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ANALYSIS OF HEALTH EFFECTS RESULTING FROM POPULATION EXPOSURES TO AMBIENT PARTICULATE MATTER

HEALTH AND ENVIRONMENTAL EFFECTS DOCUMENT

1983

Prepared by:

Harvard University
Energy and Environmental Policy Center
140 Mt. Auburn St., Cambridge, MA 02138

Assessments performed under the direction of:

J.D. Spengler, Ph.D. - P.I.
Harvard School of Public Health

J.J. Harrington, Ph.D. - Co-P.I.
Division of Applied Sciences, Harvard University
and Harvard School of Public Health

N.M. Laird, Ph.D. - Co-P.I.
Harvard School of Public Health

F. Speizer, M.D. - Co-P.I.
Harvard Medical School

R. Wilson, Ph.D. - P.I.
Physics Department, Harvard University

Principal Authors of the report:

H. Özkaynak, Ph.D. (Project Manager); G.D. Thurston, Sc.D.;
T.D. Tosteson, M.A.; C.M. Smith, M.S.; P.L. Kinney, M.S.; B.Beck, Ph.D.;
W. Skornik, M.A.; S.D. Colome, Sc.D.; A. Schatz, M.S.

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EXECUTIVE SUMMARY

Combustion-related energy systems represent a major source of airborne particles. An assessment of the current and future health impacts of energy systems requires an understanding of the nature, magnitude and uncertainty of potential health effects from these particles. This generic Health and Environmental Effects Document (HEED) on airborne particles presents results from the second year of an ongoing study of human exposure and response to ambient particulate matter. As such, it also draws from information included in our 1982 HEED. The 1983 HEED emphasizes our efforts over the past year and continues to develop estimates of the magnitude and range of potential health effects from exposure to particles.

Using published findings and re-analyses of data available from epidemiologic, toxicologic and aerometric studies, we have, in this report, attempted to evaluate effects of particles. Where the available data permit, we have related health effect outcomes (which include morbidity and mortality) to concentrations of particulate matter according to size, composition and source of aerosol.

Special attention is given to the uncertainty associated with estimates of effects. Deficiencies are identified in the data bases required to make assessments, and recommendations are given for future studies and analytical efforts which would serve to better identify and quantify impacts.

INTRODUCTION

A wide variety of particles exist in the ambient environment. These particles have been found to vary in size, shape, concentration and composition, both spatially and temporally. Through condensation, evaporation and chemical transformations gases may become particles and vice versa. Moreover, different forms and types of particles are known to have varying biological activity, so that a characterization of airborne particles for health studies is complicated (Section III.1). In this work, we have recognized these differences (see Appendices I and II), and have expended considerable effort to characterize aerosols in order to examine the influences of particle size and composition on the estimation of health effects.

There are many complications involved in applying epidemiologic or laboratory analyses of particle pollution to assessments of human health risk. Observational epidemiologic studies of community air pollution exposures have not generally been designed to provide dose-response relationships suitable for risk assessment (Section II.1 and Appendix II). Therefore, the existing data base is limited. Most exposure measurements for these studies were for the total mass of suspended particles, or for the reflectance of light off bulk particle samples such as British Smoke (BS). These qualities are incomplete characterizations of an aerosol and, more importantly, are probably not

parameters of greatest interest for an understanding of health effects. Furthermore, the frequency and duration of pollutant measurements employed were usually too limited in scope to allow a separation of the chronic versus acute effects of particles. Additionally, the observational epidemiologic literature represents exposure levels that are generally above current and projected concentrations in the United States. As a result, assessments of risk have relied heavily on the limited data bases that are available for lower concentrations and/or extrapolated findings from the studies of higher concentrations. Thus, currently available literature on health effects from community air pollution cannot alone be expected to fully disentangle the separate actions of individual pollutant sources or aerosol components from one another. In contrast, laboratory studies of humans, animals or cellular systems provide control of factors not possible in observational epidemiology. Insights may be provided into mechanisms of action and relative potency for different particle sources and components. However, the control of experimental parameters brings with it new difficulties in projecting back to the more complicated free-living human environment. Thus, while historical epidemiologic and laboratory studies provide valuable sources of information on the health effects of particle air pollution, each methodology also has inherent limitations.

