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Analysis of Health Effects Resulting from Population Exposures to Acid Precipitation Precursors

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Types of available studies relevant to the quantification of air pollution health effects and their principal limitations are discussed. Assessments are provided based on review and re-analysis of previously reported data bases, synthesis of published findings, and original analysis of health data sets using new methods or recent size-specific particle mass measurements. Interim results from ongoing research activities on airborne particle health effects are presented. It is shown that preliminary results obtained from cross-sectional and time-series mortality studies appear to be consistent, indicating that particulate air pollution, even at current levels, could be of concern for public health. Throughout the paper, methodological deficiencies and remaining gaps in knowledge are identified. In particular, uncertainties associated with the reported exposure-response coefficients are assessed. Finally, by characterizing the limitations of analysis we propose various recommendations for future studies and research that will serve to further define the nature, magnitude, and uncertainties of air pollution health risks.

Introduction

A wide variety of particles and gases that exist in the ambient environment have either been directly or indirectly linked to the phenomenon of acid rain formation. A significant fraction of these acid precipitation precursors are due to emissions from fossil fuel combustion used for energy generation. Upon release into the atmosphere through condensation, evaporation, and chemical transformations gases may become particles and vice versa. Sulfate or sulfuric acid aerosol formation by the oxidation of sulfur dioxide (SO_2) is a primary example of this phenomenon. These (secondary) particles have been found to vary in size, shape, concentration, and composition, both spatially and temporally. Therefore, developing quantitative relationships between the precursor pollutants of acid precipitation and human health effects requires consideration of a number of factors. Because different gases and types of particles are known to have varying toxicity or biological activity, characterization of gases and airborne particles for health studies becomes further complicated.

Recognizing these difficulties and data base limitations, we have concentrated here on the analysis of population health effects resulting from exposures to ambient particulate matter. Rather than an exhaustive review, our approach has mostly been the evaluation of recent literature on the mortality and morbidity effects of air pollution. We have relied extensively on the results from a multidisciplinary study at Harvard University investigating the health effects of population exposures to airborne particles.

Using published findings and analyses of data available from epidemiologic studies, we have attempted in this paper to evaluate the health effects of particles. However, there are many difficulties involved in applying epidemiologic analyses of pollution measurements to assessments of health risks, mainly because observational epidemiologic studies of community air pollution exposures have not generally been designed to provide dose-response relationships suitable for risk assessment. Therefore, prior to presenting quantitative exposure–response estimates for some of the important acid precipitation precursors, it is important to discuss the general types of studies relevant to quantification of health effects and their principal limitations.

Health Effects Studies and Their Limitations

There are three main categories of studies relevant to the assessment of human health effects resulting from exposures to ambient pollutants. These include: animal studies/short-term bioassays, controlled human studies, and epidemiologic studies.

Animal studies offer the opportunity for controlling most of the experimental and environmental parameters and they also provide important insights into mech-

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anisms of action. However, extensive data bases from these studies are often lacking, and extrapolation between species poses significant technical challenges. Although increased interest in short-term bioassays have recently resulted in the development of considerable data bases to support risk-analytic studies, again, unfortunately, the techniques for extrapolation are not yet established.

Controlled human studies are usually relevant only to the subgroups of populations that are selected for studies (e.g., young adults, asthmatics). In general, information on many complex particle types are lacking from these studies. Most important, frequency and duration of exposures in controlled human studies are not representative of most short- or long-term ambient exposures to toxic pollutants.

In contrast, observational epidemiology has a high degree of relevance to population-based health effects investigations. Quantitative risk assessment for air pollution relies on health damage estimates derived from epidemiology. Although it does offer great advantages for health risk assessment, observational epidemiology also has certain shortcomings. Because the assessments reported in this paper are primarily based on epidemiologic investigations, we will address the limitations of these studies in some detail.

In almost all of the available observational studies of air pollution epidemiology, population exposures were derived from monitoring data gathered by fixed-site ambient monitors. These ambient measurements were then used to represent, uniformly, the community-wide concentrations of all the individuals living in the study area. The concept of personal or source-specific exposures was not adopted, that is, these studies did not attempt to differentiate population exposures based on pollution source types, housing characteristics, time-activity patterns, indoor, outdoor, or occupational exposures. The general assumption was that the differences in outdoor concentrations of some pollutants between cities or subdivided regions within a community were more important determinants of population exposures than source-specific or personal factors. To the extent that the crude measures of exposures—represented for example by outdoor Coefficient of Haze (COH), British Smoke (BS), total suspended particulate matter (TSP) and sulfate (SO_4^{2-}) levels—are surrogates for the harmful agents of airborne particles, the detailed characterization of aerosols may be unimportant, as long as the principal compositions of aerosols remains unchanged over time. However, emission controls, relocation of facilities, changes in the available fuel has, in fact, reduced TSP levels and decreased the sootiness of the aerosols in most urban areas in the U.S. Consequently, in most parts of this country, TSP is now dominated by the soil fraction. On the other hand, ozone (O_3) concentrations and the concentrations of fine particles (FP) and sulfates, which may represent an important toxic component of airborne particles, have not decreased. Therefore, accurate characterization of ambient aerosols and their sources, in relation to particle health effects investigations, becomes especially important for epidemiologic studies that rely on pollution data gathered within the last 10 to 15 years.

