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Evidence of Health Impacts of Sulfate and Nitrate Containing Particles in Ambient Air

Dr. Rick Reiss

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Office of Management and Budget

Introduction

- **Presentation is based on a submitted paper titled "Evidence of Health Impacts of Sulfate and Nitrate Containing Particles in Ambient Air"**
  - Authors include Rick Reiss (Exponent), Elizabeth Anderson (Exponent), George Hidy (Aerochem), Carroll Cross (UC Davis), Roger McClellan (independent consultant), David Hoel (University of South Carolina), and Suresh Moolgavkar (Fred Hutchinson Cancer Research Institute)
    - Includes atmospheric chemistry, risk assessment, toxicology, and epidemiologic expertise
  - In review at *Inhalation Toxicology*
  - Sponsored by the Edison Electric Institute

Overview of Presentation

- **Background on PM NAAQS**
- **Charge of National Research Council to address effects of PM constituents**
- **Toxicological data**
- **Epidemiologic data**
  - Focus on sulfate, as few studies have considered nitrate
- **Summary**

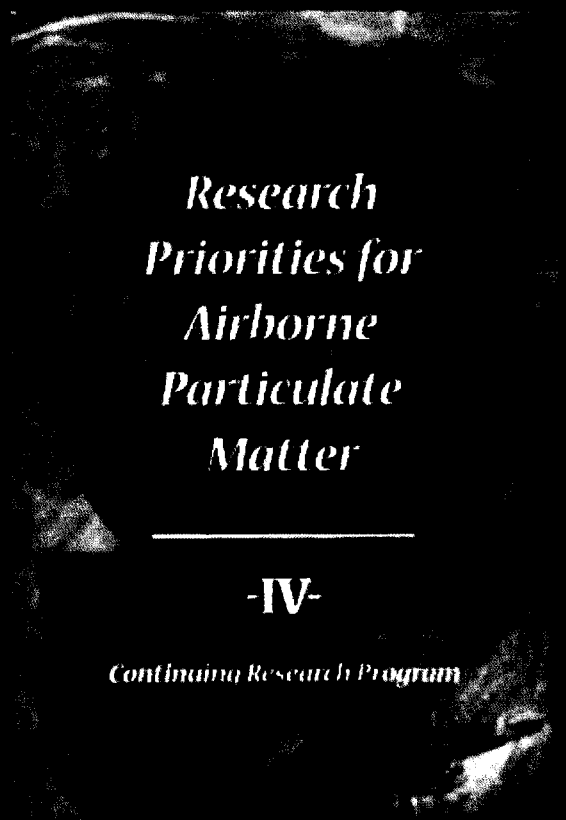
A Particle is Not a Particle is Not a Particle

- **Particles are collections of different chemical material**
  - Includes metals, inorganic ions, organic, crustal
  - Concentrations of each constituent vary with time and location

- **The PM NAAQS is the only NAAQS that is not chemical specific**
  - Set principally based on epidemiologic data

- **Instead, the PM NAAQS includes all particulate matter in given particle size ranges:**
  - 1971: TSP
  - 1987: PM_{10}
  - 1997: $PM_{2.5}$

National Research Council Review



- The "current NAAQS for PM is both size and mass-based and implicitly assumes that all particles of a given size have the same toxicity per unit mass, irrespective of chemical composition. In the Committee's judgment, the mass-based NAAQS greatly oversimplifies complex biological phenomena."
- Similar mandate from OMB