Recognizing the above-noted data analysis limitations, we began to combine the evidence and understanding from individual toxicologic, epidemiologic and exposure assessment data sets into a single coherent and consistent analysis. In most cases, it was necessary to take aerometric data sets developed for other purposes (e.g., the EPA's fine particle network data) and apply them to compatible epidemiologic and toxicologic data. Major efforts undertaken this year to derive health potency factors for airborne particulate matter included:

(1) Improvement of particle exposure estimates. This was accomplished using recent fine particle data sets to develop general relationships with atmospheric visual range records, as well as with historic records of other particle metrics.

(2) Application of improved estimates of particle exposures to existing cross-sectional mortality and morbidity studies. The data examined included the 1960 and 1979 total mortality data for U.S. Standard Metropolitan Statistical Areas (SMSA) and the 1979 National Health Interview Survey (HIS) morbidity data for 12 SMSAs.

(3) Evaluation of carcinogenic and non-carcinogenic potential of airborne particles using *in vitro* and *in vivo* bioassay data. Available data were restructured and a comparative relative potency model applied to Ames bioassay data for a variety of particle types.

A major objective of this HEED has been to address uncertainties and gaps in understanding when reporting epidemiologic, toxicologic and exposure results, thereby providing an integrated framework useful for both risk assessment and policy making. Where possible, quantitative risk estimates are derived. The source of these estimates and their associated uncertainties are described in the following sections. Throughout this effort we have also identified remaining gaps in knowledge and data base limitations. This has led to recommendations for future studies and analyses that will serve to further define the nature, magnitude and uncertainties of particle pollution health risks.

EPIDEMIOLOGIC ASSESSMENT

In this HEED, we have continued our analyses of the health effects of particulate matter in the general population. This work (presented in Section II) includes the review and reanalysis of previously reported data bases, a synthesis of published findings, and an original analysis of health data using new models or recent data. The objectives of this work are to: (1) identify health outcomes associated with different levels of pollutants; and, (2) characterize the uncertainties of findings and the sensitivities of results to choice of data base and analysis methods.

Observational Epidemiology: Review of Morbidity Literature

Existing epidemiologic literature on the morbidity effects of human exposure to particulate matter has been summarized herein. The outcomes considered are various measures of respiratory health, including symptoms and pulmonary function. Uncertainty is introduced in the relationships between the measured outcomes and particulate pollution because of uncertain exposure estimates, confounding variables, and the high pollutant concentrations typical of this literature. Upper and lower respiratory symptoms and reduced pulmonary function has been found in associaton with long-term exposure to TSP-equivalent concentrations in excess of 180 ug/m^3 (Ware et al., 1981). Short-term (24-hour) concentrations of particles have been associated with hospital admissions. A recent study indicates a relationship between total and respiratory emergency room admissions with particulate matter over a wide range of particle concentrations (Samet et al., 1981). The role of particles in that study was statistically significant, but it explained only a small proportion of the variance in emergency room visits. Particulate matter is not expected to have a greater role in emergency room admissions, but the size of its effect leaves open the possibility that other factors (not accounted for in the analysis) could be responsible for the observed relationship. Very few studies have addressed acute health effects of particle pollution below levels of 1000 ug/m^3 (measured in 24-hour average TSP equivalent concentrations). Those which have studied effects at lower concentrations (Martin, 1964; and Lawther et al., 1958 and 1970) show an increase in hospital admissions for cardiac and respiratory illness as well as for bronchitis symptoms. Even in these

studies, the average ambient concentrations of TSP were high relative to current levels in the U.S. However, the data for short- and long-term exposures to particulate matter do not suggest existence of effect thresholds. For this reason, simple linear coefficients have been derived relating particle concentrations to respiratory infections, hospitalization, and symptoms of chronic bronchitis (see Table 1).