Related to the historic changes in the composition and the concentration of ambient pollution are the associated changes in the relative roles of indoor and outdoor pollution. During the years when ambient air pollution was higher, the relative importance of indoor concentrations would have been small compared to outdoor pollution. Because indoor exposures can substantially affect the health outcomes associated with air pollution, this phenomenon of temporal changes in the historic indoor/outdoor exposure patterns can lead to significant biases due to misclassification of exposures. Exposures to certain pollutants in locations other than indoor (at home) or outdoor environments, for example, at work or in-transit, could also result in observable health effects. Depending on the distribution of the effects among the population subgroups, systematic or random bias could occur. Although outdoor pollutants are typically found at lower concentrations in enclosed environments, it is likely that the effects typically associated with outdoor concentrations may have actually occurred at lower concentrations due to exposure misclassification.

Results of studies which fail to explicitly account for these problems can be misleading in some cases. For example, when personal exposures are affected mostly by other than outdoor sources, e.g., due to indoor exposures to respirable particles (RSP), nitrogen oxides (NO_x), tobacco smoke, etc., or if the potency or the relative toxicity hazard of, for example, indoor or in transit exposures is different from those from outdoor pollutants, then the health risk coefficients derived from regressions using only outdoor pollutant concentrations can be significantly in error.

Moreover, as discussed in Ferris and Spengler (*1*), due to various types of uncertainties associated with the quantification of personal exposures to the toxic fraction of ambient aerosols, lack of demonstrated effects from air pollution epidemology should not be interpreted as proof of the null hypothesis (i.e., no effect). The implications of incorporating refined exposure estimates into epidemiologic risk assessments are known to be quite important. As shown in Özkaynak et al. (*2*), the statistical bias due to misclassification of exposures typically results in lower estimates of relative risk and reduced precision in conventional studies of observational epidemiology. Thus, due to limitations of both sample size and information on "true" (personal) exposures to toxic components of ambient aerosols, it is likely that for certain pollutants we have not yet been able to detect measurable health effects or significant exposure-response associations.

For the reasons described above, it is difficult to use the published air pollution epidemiology to quantify pollutant-specific, exposure-response coefficients for either the morbidity or mortality effects of airborne particles. Cross-sectional studies that have examined long-term health effects do not seem to have the power to detect these chronic effects as distinct from contemporary ex-

posure or potentially acute effects of air pollution (*3*). Unless the indoor/outdoor exposures are properly separated, the number of people in prospective investigations will be too low to detect health effects. Pertinent to this is the importance of indoor air pollutant exposures that can either confound or systematically bias results.

Thus, predictions regarding the extent of association between air pollution and human mortality or morbidity are hampered by data base limitations as well as methodological difficulties. In principle, only after carefully considering all relevant sources of error and utilizing improved exposure estimates in epidemiologic assessments, can one expect to develop reliable health risk coefficients for airborne particles and gases.

Findings from Recent Epidemiologic Studies

Research conducted within the past three years at the Energy and Environmental Policy Center at Harvard University has focused on the data analysis limitations noted above. The primary goal of our efforts was to examine the scientific evidence from individual aerometric and health data sets for coherence, and to consistently quantify exposure-response effects by air pollutant components. The detailed description of findings from analyses of health effects resulting from population exposures to ambient particulate matter can be found in Özkaynak et al. (*4–6*). The principal conclusions from these assessment activities provided here are based on the review and reanalysis of previously reported data bases, a synthesis of published findings, and original analyses of health data using new methods or recent information. The main objectives of our work have been to: identify health outcomes associated with different pollutants levels; characterize the uncertainties of estimates; and demonstrate the sensitivities of results to the choice of data base and analysis methods.

Basically there were two approaches available to characterize the health impacts associated with the airborne particles and SO_2. One was to rely heavily on EPA's recent criteria document on particulate matter and sulfur oxides (*7*) and the other was to conduct or rely on a risk analytic approach oriented towards providing numerical exposure-response information. In this work we have selected the second approach primarily because neither the EPA's criteria document nor the EPA Office of Air Quality Planning and Standards (OAQPS) staff review of the criteria document (*8*) provide quantitative exposure-response information applicable to concentrations most typically found in the U.S. today. We have, however, used the EPA documents as a guide for selecting toxicologic and epidemiologic data bases that could be used to estimate exposure-response coefficients.

In order to quantify air pollution health effects we have turned to observational studies as well as studies utilizing vital statistics data. In particular, we have conducted studies on the mortality and morbidity effects of air pollution. The mortality studies included: cross-sectional mortality analysis using 1960 and 1980 vital statistics and air pollution data, and time-series mortality using 14 years of daily mortality and air pollution records from New York City. The morbidity studies included: analysis of the 1979 NCHS Health Interview Survey, analysis of the respiratory symptoms from NHANES I, and analysis of respiratory symptoms and pulmonary function data from a study of children at a summer camp in Canada.

Cross-sectional mortality studies have the utility of considering a much wider range of exposures than usually examined in observational studies involving relatively few cities. However, they suffer from methodological difficulties associated with the correct specification of the model variables necessary to account for the essential demographic, environmental, and other differences in the large number of cities analyzed. On the other hand, time-series investigations of daily mortality in large metropolitan areas such as New York City, Los Angeles, or London offer the opportunity to detect the likely but small effects of air pollution, after controlling for causes other than air pollution, such as environmental and socio-economic factors and epidemics.

The national health surveys conducted by the National Center for Health Statistics (NCHS), such as the Health Interview Survey (HIS) or the National Health and Nutrition Examination Survey (NHANES I and II), provide the opportunity to assess air pollution health effects differentially on aggregate populations or on some subset of a potentially sensitive population such as children or the chronically ill. Finally, recent studies of childrens' daily lung function measurements and air pollution at summer camps are also very important in providing insights into the acute but mostly reversible respiratory effects of air pollution.