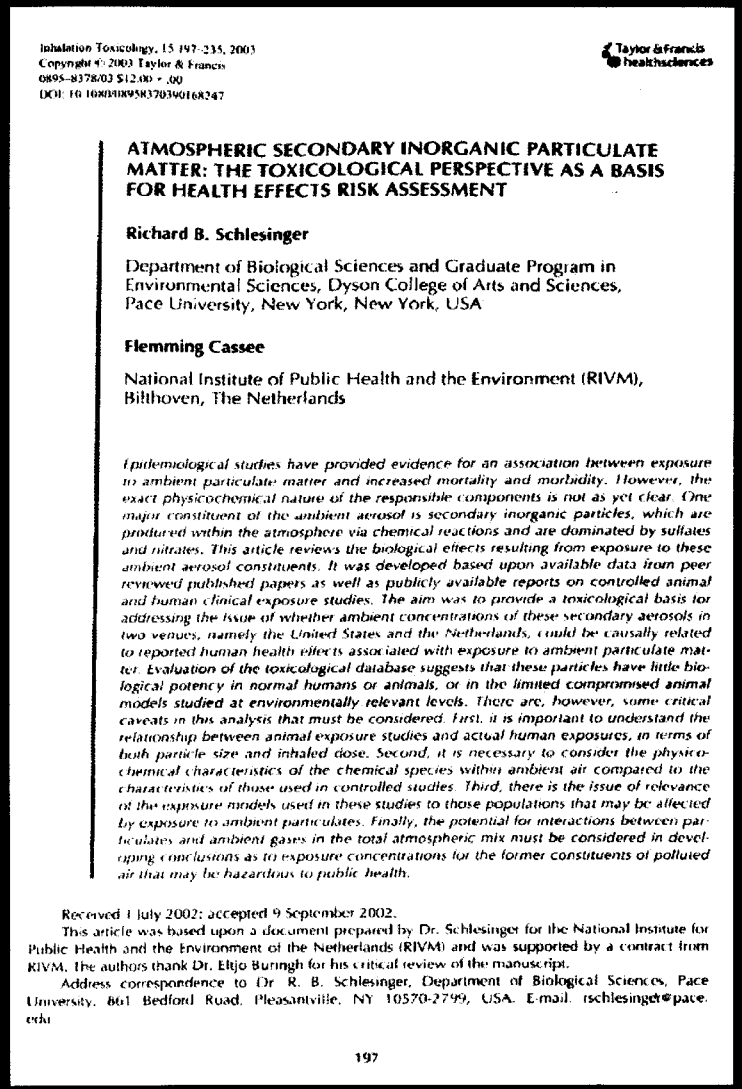
Properties of Particles That May Influence Toxicity

- **Physical characteristics**
  - Size, surface, morphology, mass, number, electrical properties
- **Physical chemistry**
  - Hygroscopicity, hydrophilicity, lipophility, bioavailability, acidity, redox potential
- **Chemical**
  - Metals, carbon, biogenic, sulfate, nitrate, dust

Several Ways to Look at Possible Sulfate and Nitrate Health Effects

- **Toxicology**
  - Traditional animal studies
  - Human chamber studies
  - Concentrated Ambient Particles (CAPs)
- **Epidemiology**
  - Short-term time-series studies
  - Long-term cohort studies
- **Combined weight-of-the-evidence**

Schlesinger and Cassee Review of Sulfate Toxicology Database



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ATMOSPHERIC SECONDARY INORGANIC PARTICULATE MATTER: THE TOXICOLOGICAL PERSPECTIVE AS A BASIS FOR HEALTH EFFECTS RISK ASSESSMENT

Richard B. Schlesinger

Department of Biological Sciences and Graduate Program in Environmental Sciences, Dyson College of Arts and Sciences, Pace University, New York, New York, USA

Flemming Cassee

National Institute of Public Health and the Environment (RIVM), Bilthoven, The Netherlands

Epidemiological studies have provided evidence for an association between exposure to ambient particulate matter and increased mortality and morbidity. However, the exact physicochemical nature of the responsible components is not as yet clear. One major constituent of the ambient aerosol is secondary inorganic particles, which are produced within the atmosphere via chemical reactions and are dominated by sulfates and nitrates. This article reviews the biological effects resulting from exposure to these ambient aerosol constituents. It was developed based upon available data from peer reviewed published papers as well as publicly available reports on controlled animal and human clinical exposure studies. The aim was to provide a toxicological basis for addressing the issue of whether ambient concentrations of these secondary aerosols in two venues, namely the United States and the Netherlands, could be causally related to reported human health effects associated with exposure to ambient particulate matter. Evaluation of the toxicological database suggests that these particles have little biological potency in normal humans or animals, or in the limited compromised animal models studied at environmentally relevant levels. There are, however, some critical caveats in this analysis that must be considered. First, it is important to understand the relationship between animal exposure studies and actual human exposures, in terms of both particle size and inhaled dose. Second, it is necessary to consider the physicochemical characteristics of the chemical species within ambient air compared to the characteristics of those used in controlled studies. Third, there is the issue of relevance of the exposure models used in these studies to those populations that may be affected by exposure to ambient particulates. Finally, the potential for interactions between particulates and ambient gases in the total atmospheric mix must be considered in developing conclusions as to exposure concentrations for the former constituents of polluted air that may be hazardous to public health.

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Address correspondence to Dr. R. B. Schlesinger, Department of Biological Sciences, Pace University, 861 Bedford Road, Pleasantville, NY 10570-2799, USA. E-mail: rschlesinger@pace.edu

- "the available evidence suggests that the minimally effective concentration of sulfuric acid ... to alter pulmonary function ... in normal humans following acute exposure is >1000 μg/m^3, but in asthmatics it may be around 68-100 μg/m^3" (Sulfuric acid was sulfate-species with the most data)
- Sulfate concentrations average about 3 μg/m^3 across the U.S.
- Toxicological results were similar for nitrate, though there are fewer studies.