While the above-noted extrapolation problem is a major contribution to uncertainty of morbidity risk estimates, other sources of uncertainty are also important. These can be categorized into sampling and non-sampling errors. Sampling errors refer to the lack of precision or the representativeness of a sample result. This error occurs when a particular sample analyzed happens, by chance, to be dissimilar from the general population in some way. Non-sampling errors, on the other hand, include: biases in determining personal exposures from central site monitoring data; a lack of historical chemical- or size-selective measurements of particles; confounding factors related to personal habits such as active and passive smoking, alcohol consumption, etc.; and, cross-community difference in particle source composition, fuel mix, type of housing, and population migration, among others. Such sampling and non-sampling errors are inherent, not only to the morbidity effects discussed above, but also to all of the other morbidity and mortality investigations which follow.

Morbidity Analyses from the National Health Interview Survey

The 1979 National Health Interview Survey of the National Center for Health Statistics provides a data base on individual level health status for approximately 100,000 people. The 1979 survey used a two-week reference period for the health questions and collected a variety of economic and demographic information. On one-third of the sample, the survey also included a detailed questionnaire on smoking habits for adults. In this phase of our research, we used the HIS outcomes of total Restricted-Activity Days (RAD) and Work-Loss Days (WLD), relating them to particle exposures in different SMSAs. Unfortunately, particle mass measurements in the U.S. have typically been made every sixth day in most communities. Since the HIS data base specifies the health effects outcomes in terms of incidences over a two-week period, it became essential to improve upon the available exposure metrics.

Using fine particle and visibility data collected in an initial set of 12 SMSAs, we were able to develop site-specific daily estimates of fine particle exposures, which could then be averaged over the two-week recall periods employed by the survey. In Appendix 1 of our 1982 HEED, we developed the theoretical basis of this approach for estimating fine particle exposures using aerosol extinction coefficient (from airport visibility data). As indicated by numerous researchers [see, for example, Trijonis and Yuan (1978), U.S. EPA (1979a) and Section II.2 of this HEED] under most circumstances, this method yields reliable

Table 1

Summary of Principal Results from the Assessment of Population Health Effects Resulting from Exposures to Airborne Particles*

Assessment Category	Type of Analysis	Type of Health Response Considered	Exposure Variable or Particle Type	Estimated Exposure/Response Coefficient(s)	Units of Estimated Coefficient	Principal Sources of Uncertainty
Morbidity Effects	Review of Morbidity Literature	Childhood Lower respiratory infections	BS	60 ± (**)	Cases/year per 10^3 persons per ug/m^3	•Data base limitations (inappropriate study design; limited observations of health and pollution variables; relevance of exposure metrics selected to physiologic responses studied) •Problem of low dose extrapolation •Confounding due to socio-economic, demographic and behavioral factors •Difficulty in dealing with large sampling and non-sampling errors
		Chronic bronchitis	BS	0 ± σ to 170 ± σ(***)		
		Acute respiratory disease	TSP	100 ± σ to 540 ± σ		
		Excess emergency room visits for respiratory diseases	TSP	8 ± σ to 13 ± σ		
		Excess total emergency room visits	TSP	20 ± σ		
	Analysis of 1979 Health Interview Survey and the EPA's IP Network data	Restricted-Activity Days (RAD) (for persons with chronic limitations)	FP	0 - 0.01	RAD per ug/m^3 FP per 2-week exposure	•An estimate rather than a direct measure of FP mass is used •Confounding effects of other pollutants and passive smoking, not considered •Statistical models used in the analysis may not be best suited to analyzing the HIS data •Confounding variables other than those included in the model may be important •Missing data question is not addressed •Difficulty in precisely matching the 2-week recall period with FP exposures
		Work-Loss Days (WLD) (for persons with chronic limitations)	FP	0 - 0.004	WLD per ug/m^3 FP per 2-week exposure	
Mortality Effects	Time-Series Analysis	Daily Mortality	COH	0.01 ± 0.007† to 0.02 ± 0.008	Deaths/day per 10^3 persons per COH	•COHs are mostly related to elemental carbon rather than particle mass •Questionable biological plausibility of using COH to study mortality effect of air pollution •Errors in estimating exposures for the population living in NYC by using single-station monitoring data •Model-based uncertainties
	Cross-Sectional Analysis	Annual Mortality	FP	1.3 ± 0.6	Deaths/year per 10^3 persons per ug/m^3 FP	•Analysis employed FP mass exposure estimates based upon central site data •Possible confounding variables not considered (e.g., gaseous pollutants) •Applicable to typical ambient aerosol composition and may not apply to extreme aerosols •Causality questions between ambient level exposures and mortality
			$SO_4^=$	2.6 ± 1.4		
Bioassay Considerations	Application of Relative Potency Model to Ames (TA 98, 89**) data	Increment in Relative Risk (RR) and Lung Cancer	Light-duty diesel	5 X 10^{-4} - 0.4††	Increment in RR of lung cancer per ug/m^3 extractable organics-years	•Limitations of human health data and characterization of true exposures •Adequacy of the relative potency model and the linearity assumption used in relating exposure to response •Exclusion of interactive effects •Variations in potency by different extraction protocols •Insufficient characterization of particle source types in terms of mass extractable organics
			Catalyst spark engine	6 X 10^{-6} - 0.3		
			Non-catalyst spark engine	3 X 10^{-7} - 0.3		
			Woodstove	5 X 10^{-7} - 0.03		
			Residential heater	4 X 10^{-7} - 0.03		
			FBC	4 X 10^{-6} - 0.3		
			Coal Combustion	1 X 10^{-6} - 0.1		
			Oil	1 X 10^{-6} - 0.2		