In all of these investigations our approach has been to improve upon the definition of ambient particulate matter by employing the fine particle (FP) fraction and sulfates. In some analyses we have developed empirical as well as theoretical relationships between aerosol concentrations and visual range measurements reported by airports in the U.S. The advantages of using visual measurements are that they historically predate particle measurements by several decades and records are available for hundreds of locations in the United States and for almost every day. More recently we have applied Principal Component Analysis (PCA) to multi-elemental aerosol data sets to demonstrate source contributions to ambient concentrations in an effort to characterize the mortality and morbidity effects of air pollution by source class (*9*). These source compositions in turn are now being used in cross-sectional analyses of the 1980 mortality and air pollution data.

In the following we summarize the main results from our ongoing research on airborne particle health effects. It should be emphasized, however, that the quantitative estimates reported here are interim results and are still

preliminary. Therefore, we do not recommend that they be used in risk assessment, at least until more refined analysis with the existing data is completed. Furthermore, since our studies with NHANES I and the childrens' lung function data are still in the initial phases of analyses, we are not in a position to report results from these investigations.

Cross-Sectional Mortality Analysis

Cross-sectional mortality analysis refers to the study of the relationships between air pollution and health by analyzing statistically the geographic differences in (annual) mortality and the corresponding pollution levels. Many investigators have adopted this type of epidemiologic analysis of vital statistics data, perhaps most notably Lave and Seskin (*10*). Their analysis of data for 117 Standard Metropolitan Areas (SMSAs) from 1960 produced results that showed significant, positive association between mortality and TSP and TSP-sulfates. A review of the relevant cross-sectional mortality literature and the re-analysis of Lave and Seskin's 1960 data in Evans et al. (*11*) and in Özkaynak et al. (*5*) confirmed the positive associations that Lave and Seskin described. In addition, Evans et al. (*11*) reviewed the limitations of major cross-sectional studies (such as misclassification and confounding) and examined the sensitivity of results to model specification. Using several plausible models on a single data set (98 SMSA 1960 annual total mortality and annual pollution), Evans and his colleagues produced mortality risk coefficient estimates for sulfates which varied typically by a factor of about 3 and estimates of the standard errors of these coefficients which varied by a factor of nearly 2.5. In their sensitivity analysis of the 1960 98 SMSA data base, using a basic seven-variable model, they obtained an estimate of the mean sulfate coefficient and its standard error as 2.63 ± 1.40 deaths/year/100,000 persons per $\mu g/m^3$. The estimate was higher (3.72 ± 1.90 deaths/year/100,000 per $\mu g/m^3$) when a 66-SMSA subset was analyzed. For the 66-SMSA data set the TSP mortality (i.e., concentration-response) coefficient was 0.34 ± 0.20 deaths/year/100,000 per $\mu g/m^3$. However, when jointly estimated (using the 66-SMSA data base), the coefficients for sulfates went down to 2.77 ± 2.28 and the coefficient for TSP went down to 0.18 ± 0.24, both becoming nonsignificant at the $p = 0.05$ level. As pointed out by Evans et al. (*11*), this result highlights the interdependence (or collinearities) of the coefficient estimates. Perhaps the more important finding is that in both the single and joint pollutant estimations, the choice of sample size ($n = 98$ or 66 SMSA, for example) and the characteristics of the SMSAs included or removed from the analysis strongly influence the results.

Most of the publications on cross-sectional mortality analysis (*10–12*) have already pointed out the importance of regionally distributed factors that could affect the analysis and residuals. Although this has again recently been noted by Lipfert (*13*), we believe that this issue has not yet been satisfactorily treated. Lipfert (*13*), in his recent paper citing Viren (*14*), points out the need to account for the broad regional variations in mortality before the more localized variations in pollution can be analyzed in order to minimize the influence of various regional biases. Spatial autocorrelations in the data can lead to spurious correlations or inflated estimates as in the case of time-series mortality analysis (see also below) when seasonal cycles or long-term trends are not properly filtered out from raw data.

The 1960 Lave and Seskin data set included variables to control for occupational mix, unemployment, climate, and home-heating fuel. Lipfert's recent analysis of 112 SMSA 1970 U.S. mortality and air pollution data included variables on drinking water quality, diet, an index of cigarette smoking, net population migration, and coal and wood home heating, in terms of fraction of all dwellings. In addition, for a subset of 69 SMSAs, annual average ozone exposure estimates (based on 1975 measurements) were also included. Lipfert's extensive regression analyses resulted in air pollution mortality risk coefficients which were sensitive to both the inclusion of the new independent variables and the selection of data sets (111 SMSA vs. 69 SMSA). Drinking water quality, ozone concentration, percentage of net migration, and redefined nonwhite variables all had important effects on the regressions. Coefficient estimates for ozone, although considered exploratory in nature, were often found statistically significant either alone or with the TSP coefficient, which also was significant in these joint regressions at the $p \leq 0.05$ level. The estimates of TSP mortality risk coefficient when found to be significant were typically around 0.7 deaths/year/100,000 per $\mu g/m^3$. The annual average ozone coefficient was fairly stable, with values around 1.3 deaths/year/100,000 per $\mu g/m^3$, again only in regressions which yielded significant estimates for this variable. Estimates of the sulfate coefficient were less robust and often found nonsignificant at the $p = 0.05$ level. It is not clear, however, that the poor associations found between annual mortality and sulfates are due to collinearities among the air pollution variables or because of collinearities among sulfates and some of the other controlling variables included in those regressions. Because correlation of the estimates and partial coefficients of determination are not reported in the Lipfert paper, it is difficult to interpret the air pollution effects of individual pollutants separately. In the stepwise (optimal) regression models, prior to inclusion of ozone and/or TSP (which, incidentally, produced a significant sulfate coefficient in all of the first five steps), the regression estimates for sulfates were around 3.5 deaths/year/100,000 persons per $\mu g/m^3$. Finally, Lipfert (*13*) provided regression results of total mortality by sex and age group (≥ or ≤ 65 years) for models with and without threshold.