Concentrated Ambient Particle (CAPs) Studies

- **Researchers expose humans and animals to CAPs and attempt to correlate response with CAPs constitutents**
  - No consistent effects with sulfate
  - New, promising avenue of research, but a biologically plausible mechanism for PM effects, let alone effects from sulfate, has not yet been identified

Issues in Interpreting Epidemiologic Studies

- **Use of central monitors to represent exposure of all populations**
- **Risks are very small**
  - Creates added concern for confounders
- **How to interpret large heterogeneity of results**
  - Are the results consistent?

Issues Specific to Sulfate

- **Sulfate is a large part of $PM_{2.5}$**
  - On average, 22% of $PM_{2.5}$ is sulfate (2004)
  - Sulfate and $PM_{2.5}$ are well correlated spatially and temporally
    - Difficult to tease apart effects
    - Associations with sulfate do not necessarily imply true causal associations

- **Sulfate exposure is better represented by central monitors than $PM_{2.5}$ or other constituents of PM**
  - All else equal, more likely to see effect for sulfate than other constituents

Potential Masking of Effects

- Ito et al. (2004): "Thus, if a single monitor's or a few monitor's data are used to estimate the entire city's population exposure, then the potential health effects of individual PM species that have low monitor-to-monitor correlation such as EC would be masked or underestimated compared to PM species which have high monitor-to-monitor correlation (e.g., sulfate)."

- Effects included in sulfate risks may include risks from other constituents due to temporal and spatial correlation with those constituents

Guidance in Interpreting Epidemiologic Studies

Comparison of Statistical Significance	Possible Explanation
$PM_{2.5}$ = Sulfate	$PM_{2.5}$ and sulfate equally toxic; or sulfate effect due to correlation with $PM_{2.5}$
$PM_{2.5}$ > Sulfate	$PM_{2.5}$ more important
$PM_{2.5}$ < Sulfate	Sulfate more toxic, or sulfate masks $PM_{2.5}$ effect