IMPORTANT NOTES

*The uncertainties surrounding all of the risk coefficients shown in this table are so large that the possibility of no effects (i.e., zero risk) should always be considered in mentioning or using them. Furthermore, the application of these coefficients demands extreme caution and specification of statements of qualifications and uncertainties. The reader is urged to consult the appropriate section of this NEED (Sections II.1, II.2, II.3, II.4 and III.1) for further information and guidance.

**Since these are mean estimates and do not include sampling and non-sampling errors, we suggest that, at the present time, the standard error (σ) of the estimates be considered half as large as the estimates themselves.

***These types of expressions are not confidence intervals, but rather the ranges of possible point estimates of exposure/response coefficients.

†Best estimate of coefficient range. However, alternative model formulations have been shown to give exposure/response coefficients up to 7 times higher than shown.

††Log-based confidence intervals.

estimates of fine particle concentrations. Moreover, because it provides area-wide as opposed to local exposure information, this technique is preferred over estimating fine particle mass from hi-vol measurements of TSP mass (cf. Appendix I.2).

In our preliminary analysis, two multivariate models (ordinary least squares and logistic regression) have been used to relate the fine particle exposure estimates to the health outcomes, while accounting for weather-related, demographic and available behavioral health variables. The continuing analysis of these data is reported in Section II.2 of the text, and a summary of the preliminary results is provided in Table 1. According to these estimates, persons with chronic limitations are expected to experience in a two-week exposure period 0 to 0.01 RADs and 0 to 0.004 WLDs per ug/m^3 of average fine particle mass concentration. However, since further model refinements are in progress, these numbers must still be considered to be tentative.

Uncertainties are introduced in this morbidity analysis through the use of a particle pollution index and through errors in measurement of the health outcomes. To this date, we have considered a single measure of pollution based upon a derived relationship between particle mass concentrations and visibility. The physical relationship between inverse of visual range and Fine Particle (FP) mass measurements is consistently linear (see Section II.2), but other pollutants have not been considered that might be related to fine particle and visibility levels. For instance, nitrogen dioxide is known to contribute to visibility reduction, while ozone covaries with sulfates (a major FP component) at some locations. Also, since we do no know the exact day of interview, the pollution measures are not perfectly matched with the periods considered by the retrospective health interviews. However, unlike past efforts to analyze such data, we have been able to obtain estimates of daily fine mass concentrations for the entire period, rather than occasional sampling data (e.g., every sixth day). As is always the case, confounding variables might include the effects of passive smoking or other unidentified factors related to personal exposures. With these caveats in mind, the major conclusion is that the models employed indicate an acute air pollution health effect, even when controlling for all available factors thought to relate to health outcomes. The outcome measure most sensitive to the effects of air pollution is restricted-activity days among people reporting chronic conditions including asthma, emphysema, chronic bronchitis, heart and mental conditions, among others.