It is clear that significant controversy still exists in the area of cross-sectional mortality analysis. Researchers in this field have produced air pollution risk coefficients which ranged from statistically not different from zero to positive and highly significant estimates. Re-

searchers at Mathtech, Inc. (*15*) have recently summarized the TSP coefficients derived from cross-sectional mortality studies as a range of 0–0.47 deaths/year/100,000 persons per $\mu g/m^3$. Both the Evans and Lipfert analyses have generated nonsignificant (i.e., statistically not different from zero) as well as significant sulfate coefficients as high as 4 deaths/year/100,000 persons per $\mu g/m^3$. Unfortunately, the problem of omitted true causal variables or the proper specifications of the regression models is the main source of argument regarding what pollutant surrogate (if any) to choose in risk assessment based on cross-sectional evidence. We believe that by improving the exposure metric used in these studies, by examining spatial autocorrelation and by employing other forms of residual analysis, we can substantially reduce specification errors in cross-sectional mortality investigations.

The preliminary findings reported below from our latest research conducted at Harvard originates from our attempts to improve the exposure metric used in coventional cross-sectional mortality studies. However, since we have not yet constructed the final or "best" set of models to be used in estimating mortality risk coefficients for particle and gaseous pollutants, the findings presented here should be considered interim. More specifically, we suspect that the magnitude of the coefficient estimates from our current basic model will change after including other variables and controlling for regional effects following the spatial autocorrelation analysis.

Exploratory Regression Analysis

It is well documented that the most toxic substances contained in ambient particles are highly concentrated in the fine particle (FP) mass ($d_a \leq 2.5$ μm). Moreover, it is these fine particles which can reach the deepest recesses of the lung and thus have long residence times in the body, increasing their damage potential. It is likely, therefore, that our ability to detect health effects of exposures to particle pollution through epidemiologic studies will substantially improve when better particle measures are employed. Using fine particle or inhalable particle (IP) mass ($d_a \leq 15$ μm) as new particle exposure variables, we hope to determine which components of TSP are associated with mortality (or morbidity) caused by population exposures to air pollution. For this purpose, we recently examined 1980 cross-sectional mortality in the U.S. using fine and coarse particle data collected as part of EPA's Inhalable Particle Monitoring Network (*5*, *6*).

To facilitate a comparison of 1980 results with those from a 1960 analysis, the multiple regression model described in Özkaynak et al. (*4*) and in Evans et al. (*3*) was chosen for our preliminary analysis. In re-analyzing Lave and Seskin's 1960 data, a relatively simple base model consisting of seven socioeconomic explanatory variables and total mortality rate (TMR) as the dependent variable was used. Various pollution variables, alone and in combination, were added to the base model to assess the mortality effect of each pollutant or combination of pollutants.

The socioeconomic variables are controlling variables intended to explain nonpollution-related mortality and to prevent confounding. The choice of variables was justified on the basis of physical plausibility and explanatory power in previous analyses. The variables included in our recent regression-based analysis were: percentage of population over 65 years of age, median age of the population, percentage of the population who were nonwhite, decimal logarithm of the population density, percentage of the population with four or more years of college, and percentage of poor.

The model that we employed contained the same socio-economic variables used in the 1960 SMSA data set with the exception of the smoking index. The pollution variables studies were annual average TSP, sulfates, fine particles, inhalable particles, and source-specific components of FP. For each pollutant in each of 113 SMSAs data from a single monitoring site (preferably center city-commercial sites) were used to represent that SMSA's mean pollution.

The most important analyses of the 1980 SMSA data were performed on one of three subsets of the full data base after removing two or three outliers (El Paso, TX, Tampa, FL, and Phoenix, AZ, in analyses involving the inhalable particle mass) and missing values. The first subset contains the 98 SMSAs with usable sulfate data; the second set contains 89 SMSAs with sulfate and estimated IP and FP data; and the third subset contains the 38 SMSAs with measured IP and FP data. TSP data were available for all of the SMSAs included.

Approximately 50 regressions were performed. Two-thirds of these regressions focused on relationships between airborne particles and total mortality rates. The regressions involved 11 measures of airborne particles and were performed using the three basic subsets of the data.

The most essential regressions were single or joint pollutant estimates with TSP, SO_4, estimated fine particle mass (E-FP), and estimated inhalable particle mass (E-IP). For the 98 and 89 SMSA analysis, estimates of IP and/or FP were needed for the cities in which these pollution variables had not been monitored. IP levels were estimated using the approach of Trijonis (*16*). Although different techniques were tested to estimate FP concentrations, the final method selected was based on the regional FP equations developed by Özkaynak et al. (*17*). This method provided estimates for 89 SMSAs. For the 98-SMSA analysis, FP estimates from Trijonis (*16*) were used for the 9 SMSAs which could not be adequately represented by the FP equations in Özkaynak et al. (*17*). It is important to note that seven of these nine SMSAs had TSP and E-IP concentrations considerably higher than the overall mean TSP and E-IP levels, whereas TMR for these SMSAs were lower than the average value of 849 per year per 100,000.

Except for the 89-SMSA analysis, TSP and E-IP coefficients were not found to be statistically significant at the $p = 0.05$ level. Furthermore, in all of the joint regressions, either with sulfates or with E-IP, both the

TSP and the IP coefficients were also found to be nonsignificant. In contrast, the mean sulfate variable was the most consistent predictor of mortality. This was true for total mortality, total mortality adjusted for accidental deaths, residual total mortality, and for cardiovascular and neoplastic disease-specific mortality. The sulfate coefficients were typically positive and were commonly significant at the $p < 0.001$ level. The FP coefficient was also statistically significant at the levels of significance $p = 0.05$ or better. The highest FP coefficient estimate and its associated significance level of $p < 0.001$ was for the 89 SMSA analysis. In joint regressions with the sulfate variable, either the fine particle coefficient (the 98 SMSA analysis) or both of the coefficients (the 89 SMSA analysis) became nonsignificant. This result was not unexpected because of the substantial collinearity between the two variables ($r = 0.67$).

