correlated with specific particle components, and suggests that the pulmonary vasculature might be an important target for ambient air particle toxicity.

With the repeated finding in both dogs and rats of increased pathologic responses to inhalation of concentrated urban air particles and the identification of silicon (as silicate) as an element associated with some of these responses, we carried out studies to determine whether there is a change in toxicity as silicon-containing particles pass through the Harvard Ambient Particle Concentration (HAPC) (Savage et al., Submitted 2002). Using silicate rich Mt. St. Helen's volcanic ash, (MSHA) we exposed 3 groups of Sprague-Dawley rats by inhalation for 6 hours to filtered air, MSHA, or MSHA passed through the HAPC. Twenty-four hours following exposure, BAL was performed to assess total cell count, differential cell count, and protein, lactate dehydrogenase, and n-beta glucosaminidase levels. Peripheral blood was examined for packed cell volume, total protein, total white cells, and differential cell count. In another group of rats L/W ratios were determined on the pulmonary vessels. No significant differences were observed among any of the groups in any parameter measured. Power calculations indicate sufficient power to find differences among all of these parameters. Scanning electron microscopy and X-ray analysis was performed to identify particles in the lungs, revealing silicates typical of MSHA throughout the lung. Our findings suggest that particles passing through the HAPC have no change in their toxic potential in an exposure setting where substantial particle deposition has occurred. This study validates the use of the HAPC as a method of creating concentrated aerosol of fine urban air particles without altering their physical properties or potential for toxic insult.

Based on these findings, we postulated that the silicates are travelling in CAPs with a more toxic partner that is responsible for the pathologic responses to exposure that our group has documented. Silicates identified in these studies associate strongly with markers of soil dust such as calcium and aluminum, and there is a fraction of soil particles found below 2.5 microns (the upper limit of concentration by the HAPC). The remaining mass of this factor most likely includes urban road dust, which is enriched with combustion derived materials, organic semi-volatile compounds, latex, sulfate and nitrate, and tire and brake derived particles. Bioaerosols such as pollen and fungal spores are also found in road dust. Accordingly, we have begun instillation studies of road dust from a major urban thoroughfare (located between the HAPC inlet and the adjacent street) gathered on a PUF sampler (0.7 - 7 micron size selection) to examine the relative toxicity of this material. We exposed 5 groups of Sprague-Dawley rats by intratracheal instillation to either saline, saline plus PUF, 0.01 mg/kg road dust, 0.1 mg/kg road dust, or 1 mg/kg road dust. Twenty-four hours following exposure, we performed bronchoalveolar lavage to assess total cell count, differential cell count, total protein, lactate dehydrogenase, and n-beta glucosaminidase. Blood was examined for hematocrit, total protein, total white cell count, and differential. Intratracheal instillation of glutaraldehyde was performed for pulmonary vascular morphometric analysis, and scanning electron microscopy and X-ray analysis of particles in the lung. Our initial findings show significant differences in differential cell count from bronchoalveolar lavage fluid, and the complete analysis of these studies is in progress

In the context of this Project, we have started to support and include the innovative work of Dr. Beatriz Gonzales-Flecha's laboratory. Their studies focus on oxidant mechanisms to explain cardiac responses. Dr. Gonzales-Flecha and her colleagues have reported rapid increases in the steady-state concentration of reactive oxygen species in the lungs and heart associated with ambient particle exposures Gurgueira et al. (Gurgueira et al., 2002). More recently, they confirmed the role of oxidants in the inflammatory response to CAPs adult rats. The experimental protocol included exposures to filtered air (Sham) or CAPs aerosols (CAPs, 5 hours exposure, average mass concentration: $1100 \pm 300 \mu\text{g}/\text{m}^3$) in the presence or absence of 50 mg/Kg i.p. NAC. BAL, tissue and blood samples were collected 24 hours after exposure. The results of this study suggested a dramatic increase of PMN number in BAL as a result to CAPs exposures. This increase was mediated by oxidants, since pre-administration of NAC effectively prevented PMN influx into the lung. Additional recent data support our hypotheses that CAPs promotes oxidant-mediated inflammation in the lung and that sympathetic activation after CAPs deposition in the lung is critical for CAPs cardiotoxicity. Studies will continue in this important area in the coming year.