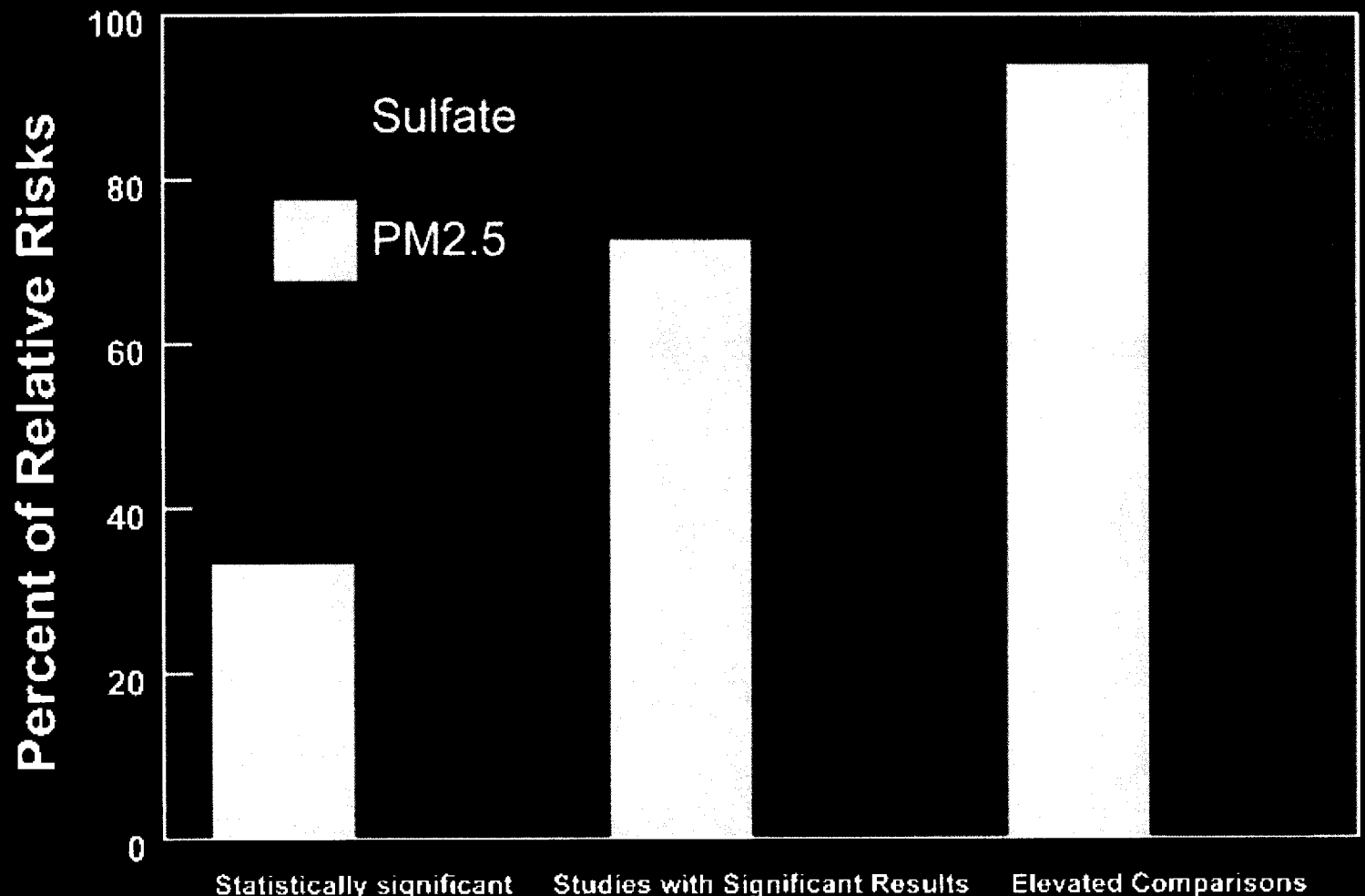
Short-Term Epidemiology Studies

- **Time-series studies compare timing of health effects (usually mortality) with pollution levels**
  - Conducted in a city or a group of cities
  - Exposure is estimated from central monitors
  - Often use 1 or 2-day lagged pollution levels
  - Statistically adjust for effects of meteorology
    - Paper addresses the complexities of these adjustments
  - Virtually all studies include $PM_{2.5}$, while a subset include sulfate.
    - Sulfate is most frequent PM species included in epidemiologic studies

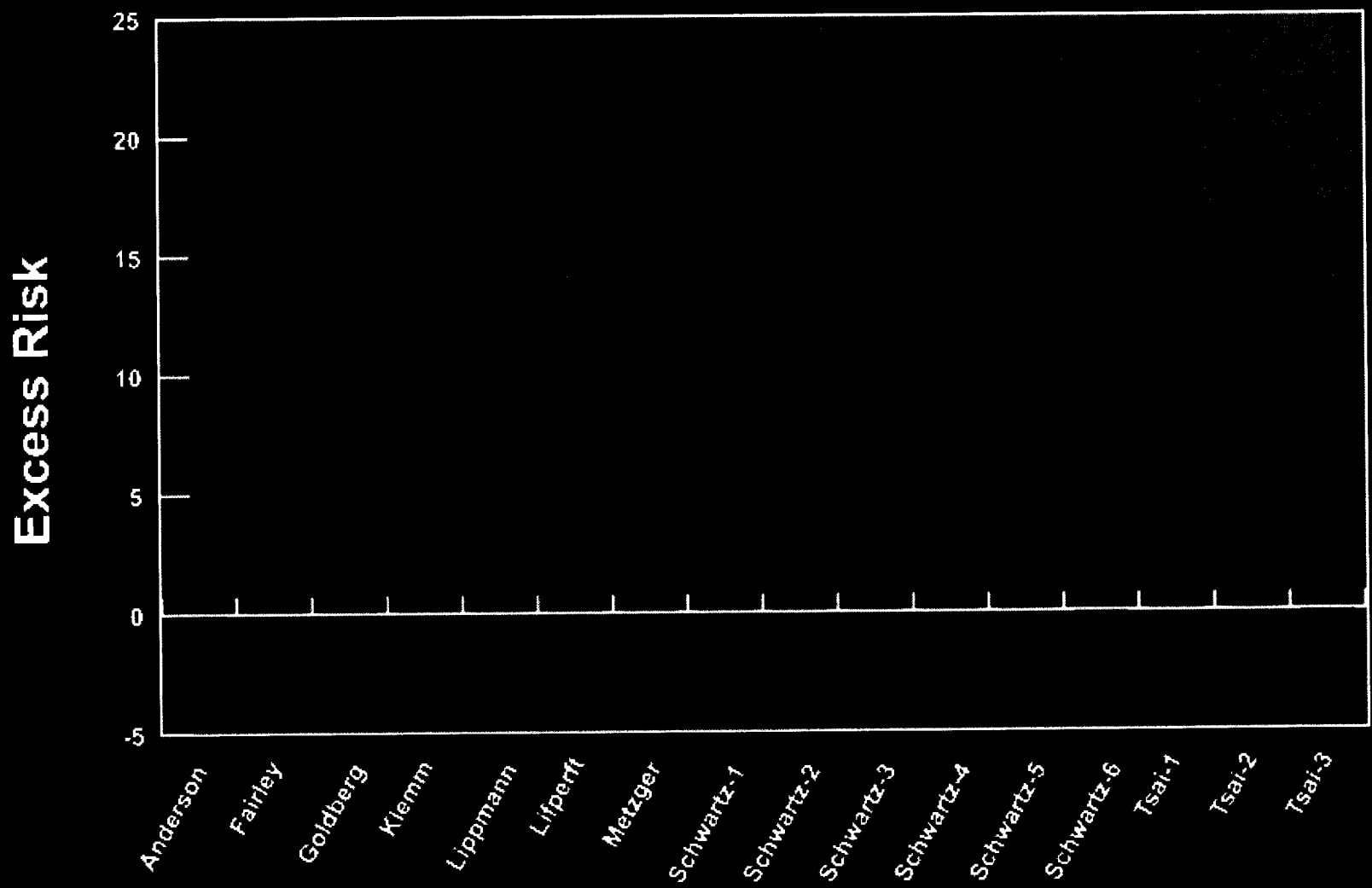
Detailed Analysis of Short-Term Studies that Include Sulfate and $PM_{2.5}$