The results from these preliminary cross-sectional mortality analyses can be summarized in terms of ranking of the estimated partial regression coefficients (B_i) for the pollutants and the corresponding elasticities (e_i)—that is, change in the expected total annual mortality with a unit of change in the level of ambient pollution. Therefore, in summary:

Overall or average from three sets of analyses indicated that:

$$B_{TSP} < B_{IP} < B_{FP} < B_{SO_4}$$
$$e_{TSP} < e_{IP} < e_{FP} < e_{SO_4}$$

In the 89 SMSA analysis in which all of the B_i were significant, we found:

$$B_{TSP} < B_{IP} < B_{FP} < B_{SO_4}$$
$$e_{TSP} < e_{IP} < e_{SO_4} < e_{FP}$$

The predicted air pollution mortality effects or elasticities were somewhat higher than those obtained from the Evans et al. (*3*) study of the 1960 cross-sectional mortality (in that analysis typically 3 to 4% of total mortality was associated with sulfate pollution). However, the preliminary sulfate or FP elasticities from our work are generally consistent with the range of elasticities implied by the significant coefficients reported in Lipfert (*13*).

The above noted trends of increasing magnitude and statistical significance of the pollutant effect, as the surrogate is changed from TSP to IP to FP or SO_4, is consistent with biological and statistical expectations. Biologically, fine particles or sulfates represent the respirable component of particles which often contain the most toxic compounds (e.g., trace metals, acid sulfates, organics, etc.). Statistically it is expected that the inclusion of nonrespirable coarse particle mass into the analysis (as part of the IP or TSP mass measures) introduces measurement errors, thus decreasing the magnitude and the precision of the estimates.

In conclusion, we note that the results from the preliminary cross-sectional mortality analysis of the 1980 data indicates the importance of considering correct particle size and composition data in modeling of particle pollution. However, while the results were generally plausible and consistent, because of the preliminary nature of the analyses, they must be viewed as suggestive. The basic but simple model used in these investigations suggests the need for testing other model specifications including further diagnostic tests to study the spatial correlation structure of the residuals.

Time-Series Mortality Analysis

In the absence of long-term studies designed specifically to detect the mortality effects resulting from exposures to air pollution, attempts have been made to utilize available mortality and pollutant index data to search for a possible cause-effect relationship. Time-series analysis provides one means by which to test for such a relationship. Using many years of daily observations, the time-series approach uses statistical methods to estimate the influence of daily air pollution on daily mortality. There are, however, several issues which preclude direct estimation of effects and cloud the interpretation of the results obtained. One issue is that of "temporal confounding" (i.e., the potential existence of variables which are correlated in time with air pollution and exert influence on mortality independently of air pollution. Temporal confounding has been considered as: low frequency (seasonal cycles or trends) and high frequency (day to day variations). For this reason most time-series investigations have included weather variables (after appropriate filtering) in their regressions. In particular, Schimmel (*18*) included nine functions of temperature as explanatory variables in his regressions. Clearly, too little control could lead to overestimates of pollution effects, while too much control could lead to underestimates. Thus, without a sound basis for choice of model, it is impossible to know whether any particular choice leads to too little or too much control. However, in the absence of better information, the procedure of choice is to continue filtering until the residuals behave like white noise.

Another issue limiting the interpretation of time-series results is the expression of coefficients for particle air pollution effects in terms of Coefficient of Haze (COH) or British Smoke (BS), rather than, for example, total suspended particulate (TSP) or fine particle (FP) concentrations. The latter set of units (or other particle-size-classified mass concentrations) would be of more direct use to policy analysts and might also be physiologically interpretable. However, soiling data are almost always used in time-series studies because they are the only historic data generally available on a daily basis for extended periods in large cities.

As previously mentioned, the lack of theoretical underpinning of the temporal confounding hypothesis may lead to uncertainties in choosing methods for its control. In this paper, we present the preliminary results of our continuing examination of 14 years of daily mortality and air pollution records for New York City. We summarize here our results from both the initial and more

recent time-series investigations which tested the sensitivities of results to plausible modeling choices and to the application of more rigorous time-series methods.

Exploratory Sensitivity Analysis

The data used in the sensitivity analysis was a subset of the New York City data set obtained from Dr. Herbert Schimmel (*18*). It consisted of 14 years (1963–1976) of daily measurements of mortality (the sum of heart, other circulatory, respiratory, and cancer mortality), coefficient of haze, sulfur dioxide (SO_2), and temperature.

Prior to regression analysis typical of time-series mortality studies (*18,19*), an attempt was made to remove the assumed low-frequency confounding by passing each variable through a "filter" that removed its slow-moving components. A filter commonly used by Schimmel was one which re-expressed each variable as residuals from its centered 15-day moving average. Since we viewed the 15-day moving average as a somewhat arbitrary choice, we sought to examine the properties of, and the sensitivity of results to, other filters.

Our initial exploratory analysis involved estimating regression coefficients for COH and SO_2 after all variables were preprocessed with one of several filters (*5*). The first set of three filters consisted of taking residuals from 7-, 15-, or 21-day moving averages of the data. These three filters removed primarily low-frequency components from the data. The next three filters were "ideal" in the sense that they performed precise frequency cuts. They removed all cycles in the data which fell beyond the indicated period measured in days. For example, the ideal 2-4 filter removed all cycles with periods of greater than 4 days. The three ideal filters (ideal 2-4, ideal 2-7, and ideal 2-14) focused on high-frequency bands of varying widths.