Time-Series Mortality

In the absence of long-term studies designed specifically to detect the mortality effects of air pollution exposures, 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.

In Section II.3, we have re-analyzed 14 years (1963 - 1976) of data on mortality and air pollution for New York City. Utilizing a range of models designed to correct for assumed confounding due to low-frequency (seasonal) cycles and the effects of temperature on mortality, we have obtained a range of coefficients (see Table 1 and also Table II.7, in Section II.3) estimating the association between daily mortality and Coefficient of Haze (COH), a crude surrogate of exposures to ambient particles. The range of results provides a measure of the magnitude of uncertainties in risk coefficients due to uncertainties in modeling assumptions. The risk coefficient reported by Schimmel (1978) is near to the lower end of our coefficient range. Superimposed on our range of risk coefficients are the statistical uncertainties in each estimate, as quantified by its standard error. These range from 30 to 60 percent of the mortality risk estimates.

Combining the modeling and statistical uncertainties yields a range of daily risk that extends from 0 to 0.03 deaths per 10^5 persons per day per unit COH. However, as we discuss in Section II.3, this range is probably still too narrow because: (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 models we fit may not have been diverse enough. For example, independent weather influences on mortality may not have been fully considered. The first two issues tend to bias the estimated risk coefficients toward zero, while the third issue might result in positive bias.

Finally, the results quoted here (and summarized in Table 1) apply directly only for the mix of sources and time pattern of concentrations observed in New York City between 1963 and 1976. The general applicability of these results will not be certain until validation studies in several other cities with different pollution characteristics and weather patterns are undertaken.

Cross-Sectional Mortality

Cross-sectional analyses of mortality during one time interval (e.g., during a given year) provide another means by which to search for a particle pollution mortality relationship. Using recent (1979-1981) data on inhalable and fine particle mass, we have conducted preliminary cross-sectional regressions of total mortality on both socio-economic and particle pollutant variables. This analysis was performed to investigate the influence on cross-sectional analyses of particle measures such as IP and FP rather than TSP. Table II.11 in Section II.4 compares regression results for the various measures of particle pollution employed in the analysis. The regressions repeat prior analyses of 1960 SMSA data (see 1982 HEED, Section IV) incorporating recent information on particle size relationships and 1979-1980 Census, mortality, and fine particle pollution data. Important socio-economic variables (e.g., age, percentage

of non-white population, population density, etc.) are controlled for in these analyses, with the various particle size mass concentrations being sequentially replaced by one another as the particle pollution index in the regressions. These regressions indicate that, as coarse particles are eliminated from the measure of exposure (in going from TSP to IP to FP), the general tendency observed is a reduction in standard errors, an increase in statistical significance, and a stronger relationship between particle air pollution and mortality. This is consistent with the hypothesis that the IP fraction (especially FP) includes the component of particulate matter responsible for health effects. If the coarse fraction acts as a biologically non-significant, random component on top of the IP fraction, the coefficient for TSP is expected to be biased downward (i.e., too low) in a manner consistent with the results of this work.

If one wishes to apply a coefficient from the available cross-sectional mortality analyses to predict the health effects of particle pollution, then we would recommend the use of a fine particle risk coefficient (e.g., 1.3 $\pm$ 0.6 deaths/year/10^5 persons per ug/m^3 FP, as shown in Table 1), rather than a TSP or sulfate coefficient. The problem associated with using a TSP coefficient is that a major portion of that mass is not inhalable by humans, while sulfates represent only a portion of a total mix of ambient fine particles. In the absence of FP data, the coefficient noted in Table 1 for sulfates may be applied with caution. However, if a sulfate coefficient were to be applied in cases in which sulfates are present in substantially less or greater than usual proportions (e.g., relative to organic particles or trace metals), then the results would be misleading. It can be expected that the use of the entire fine particle mass should be less sensitive to errors introduced by compositional variation from case to case. Also, it should be kept in mind that the FP coefficient is most representative for an "average" urban aerosol composition and will, to some extent, be subject to the biases noted for sulfates when applied to aerosols having a makeup very different from the mean composition. It may be that this problem can be addressed through the development of coefficients for each of the numerous aerosol components (e.g., auto particles, soil particles, oil combustion particles, etc.). However, until aerosol component-specific coefficients are developed, the use of fine particle coefficient (rather than a TSP or sulfate coefficient) appears to provide the more acceptable alternative for risk analysis at this time.