- **Restricted to last decade**
  - 13 studies
  - 18 geographic areas
  - 48 relative risk (RR) estimates
  - 15 RRs for all-cause mortality
  - Only relied on results that were reanalyzed for convergence problems with Generalized Additive Models (GAMs)
    - Studies conducted prior to discovery of GAM convergence issue are flawed and potentially misleading

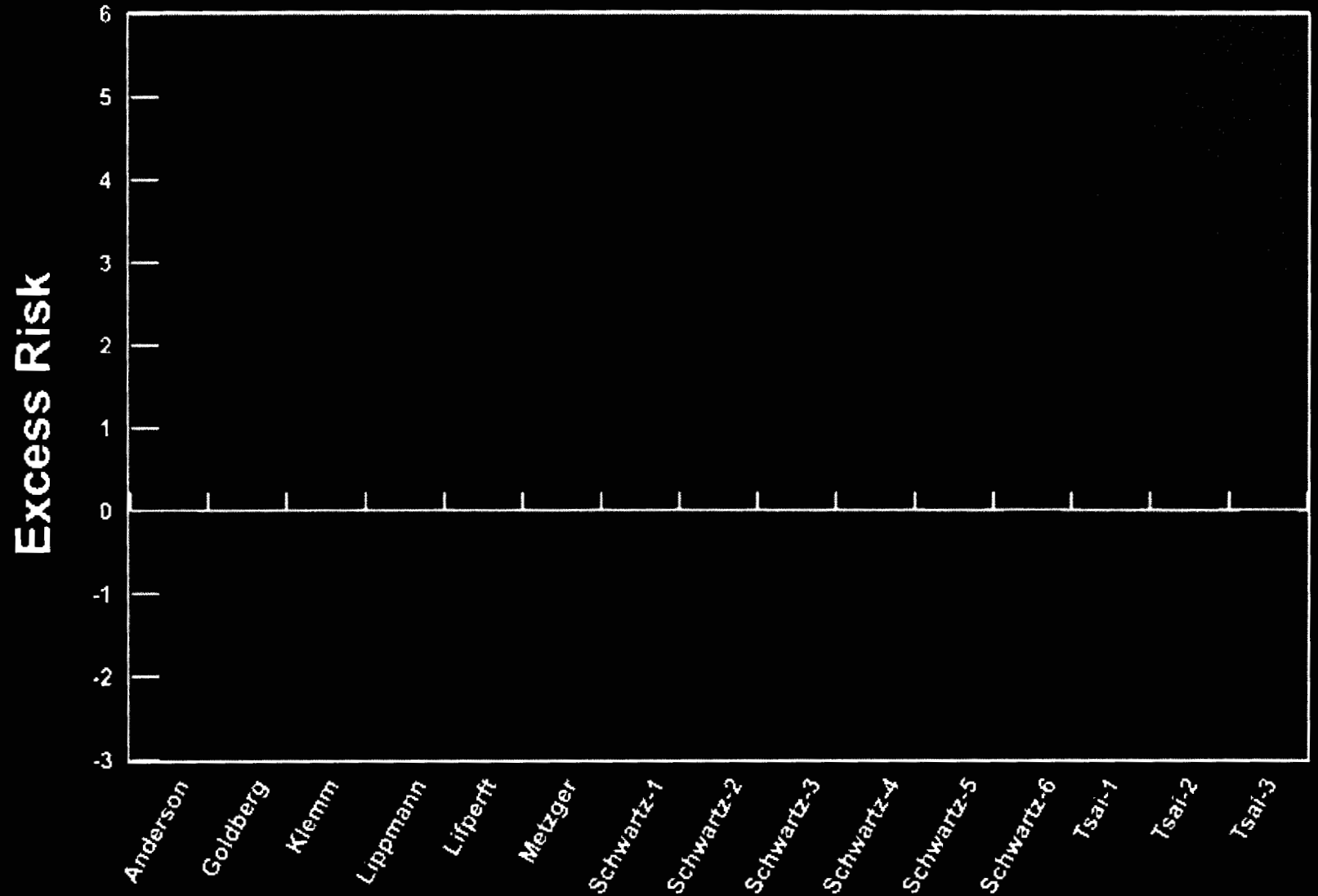
Comparison of Short-Term Results: Tabulation of Relative Risks