Overall, the regression coefficients for COH ranged from 1.2 to 5.4 daily deaths per unit COH, most of them being statistically significant ($p \leq 0.05$). The lowest value was obtained when only periods of 2 to 4 days were evaluated. The highest coefficient resulted when no filtering was applied. For the six filters which isolate various high-frequency bands, the results ranged from 1.2 to 2.0 daily deaths per unit COH. The results were also in qualitative agreement with pollution coefficients increasing as the frequency band width increases or longer periods are included in the regressions. Since these six filters represented a range of reasonable approaches to removing low-frequency confounding from the analysis, we concluded that the range of coefficients derived from them should also provide the relevant sensitivity measure. Similarly, a reasonable range of variations in the specification of temperature resulted in coefficients ranging from 1.3 to 1.8 deaths per unit COH. The range of results from these initial sensitivity analyses provided a measure of the magnitude of uncertainties in the risk coefficients due to uncertainties in modeling assumptions. The risk coefficients reported by Schimmel (*18*) were near to the lower end of our coefficient range.

In summary, by performing a number of sensitivity analyses we were able to generate a fairly consistent set of estimates. However, as mentioned in Özkaynak et al. (*5*), these initial estimates were influenced by the following technical limitations: (1) population exposure misclassification occurs in utilizing pollution data from one fixed ambient monitoring site; (2) the exposure metric, COH, is imperfectly related to respirable particle mass concentration; and (3) the range of exploratory models we initially fit may not have been diverse enough. To overcome some of the above noted limitations we have recently undertaken a new analysis of the same data. Preliminary results from this ongoing investigation are summarized in the following section.

Recent Re-analysis of the New York City Data

Our latest re-analysis of these data differs methodologically from Schimmel's and leads to somewhat different conclusions. The primary methodological difference is that our analysis uses standard time-series methods to control for covariates such as temperature and to handle the problem of autocorrelation. In application of these methods we sought parsimony. The previous analysis was extended by adding records of visibility and weather from three New York area airports—JFK, LaGuardia, and Newark. The purpose of including daily visibility records from the three New York area airports was (a) to examine the spatial homogeneity of daily air pollution in New York City and (b) to use visibility as a surrogate for aerosol extinction (b_{ext}) or for fine particle pollution as discussed in Özkaynak et al. (*17*). The data set and the preliminary results presented here are described more fully in Garsd et al. (*20*).

The principal findings from our recent analyses can be summarized as follows. The most salient feature of the mortality series was the occurrence of a seasonal component. Seasonality was also noted to exist in the other series considered, thereby (due to spurious correlations) confounding direct regressions involving mortality, air pollution, and weather variables. Therefore, a simple trigonometric expression was used which removed the temperature cyclic component and rendered nonseasonal temperature nonsignificant. However, the mortality records also showed an additional seasonal component above and beyond seasonal temperature, but weekly and monthly cycles were found nonsignificant. For this reason, in conjunction with the seasonal component, a simple, stationary autoregressive term was employed to exhaust the time-series structure of the mortality records. Also in the analyses performed, consideration of interactions, as well as lagged regressions, did not improve the model's predictive ability.

Description of Model and Results

A simple linear model of the following form was used in most of our investigations:

$$Y_t = B_0 + B_1(X_1)_{t-k} + B_2(X_2)_{t-k} + \ldots + B_{p-1}(X_{p-1})_{t-k} + E_t \quad (1)$$

This expression is called a first-order model with $p-1$ independent variables. In our investigations Y_t corresponds to either total mortality (M_t) or respiratory mortality $(\mathrm{RESPM})_t$; the B are parameters to be estimated from the data; E_t in this case is a purely random process with zero mean and constant variance; the $(X_i)_t$ are known constants, namely, the recorded values of the air pollution and temperature measurements at time t. For integer values of $k(0$, the model represents lag effects of $(X_i)_t$ on Y_t. Obviously, Eq. (1) and its assumptions do not exhaust the possible cases of interest. For this reason, we have also considered other extensions of this model (*20*). In this paper, however, most of our results are related to analysis performed with this basic model and with its modifications.

Because seasonality was the most explicit feature of the mortality data, this component dominated the estimated autocorrelation functions. Therefore, we investigated this matter further by utilizing a simple time-series term containing a cycle such as:

$$(X_i)_t = B_i' \cos(\omega t + \phi) + E_t \quad (2)$$

where B_i' is the amplitude, ω is the (angular) frequency, and ϕ is the phase angle in radians. The period P is assumed to be 365 days and is related to ω by the equation: $\omega = 2\pi/P$.

It should be noted at this point that in addition to M_t, all the series considered also contained components of the type in Eq. (2). In particular, pollution-related variables showed significant clear seasonal behavior with a peak in the winter for COH and SO_2, and in the summer for B_{ext} (estimated from visibility records from the JFK airport). However, the strongest case corresponds to temperature, for which the trigonometric expression (2) accounts for up to 90% of its variability.

With the introduction of Eq. (2), the autocorrelation structure of the residuals was cleared of a seasonal component. Moreover, weekly, monthly, bimonthly, quarterly, and semiannual components fit to those residuals failed to be significant. The remaining autocorrelation in the residuals, however, does not correspond strictly to one of white noise; rather, it is suggestive of the occurrence of a strong autoregressive component and is also consistent with the presence of a declining trend. Because nonstationary autoregressive components are capable of representing trends, we considered in our analysis a simple autoregressive expression of the form:

$$(X_i)_t = B_i'' (X_i)_{t-1} \quad (3)$$

Time-series were then performed with the model given by Eq. (1) and in a multivariate context by including the relationship defined in Eq. (2) and (3) into the linear model specified by Eq. (1).