Although the use of a fine particle mortality coefficient should provide an improvement over previously used cross-sectional indices of particle air pollution, we must emphasize the large uncertainties surrounding any such damage coefficient. Indeed, despite the fact that the coefficient is statistically greater than zero, uncertainties not considered by such analyses (e.g., errors in the measurement of the exposure variable) make it possible that the mortality risk might in fact be zero. Such coefficients have in the past been applied without adequate attention to their actual applicability to the situation and the

uncertainties involved. We refer readers to the limitations regarding the application of mortality risk coefficents noted in Section II.4 of this report, as well as in Section IV and the Executive Summary of the 1982 HEED.

TOXICOLOGIC ANALYSIS

The 1983 HEED toxicity analyses have concentrated on the evaluation and ranking of carcinogenic potentials and non-neoplastic health risks of particles. These assessments have been based upon a number of *in vitro* and *in vivo* bioassays. Such information may be useful in the ranking of risks which are not separable using epidemiologic tools to confirm epidemiologic observations, to extend analyses into areas where epidemiologic studies have not been undertaken and to provide insight into biological mechanisms of damage. The uncertainties discussed underscored the current lack of fundamental knowledge regarding the biological processes involved, and point toward the need for further research to clarify disease mechanisms.

Carcinogenic Effects of Particles

The main objective in this area was to obtain estimates and ranks of the carcinogenic risks posed by various sources of airborne particles, including those derived from coal, oil, wood, diesel, and leaded and unleaded gasoline combustion. A comparative potency statistical model, based upon a number of short-term bioassays and human epidemiologic data, was developed (see Section III.). Application of the model to data generated using the Ames Salmonella typhimurium bioassay provided estimates of increased relative risk of cancer and associated degrees of uncertainty. Ames bioassay data were used primarily because it was the only assay for which sufficient information was available in the published literature to allow for comparative analyses between the particle types of interest to our group.

In this analysis, estimates of human cancer risk from extractable organics were presented as increments in relative risk per ug/m^3-years. As shown in Table 1, estimates were generated for emissions from light-duty diesel vehicles, catalyst spark engines, non-catalyst spark engines, woodstoves, residential heaters, fluidized bed coal combustion, conventional coal and oil combustion. These estimates produced increments in relative risk per ug/m^3 extractable organics-years ranging from approximately 10^{-3} to 10^{-6}. Due to various sources of uncertainty (predominately involving inter-test potency relationships), the 95 percent confidence intervals ranged over approximately five orders of magnitude. Further, this range cannot be viewed as conservative, since certain non-quantifiable or inadequately quantified elements are not fully captured by the model. For example, these include uncertainties in the epidemiologic data to which the bioassays are linked in the statistical model, potential variations in potency due to different extraction protocols, and potential non-linearities in dose-response functions. However, given the magnitude of the range determined in this

analysis, we do not feel that the exclusion of these further uncertainties are likely to be of significance. Because of the limitations inherent in these estimates, we conclude that it is premature to use data generated from short-term bioassays of complex combustion products for anything more than for general comparisons.

The extension of this analysis to comparisons of risks due to actual exposures experienced by the population as a whole is difficult. Exposure data have generally been collected or estimated in terms of particulate mass, while the risk estimates generated by this analysis are in terms of extractable matter. An approximate interconversion between these units based upon extractable fraction (the percentage of particle mass which is extracted) for each particle type is possible. Such a conversion allows for general comparisons when source-apportioned ambient exposure data are available, but this process also introduces additional uncertainty into the analysis. Given the large uncertainties already evident, we have decided that to proceed with this analysis was not justified at this time.