Heterogeneity of Sulfate Relative Risks



Heterogeneity of Sulfate Relative Risks – Without Outlier



Other Important Results from Short-Term Studies

- **Few studies included multi-pollutant modeling**
  - Studies can only include the constituents that are widely measured, and some don't even include all measured constituents
  - Many ambient constituents are temporally and/or spatially correlated, complicating estimation of risks

- **Sulfate risk attenuated when ozone or NO_2 were included (Burnett et al., 1997; Burnett et al., 2000 and Lipfert et al., 2000)**
  - Shows that risks for studies that didn't include ozone and NO2 (most studies) may be overestimated

Long-Term Epidemiologic Studies

- **Semi-ecologic studies of associations of mortality and morbidity across different geographical regions with varying air pollution levels**
  - Cohorts are followed in each city, typically for decades
  - Exposure is estimated from central monitors in each city
  - Some individual-level confounders such as smoking may be included

Harvard Six Cities Study: Original and Follow-up

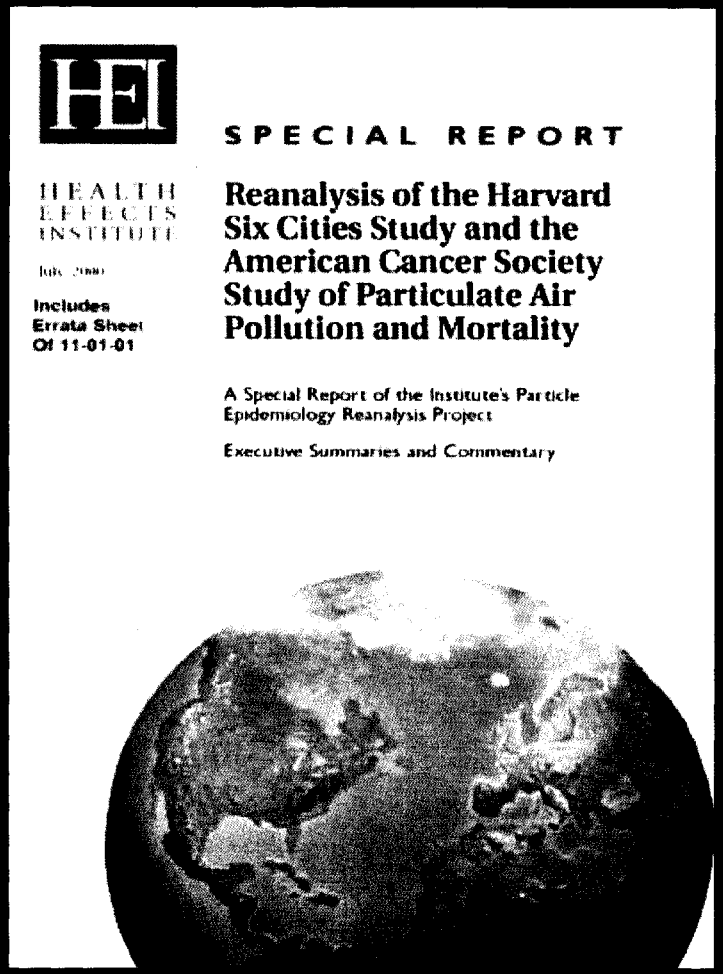
Reduction in Fine Particulate Air Pollution and Mortality

Extended Follow-up of the Harvard Six Cities Study

Francine Laden, Joel Schwartz, Frank E. Speizer, and Douglas W. Dockery

- Positive associations with $PM_{2.5}$ and sulfate in original study.
- Close correlation of $PM_{2.5}$ and sulfate – can't differentiate effects
- No significant association with $PM_{2.5}$ in any city in follow-up period (1990-98) – supports threshold
  - Sulfate not included in follow-up, but results would likely track $PM_{2.5}$ results given close correlation.