Using the results from this analysis, preliminary estimates of excess deaths (e_i) or elasticities for the pollution variables were calculated. Unlike previous analyses performed with this data set (*18*), in our time-series analysis SO_2 levels were found to be significantly correlated with mortality ($e_{SO_2} = 2.3\%$). Results indicated that in addition to SO_2, COH is also a significant contributor to the excess deaths ($e_{\mathrm{COH}} = 2.4\%$). B_{ext} variable, used as a surrogate for fine particle pollution, was also found to be significant but with a smaller contribution of excess daily deaths (about 1.2%). The total of estimated air pollution-related excess deaths was about 6%.

While these results are interim, they indicate that ambient air pollution of a large urban area is contributing to mortality. In order to verify our results, we are in the process of analyzing 1 year at a time and by each quarter. This time-series analysis appears to corroborate the results from cross-sectional mortality studies and indicates that particulate air pollution, even at current levels, could be of concern for public health. [See also Evans et al. (*3*) for the nature of the relationships between cross-sectional and time-series studies.]

There are, however, several limitations of this preliminary re-analysis. The results reflect the aggregate analysis of 14 years of data. During this period stringent air pollution controls (particularly for SO_2) were implemented. This had the dual effects of dramatically reducing the levels of SO_2 and simultaneously altering the composition of the aerosol. Although a first attempt to analyze this question failed to demonstrate differences in pollution coefficients for 1963 to 1970 and 1971 to 1976 more thorough attention to this matter is warranted. The results reported here are based on air pollution data for one monitoring station and visibility data from one airport (JFK). The importance of using these possibly crude surrogates for exposure has not been critically examined. During the 14-year period there were several heat waves and influenza-pneumonia epidemics. The influence of these events has not been considered in any detail in our preliminary analysis. The preliminary analysis focuses on total mortality, while analysis of respiratory and/or cardiovascular mortality may be of more interest. Finally, the estimated autoregressor term was very significant, explaining about 20% of mortality in the preliminary regressions. However, further efforts to determine the variables which underly this autoregressive phenomenon are needed.

Preliminary Analyses of the Morbidity Effects of Ambient Pollution from the Health Interview Survey

Published literature on observational epidemiology does not typically provide an adequate information basis on which to support studies on the nature and the extent of the relationships between human morbidity effects and population exposures to respirable particles. In particular, most of the available studies (*21–23*) examine relatively high particulate levels, and one must extrap-

olate beyond the range of concentrations observed in these studies to derive a risk coefficient appropriate for typical exposures in the U.S. This approach must be viewed cautiously as very little evidence exists to indicate whether or not the relationships observed at higher particle concentrations hold at lower concentrations. However, as noted by the EPA (*8*) and in the published literature (*24*), it is likely that there is a continuum of effects at all levels. As quoted in EPA's recent OAQPS staff paper on the review of the NAAQS for particulate matter:

> The data do not, however, show evidence of clear population thresholds, *but suggest a continuum of response* with both the risk of effects occurring *and* the magnitude of any potential effect decreasing with concentration. (emphasis added) (*8*).

In an attempt to overcome the problems of extrapolation we have been utilizing recent measures of ambient fine particles, as well as their indicators derived from routine airport visibility observations. To study the associations between ambient pollution and human disability, we have been analyzing the 1979 National Health Interview Survey (HIS) of the National Center for Health Statistics (NCHS). Our initial analysis has focused primarily on the HIS disability outcome variables, total Restricted-Activity Days (RADs) and Work-Loss Days (WLDs). In addition to the principal health outcome variables, RAD and WLD, we have studied another disability variable, minor restricted-activity days (MRAD), utilized in Portney and Mullahy (*25*). MRAD data reflect individuals who report RADs but who did not also have work-loss or bed-disability days.

In our preliminary analysis, reported in Özkaynak et al. (*26*), these health outcome variables were matched with representative ambient particle concentrations for 12 large SMSAs. The particle mass measures considered in this analysis were fine particles (FP) and sulfates (SO_4^{2-}). In order to account for the potential synergistic, interactive, or confounding effects of other gaseous pollutant species, we included a daily maximum ozone (O_3^{max}) variable. Because the 1979 Health Interview Survey reports the health status of individuals over 52 two-week recall periods, we used a two-week average for all of the exposure variables mentioned. Furthermore, in conjunction with these particles and ozone exposure variables, we used a number of demographic and behavioral health determinants in order to account for factors other than air pollution, which may influence an individual's health.

Our initial modeling efforts involved ordinary least squares (OLS) and logistic regression analysis, using HIS, to estimate the potential morbidity effects of air pollution, weather, and demographic factors. Basic categorical variables used in our regression analysis included income, city, sex, residence, work status, smoking, season, marital status, health status, and occupation. Based on previous descriptive analyses of the data, these variables were selected to control for the possible confounding.

Most of the models considered included a segment of the survey population which reported some form of chronic limitation. (We have placed special attention on this group because the preliminary descriptive analysis indicated the possibility of air pollution effects only in this category.)