Several points of significance have emerged from this investigation (see Section III.1). First, the potency values clearly contribute the largest degree of uncertainty in any analysis of specific health effects, far outweighing uncertainty resulting from exposure estimates. This underscores the need for the development of test systems which more closely approach the in vivo human situation. Such tests must await a better understanding of the fundamental mechanisms involved. Second, due to the significant overlap of the 95 percent confidence intervals, one cannot currently make any firm distinctions between the potencies of these particles. Therefore, from a policy perspective, it would appear wise to concentrate on controlling those particle sources which contribute most heavily to soluble organic exposures. In situations where the magnitudes of exposures are similar, then central potency estimates, or more conservative upper-bound risk estimates, may be used to guide policy decisions. Estimates of predicted numbers of lives lost do not appear warranted at this time due to large uncertainties involved and the obvious economic and social implications.

Bioassays Relevant to Non-Neoplastic Lung Disease

Evaluation of non-neoplastic pulmonary effects has focused on in vitro and in vivo studies of a wide range of particles, particularly metals and sulfates. The effects of particles have been evaluated using information from five categories of bioassays: (1) measurements of macrophage function in vitro using both animal and human cells; (2) pulmonary function measurements; (3) infectivity models; (4) lung lavage fluid changes; and, (5) mucocilliary transport.

Our preliminary studies in dose-response relationships (discussed in Section III.2.1) for in vitro tests of metals have determined, by linear regression analysis, the estimated concen-

trations required to produce an experimental outcome level (which is specific for each bioassay) of half the maximum effect (EC_{50}). The five metals investigated had relatively stable toxicity rankings for different bioassays (i.e., $Cd^{2+} \geq VO_3^- \geq Ni^{2+} \geq Cr^{3+} \geq Mn^{2+}$). Further, this order was consistent with ranked exposure limits for occupational Threshold Limit Values (TLV). Using an *in vivo* bioassay that assesses increased susceptibility to infection and extrapolating from experimental doses in mice to equivalent doses in man, it appears that the dose of some metals from urban exposures in man reach levels that are within a factor of 10 smaller than those doses which enhance susceptibility to bacterial infection in animals

However, no reliable scientific data exist which directly demonstrate effects in humans due to chronic exposures to these metals at ambient levels. An extensive data base does exist which demonstrates serious biological effects in a variety of animal bioassays following short-term exposure to metal concentrations above those found in ambient air. The importance of the effects and the similarities of the biological systems between animals and humans suggest that chronic exposure of humans to these metals may result in significant, but as yet unquantified, health effects.

We have focused our toxicologic review of sulfates on mucocilliary clearance and respiratory mechanics. As discussed in Section III.2.2, these effects appear to be related to the strength of the acid and, therefore, most attention is given to the effects of sulfuric acid. Following repeated exposure to sulfuric acid, several animal systems have developed persistent alterations in mucocilliary clearance rates. Histological examination of airways shows changes which account for the reduced clearance seen in airways of animals exposed to chemical irritants.

Since the sequence of events and tissue histology following sulfuric acid exposure resembles those seen in humans who smoke cigarettes, an important question is whether sulfuric acid and diminished mucociliary transport contribute to the development of bronchitis. At this time, however, the progression of clearance dysfunction in the pathogenesis of chronic bronchitis is not known.

The potential impacts of nitrates on humans and animal health has received relatively little attention. However, information on effects can be inferred from exposure studies for nitrogen dioxide, since the gas dissolves in the respiratory epithelium and forms nitrates. For example, animal inhalation studies with NO_2 exposure show production of functional decrements and anatomical changes in peripheral airways and airspaces which are consistent with impairment of respiratory defense systems (see Section III.2.3). Thus, while the effects of nitrate aerosols on respiratory disease have not been established, there is a body of toxicologic data which raises sufficient concern to justify further investigation.

CONCLUSIONS AND RESEARCH RECOMMENDATIONS

In the Executive Summary of the 1982 HEED on airborne particles, we pointed out the need for the development and use of more biologically plausible exposure indices (rather than the typically available TSP or $SO_4^=$ measures) in assessments of epidemiologic data regarding health effects and air pollution. Our second year's efforts were directed toward improving our understanding of the extent of health risks resulting from the components of inhaled airborne particles. We were partially successful in completing this task. Therefore, the research summarized in this report provides estimates of mortality and morbidity effects of exposures to ambient particles in terms of various particle mass measures (see Table 1).