ACS-II Study and Reanalysis



- By far, largest long-term study including 50-150 cities
- Original study found significant associations for $PM_{2.5}$ and sulfate with mortality
- Reanalysis considered ecological confounders, including co-pollutants
  - Risks for sulfate and $PM_{2.5}$ were attenuated below significance

Lipfert et al. Study of Veterans with Hypertension

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THE WASHINGTON UNIVERSITY–EPRI VETERANS' COHORT MORTALITY STUDY: Preliminary Results

Frederick W. Lipfert

Environmental Consultant, Northport, New York, USA

H. Mitchell Perry, Jr.

Department of Veterans Affairs Medical Center and Washington University School of Medicine, Division of Hypertension, St. Louis, Missouri, USA

J. Philip Miller, Jack D. Baty

Washington University School of Medicine, Division of Biostatistics, St. Louis, Missouri, USA

Ronald E. Wyzga

EPRI, Palo Alto, California, USA

Sharon E. Carmody

Department of Veterans Affairs Medical Center and Washington University School of Medicine, Division of Hypertension, St. Louis, Missouri, USA

This article presents the design of and some results from a new prospective mortality study of a national cohort of about 50,000 U.S. veterans who were diagnosed as hypertensive in the mid 1970s, based on approximately 21 yr of follow-up. This national cohort is male with an average age at recruitment of 51 ± 12 yr; 35% were black and 81% had been smokers at one time. Because the subjects have been receiving care at various U.S. Veterans Administration (VA) hospitals, access to and quality of medical care are relatively homogeneous. The health endpoints available for analysis include all cause mortality and specific diagnoses for morbidity during VA hospitalizations; only the mortality results are discussed here. Nonpollution predictor variables in the baseline model include race, smoking (ever or at recruitment), age, systolic and diastolic blood pressure (BP), and body mass index (BMI). Interactions of BP and BMI with age were also considered. Although this study essentially controls for socioeconomic status by design because of the homogeneity of the cohort, selected ecological variables were also considered at the ZIP code and county levels, some

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Address correspondence to Dr. Frederick W. Lipfert, Environmental Consultant, 23 Carll Court, Northport, NY 11768, USA. E-mail: flipfert@suffolk.lib.ny.us

- No significant associations between $PM_{2.5}$ and sulfate with mortality.
- Most significant mortality associations with traffic density in most recent follow-up

Enstrom Study of Elderly Californians

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Fine Particulate Air Pollution and Total Mortality Among Elderly Californians, 1973–2002

James E. Enstrom
Jonsson Comprehensive Cancer Center, University of California, Los Angeles, California, USA, and Scientific Integrity Institute, Los Angeles, California, USA

Fine particulate air pollution has been associated with increases in long-term mortality in selected cohort studies, and this association has been influential in the establishment of air quality regulations for fine particles ($PM_{2.5}$). However, this epidemiologic evidence has been questioned because of methodological issues, conflicting findings, and lack of an accepted causal mechanism. To further evaluate this association, the long-term relation between fine particulate air pollution and total mortality was examined in a cohort of 49,975 elderly Californians, with a mean age of 65 yr as of 1973. These subjects, who resided in 25 California counties, were enrolled in 1959, recontacted in 1972, and followed from 1973 through 2002; 39,846 deaths were identified. Proportional hazards regression models were used to determine their relative risk of death (RR) and 95% confidence interval (CI) during 1973–2002 by county of residence. The models adjusted for age, sex, cigarette smoking, race, education, marital status, body mass index, occupational exposure, exercise, and a dietary factor. For the 35,789 subjects residing in 11 of these counties, county-wide exposure to fine particles was estimated from outdoor ambient concentrations measured during 1979–1983 and RRs were calculated as a function of these $PM_{2.5}$ levels (mean of 23.4 $\mu g/m^3$). For the initial period, 1973–1982, a small positive risk was found: RR was 1.04 (1.01–1.07) for a 10-$\mu g/m^3$ increase in $PM_{2.5}$. For the subsequent period, 1983–2002, this risk was no longer present: RR was 1.00 (0.98–1.02). For the entire follow-up period, RR was 1.01 (0.99–1.03). The RRs varied somewhat among major subgroups defined by sex, age, education level, smoking status, and health status. None of the subgroups that had significantly elevated RRs during 1973–1982 had significantly elevated RRs during 1983–2002. The RRs showed no substantial variation by county of residence during any of the three follow-up periods. Subjects in the two counties with the highest $PM_{2.5}$ levels (mean of 36.1 $\mu g/m^3$) had no greater risk of death than those in the two counties with the lowest $PM_{2.5}$ levels (mean of 13.1 $\mu g/m^3$). These epidemiologic results do not support a current relationship between fine particulate pollution and total mortality in elderly Californians, but they do not rule out a small effect, particularly before 1983.