Preliminary analyses of the 1979 HIS survey data (and related demographic, weather, and air pollution exposure variables) suggested that a number of factors, mostly demographic and behavioral, influenced disability rates. In general, the regression analyses found only weak correlations between available pollution data FP, SO_4^{2-}, O_3, and TSP) and the health variables (RAD, MRAD, and WLD). Two-week average fine particle concentrations (based on daily estimates of FP from airport visual range observations) were noted to be associated with the observed RAD and MRAD rates more often than the other pollution variables. However, the relationship was somewhat unstable from model to model and exhibited only marginal statistical significance, i.e., $p = 0.03$ to $p = 0.09$. Because the findings presented in Özkaynak et al. (*26*) are preliminary, these results must be viewed only as useful for the purpose of sensitivity analysis. Further refinements in the selection of the most appropriate model for examining the associations between the variables of interest are definitely needed.

Summary and Conclusions

Quantitative estimation of the relationships between current levels of ambient pollution and human morbidity or mortality is hampered by the limitations of the available data bases. We have discussed several causes for this problem.

An important source of limitation in the epidemiologic analyses of air pollution health effects is the use of central-site pollution data as opposed to more accurate estimates of personal exposures. Another important limitation of existing studies is that a majority of these studies were conducted at air pollution concentrations exceeding present levels of concern for standard setting and risk evaluations. Furthermore, most of the past epidemiologic data are based on pollution mixes that are often different from the present composition of ambient aerosols. Because particles were not differentiated by size, chemical properties, metal composition, or acidity but by poor pollution measures (e.g., TSP, BS, COH) it is very difficult to reliably predict pollutant-specific exposure-response relationships. Thus, biases due to misclassification of exposures or failure to account for personal and/or indoor exposures influence the outcome of most risk assessment studies of air pollution. Finally, limitations of sample size in most observational analysis and the lack of sufficient number of studies which provide morbidity data limit our ability to detect health effects of air pollution which may be small but significant.

Taking these concerns into consideration, we have tried to estimate the likely range of mortality and mor-

bidity impacts of air pollution. In our investigations we mostly utilized recent data sets on particle pollution and human health. There were several interesting findings from our recent epidemiologic investigations of the mortality and morbidity effects of exposures to airborne particles.

Preliminary cross-sectional analyses of 1980 total mortality in Standard Metropolitan Statistical Areas (SMSAs) across the U.S. indicated that the use of either fine sulfate or particle health risk coefficients provides an improvement over previously employed particle mass measures (especially TSP). These statistical analyses showed SO_4^{2-} and FP measures to be more consistently associated with mortality health effects than either TSP or IP.

These preliminary findings were consistent with the biological expectations that the fine particles would pose greater health risks than the less toxic or non-respirable coarse particles that are included in the IP and TSP mass measures. Although quite intriguing, these results must yet be viewed as suggestive rather than conclusive because of the preliminary nature of the analyses. Further model specifications and methodological extensions are needed to confirm our findings. Also, due to statistical collinearities between the FP and sulfate variables it was not possible in our analyses to discriminate the effects of these pollutants in joint regressions. Apportioning fine particles or total sulfates into their various constituents (such as acid fraction, carcinogenic organic compounds, or toxic metals) by direct measurements or statistical methods should improve the power and utility of cross-sectional studies.

Time-series analysis of historical Coefficient of Haze (COH), aerosol extinction coefficient (B_{ext}), sulfur dioxide (SO_2), and mortality data collected in New York City indicated that all of these pollution-related measures were related to temporal variations in mortality. However, until validation studies in several other cities with different pollution characteristics and weather patterns are undertaken, the results derived from this analysis apply directly only to the mix of sources and time patterns of concentrations observed in NYC between 1963 and 1976. Nonetheless, an interesting finding was that, by using mean exposures and expressing mortality risks in terms of similar units, our latest NYC time-series analysis produced mortality risk estimates for air pollution that were similar to those predicted by recent cross-sectional analysis of U.S. mortality data. While preliminary in nature, these findings are consistent with, and seem to support, the suggestion that the mortality effects of urban air pollution can be 6% or more of the total deaths. Furthermore, the often found significant associations between air pollution and mortality in statistical studies confirms qualitatively the fact that current pollution levels in the U.S. are likely to cause premature mortality.

A preliminary epidemiologic study using the National Health Interview Survey morbidity data and an index of fine particle pollution (based upon airport visibility data) indicated a weak correlation between fine particle air pollution and human morbidity as measured by minor restricted-activity days. This relationship persisted even when the analysis was controlled for the confounding effects of other pollutants as well as for city-specific effects and socio-economic factors.

There are several avenues of research which may yield more useful assessments of the population health risks resulting from exposures to acid precipitation precursors.

For future air pollution health effects studies, we need combinations of both improved exposure and health measures. In particular, exposure and response data on acidic aerosols and oxidants involved in the formation of acid precipitation are vitally needed. We clearly need more prospective health studies to enable characterization of chronic and acute health effects. Also needed are better estimates of personal exposures to particles, acid aerosols, ozone, and nitrogen oxides, including information on indoor/outdoor particle exposures by source and chemical composition. However, since new data sets will take a decade or two to develop, existing retrospective population health data sets should continue to be re-analyzed with more representative exposures estimates by accounting for misclassification biases. Especially for the study of morbidity effects of air pollution, existing data bases should receive additional attention. For this purpose, historic data sets might be re-analyzed using relative humidity corrected airport visibility data for estimating ambient fine particle concentrations. In addition, existing health surveys such as HIS and NHANES should be expanded to better accommodate analysis of air pollution effects. In order to address questions regarding response times associated with observed biological effects of air pollution, various exposure-averaging times should be examined. Particular attention should also be paid to improving exposure estimation by incorporating available personal monitoring data and exposure modeling techniques. In particular, cross-sectional and time-series mortality analyses can be greatly improved by incorporating data on acid aerosols, H^+/SO_4^{2-} ratios, and fine particle mass measures by source-class. Finally, associations obtained between air pollution exposures and different measures of human morbidity should be compared in terms of their significance and biological plausibility.

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