Furthermore, we have developed a rat model of acute myocardial infarction (MI) to study the effects of particles on ischemia-induced arrhythmias (Wellenius et al., 2002). In these studies, a left-ventricular MI is surgically induced in Sprague-Dawley rats by thermocoagulation of the left coronary artery. Using this model, we have shown that 1-hr exposure to ROFA, but not carbon black or room air, increased the frequency of premature ventricular complexes (PVC) in a significant number (80%) of animals with pre-existing ventricular arrhythmias (Wellenius et al., 2002). We are now using this model to determine if a similar effect is observed following CAPs exposure and if this effect is modified by exposure to carbon monoxide (CO). Within 12-18 hours after surgery, diazepam-sedated animals were exposed to filtered air (FA) for 1 hr (baseline period), either FA only (n=53), FA and CO (n=22), CAPs only (n=68), or CAPs and CO (n=24) for 1 hr (exposure period), and filtered air for an additional hour (recovery period). ECG's were recorded and the number of PVC's in each period were determined. Arrhythmia counts were analyzed by repeated-measures Poisson regression with control for overdispersion. CAPs mass ranged from 60.3 to 2202.5 $\mu\text{g}/\text{m}^3$ with a mean of 566 $\mu\text{g}/\text{m}^3$ (n=29 days). The target CO concentration was 35 ppm. The mean CO concentration in the FA and CO chamber was 38.4 ± 4.3 ppm (mean \pm SEM; n=13 days) and the mean concentration in the CAPs and CO chamber was 38.8 ± 3.1 ppm (n=13 days). Exposure to CO was associated with a 71.9% (p=0.01) decrease in PVC frequency during the exposure period and a 51.8% (p=0.17) decrease during the recovery period. In contrast, exposure to CAPs had no effect on PVC frequency during either the exposure or recovery periods. There was also no evidence of interaction between the effects of CAPs and CO. Results were qualitatively similar when only animals with a transmural MI were considered. However, CO had no effect on PVC frequency in animals with a subepicardial MI. We conclude that:

- 1) the arrhythmogenic effects associated with ROFA exposure are not observed with CAPs exposure
- 2) CO monoxide exposure decreases PVC frequency in rats with transmural MI,
- 3) the effect of CO on arrhythmia frequency is not modified by exposure to CAPs.

Project IIIb: Assessing Deposition of Ambient Particles in the Lung

Original Center activities focused on the development of theoretical models used to predict PM deposition as a function of size (Tsuda & Rogers, 2002). Subsequently, a series of human ambient particle deposition studies were conducted. The total deposition fraction of fine and ultra-fine aerosols was measured in a group of six healthy adults exposed to Boston ambient particles. The deposition efficiency of particles ranging from 40 to 2045 nm was determined using the average concentration of inhaled and exhaled particles measured during these cycles. Deposition efficiencies ranged between $7.3 \pm 18.7\%$ (for particles 168 - 195 nm) and $98.6 \pm 28.1\%$ (for particles 1545 - 2045 nm). Subjects exhibited similar deposition patterns with a minimum efficiency in the size range of 100 - 200 nm. Results from ANOVA and mixed model regression analyses, suggested that deposition efficiency varied with individual and particle size. Deposition efficiencies varied mostly among subjects for particles in the size range between 100 and 1000 nm. A manuscript for publication has been submitted (Montoya et al., Submitted). Finally, over the last two years, we have continued working on the development of particle deposition models (Haber et al., In Press (2003)). No additional deposition studies have been planned.

Project IIIc: Relating Changes in Blood Viscosity, Other Clotting Parameters, Heart Rate and Heart Rate Variability to Particulate and Criteria Gas Exposures

The main objective of this Project is to investigate associations of selected inflammatory and blood clotting parameters in free living humans with particle and criteria gas exposures. This project is in collaboration with the Boston Veterans Hospital who is currently conducting the

Normative Aging Study (NAS). During the first three years the VA Hospital has been collecting data. Measurements of approximately 650 individuals out of 1200 participants have been completed. Statistical analysis, relationships to ambient pollution levels, and geographical relationships has just commenced. A plan for the data analysis was presented during the 2003 SAC meeting last March.