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The extended mortality follow-up and analyses presented in this article have been funded by the Electric Power Research Institute (EPRI). The entire funding history of CA CPS I prior to this analysis has been described elsewhere (Enstrom & Heath, 1999; Enstrom & Kabat, 2003). The author is responsible for all aspects of the article and declares no competing interests relevant to its contents. In the spirit of the Data Quality Act (OMB, 2003; Steinbrook, 2004), the author is willing to facilitate independent analysis of all the data used in the article. The author thanks Dr. Frederick W. Lipfert for proposing air pollution analyses with CA CPS I data and for contributing extensively to numerous versions of the text and tables, Dr. Ronald E. Wyzga for critiques of the article and for suggestions about making it as comprehensive and objective as possible, and Dr. Lingqi Tang for statistical assistance.
Address correspondence to James E. Enstrom, University of California, Jonsson Comprehensive Cancer Center, Los Angeles, CA 90095, USA. E-mail: jenstrom@ucla.edu

Many observational epidemiological studies have reported associations between air pollution from combustion sources and human health (Lipfert, 1994). During past severe air pollution events, such as the 1952 London fog incident (Logan & Glasg, 1953), extremely high concentrations of particulate air pollution were accompanied by major increases in coincident mortality. In more recent years, health effects have also been associated with much lower concentrations of particulate air pollution (Pope & Dockery, 1999). While much of the recent research has focused on short-term exposures, several studies suggest that long-term exposures may be more important. In particular, results from two major cohorts (Dockery et al., 1993; Pope et al., 1995, 2002) have shown significant mortality associations with outdoor concentrations of fine particles ($PM_{2.5}$, median aerodynamic diameter

- Possible small association with mortality for $PM_{2.5}$ in early follow-up period (1973-82); RR=1.04 (1.01-1.07)
- No association in later follow-up period (1983-02); RR=1.00 (0.98-1.02)
- Sulfate not included

Summary of Long-Term Studies

Study	Result
ACS-II	Sulfate and $PM_{2.5}$ risk insignificant in sensitivity analysis
VA Cohort	Sulfate not significant; risks further attenuated by including traffic density
Six Cities	No significant risks in later period
Enstrom	Did not include sulfate, but $PM_{2.5}$ risks not significant

Additional Comments on Nitrate

- **No effect concentrations in the toxicology studies are well above ambient levels**
- **Very limited epidemiologic data:**
  - One short-term study included nitrate (Klemm et al., 2004) and found no effects
  - One long-term study included nitrate (Lipfert et al., 2006) and found a significant relationship with mortality
    - Risk was attenuated below significance when traffic density was included
  - Too little data to make broad conclusions

Implications for Regulatory Impact Assessment

- **Inappropriate to assume the same benefit from reducing sulfate as $PM_{2.5}$**
  - Evidence suggests that sulfate is at least less potent than $PM_{2.5}$, if it has any potency
- **Must acknowledge large uncertainty in $PM_{2.5}$-related risks**
  - Risk estimates for $PM_{2.5}$-related effects are inconsistent

Summary

- **Toxicological data provide no basis for sulfate health effects**
- **Epidemiologic studies are "blunt" tools**
  - Short-term studies show inconsistent results for sulfate and $PM_{2.5}$
    - Sulfate is a weaker risk factor than $PM_{2.5}$, despite having lower exposure measurement error
  - Long-term studies show inconsistent results for $PM_{2.5}$ and sulfate
    - With reanalysis of ACS, sulfate was not significant in the two largest studies (ACS and VA).
    - Sulfate was significant in earlier period of Harvard Six Cities study, but sulfate and $PM_{2.5}$ are nearly perfectly correlated in this study
- **Weight-of-the-evidence does not support a casual role for sulfate in ambient air-related health effects**

Recommendations for Further Research

- Future epidemiologic studies need to employ more extensive population-based monitoring of all potentially relevant ambient species including particles and gases
  - Speciated particle measurements should be used
- Increase coordination between atmospheric chemistry, toxicology, and epidemiology fields
- Conduct similar analyses for other PM species, including carbonaceous material