A new panel study was conducted last year in St. Louis, Missouri. Forty-four elderly individuals from four senior independent living facilities were enrolled for participation in the study. To evaluate the effect of traffic-related air pollution on cardiovascular health, individuals participated in a series of four separate day-trips from their suburban residences to activities in downtown St. Louis. Each day trip included two one-hour bus rides on a shuttle bus. In order to characterize gaseous and particulate exposures before, during, and after the bus trips, a number of continuous samplers were employed. These samplers were installed on two roll-around carts and in the rear of the shuttle bus. Continuous measurements of cardiac function were also collected during each day of participation using Holter monitors. In addition, samples of exhaled nitric oxide, blood pressure, blood oxygen, and blood samples were collected from participants before and after the trips. All data have been processed and data analysis has just begun.

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Appendix A--Human Subjects:

Review of Previous Year

Table 1 presents a list of all the Harvard-EPA Center sponsored projects that had an active protocol in the last year with the Human Subjects Committee, along with the date of the last IRB review for each project.

In the last calendar year, the Human Subjects Committee (HSC), the IRB at HSPH expanded its training requirements for investigators. All investigators working on projects with data directly traceable to humans must attend an annual training on "special issues pertaining to human subjects in research" and a general IRB training every two years. Although, the HSC does not hand out certificates to participants for these training seminars, they do keep a database of attendees. All individuals listed in the annual renewals must have their training requirements fulfilled for the renewal application to be processed.

The HSC, this year, decided that protocol 9904 AMBI, the overall center project application was exempt. This application was filed to cover the overall center and to inform the HSC on the VA Boston, IRB's review of the Normative Aging Study.

Issues for Next Year:

The Health Insurance Portability and Accountability Act (HIPAA) does not directly affect HSPH, yet it may affect collaborators at other institutions or data sources. Because of HIPAA and the increased review of human subjects studies by IRBs and funding agencies, we will be reviewing the status of our exempt studies. The review will consist of centralization of exemption notices and a determination of any HIPAA implications for our collaborators. For the protection of the investigator, the HSC has recently recommended filing an exemption request for studies, even if the data is not directly traceable to human subjects. For studies in which the exemption notices have been misplaced or studies dating back to when it was not recommended to file exemption requests for these clearly exempt studies, we will be filing a new exemption request with the HSC as apart of this review process. This review is not mandated by the IRB, rather it is an attempt to keep our files updated in this area of changing interpretations and new regulations.

Quality Assurance:

In the past calendar year, field work for the project "Traffic-Related Particles and Air Pollution", which is supported partly by the Harvard-EPA Center, took place. The major quality assurance efforts for this project was the review and approval of the Quality Assurance Project Plan for the study. This project plan was all inclusive covering all aspects of the study from the environmental measures to the health measures. Data audits were conducted on the data sets for the Los Angeles and Atlanta data sets. The audit consisted of verifying that there was a written description or flow chart on file to convert the raw data to the final data set. A subset of the raw data was processed independently, using the written procedures and compared with the final values.

We are also developing a Standard Operating Manual which describes the quality control procedures for projects in which external data is used and no internal data is generated. The standard operating manual will not change the processes by which these studies are conducted, but will document the specific checks and reviews by which these studies are conducted.

The manual will document the collaborative/academic process in which hypotheses are developed, data sets are identified, analyses methods are developed, studies are designed and refined through an iterative process and papers are prepared, and the quality control steps which are an inherent part of this process.

Table 1: Harvard EPA Particle Center Sponsored Projects with Active Human Subjects Protocols

Protocol No.	Study Name	IRB w/ jurisdiction	Date of Last Review
0011 PART	Particulate Air Pollution Exposure Helen Suh, PI Petros Koutrakis	HSPH	Nov 21, 2002
9905 ASSE	Assessing Human Exposures of High-Risk Sub-Populations to PM Petros Koutrakis, PI	HSPH	Feb 17, 2003
	Normative Aging Study Volkonas	VA	May 20, 2002
9905 EPAP	Chronic Effects of Exposure to PM Dockery	HSPH	June 28, 2002
0109 TRAF	Traffic-Related Particles and Cardiovascular Health in St. Louis H. Suh, P. Koutrakis	HSPH Channing	Oct 22, 2002 Feb 2, 2003
0005 CARD 9710 CARD	Cardiovascular Vulnerability to Particulate Pollution Diane Gold, PI (Steubenville, age 65+)	HSPH-Suh HSPH-Gold Channing	May 17, 2003 Oct 22, 2002 Nov 3, 2002
9904 AMBI	Overall PM Center	HSPH	May 15, 2003