There were several interesting findings from our epidemiologic investigations of the morbidity effects of exposures to airborne particles. A survey of the existing literature on the morbidity effects of human exposures to particulate matter indicated that very few studies have addressed acute health effects of particle pollution below levels of 1000 ug/m^3 (measured in 24-hour average TSP equivalents). However, the available data for short- and long-term exposures to particulate matter did not suggest the existence of effect thresholds. For this reason, simple linear coefficients were derived which related particle concentrations to morbidity effects. Also, an original epidemiologic study using the National Health Interview Survey morbidity data and an index of fine particle pollution (based upon airport visibility data) indicated a correlation between fine particle air pollution and human morbidity. This relationship persisted even when the analysis was controlled for inter-city and seasonal effects, but was evidenced only among persons reporting periodic limitations due to chronic conditions.

Time-series analysis or historical Coefficient of Haze (COH) and mortality data collected in New York City (NYC) indicated that COH was 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 for the mix of sources and time patterns of concentrations observed in NYC between 1963 and 1976.

Cross-sectional analyses of total mortality in Standard Metropolitan Statistical Areas (SMSA) across the U.S. indicated that the use of fine particle health risk coefficients provides an improvement over previously employed particle mass measures (especially TSP). Aside from the biological plausibility of such a finding, statistical analyses showed FP measures to be more consistently associated with mortality and morbidity health effect outcomes than either TSP or sulfate. Unfortunately, as noted elsewhere in this report, the uncertainties surrounding even these new estimates remain so large that we are still compelled to emphasize the need to consider the possibility of a

zero-risk coefficient (or no effects due to exposures to airborne particles at the levels studied). It was also found that, using mean exposures and expressing mortality risks in terms of similar units, the NYC time-series analysis indicated less than half the mortality risks prdicted by our cross-sectional analysis. While preliminary in nature, this finding is consistent with the expectation that the cross-sectional studies may capture more of the chronic health effects of air pollution than would time-series studies (e.g., Evans et al., 1983).

An important source of uncertainty in the analyses discussed above is contributed by the use of central-site pollution data, as opposed to more accurate estimates of personal exposures (including separate indoor, outdoor and in-transit components). Another key contributor to the uncertainties identified (see Sections II.1 and II.4, and Appendices I and II) is in the spatial and temporal variability of the aerosol composition and its toxic components. Since size-specific mass measures do not account for these differences, it is not yet possible to better resolve the size of errors associated with the current estimates based upon particle mass. However, as these uncertainties in exposure estimates are reduced, it is expected that the resultant biasing effect (thought to be downward) on the FP coefficients will diminish and that the confidence interval of the estimates can be reduced. This will then allow further improvements in the statistical reliability of health effect assessments derived from observational epidemiology.

During our bioassay investigations, we attempted to address some of the potential source composition problems mentioned above. We studied the non-neoplastic toxicities of various metals and found their rankings to be consistent with the TLV rankings. Using a relative potency model, we also estimated the range of carcinogenic risks posed by different types of airborne particles such as those emitted from coal, oil, wood, diesel and gasoline combustion. The main conclusion arrived at after developing estimates of incremental relative risk of lung cancer (based upon Ames data) was that, due to large uncertainties, it is not possible to reliably discriminate between the potencies of different types of particles. For this reason, the population risks associated with exposures to various types of ambient particles must, at this time, be ranked on the basis of quantities of extractable (soluble) organics emitted rather than individual estimates of potencies.

After evaluating the evidence derived from epidemiologic and toxicologic components of our research, we concluded that epidemiologic risk coefficients (although quite crude and only appropriate for the development of bounding estimates) are perhaps the only useful tools readily available to air pollution risk analysts today. Nevertheless, we strongly believe that a proper application of these coefficients (preferably those based upon fine particle exposures) demands extreme caution and a specification of qualifications and uncertainties.

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

For future health studies, we need combinations of both improved exposure and health measures. For example, the use of health surveys or census data would be greatly enhanced by the addition of measures that would at least partially account for cigarette smoke and indoor exposures. 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, including information on indoor/outdoor 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 exposure estimates. Especially for the study of morbidity, existing data bases should receive additional attention. For this purpose, historic data sets might be re-analyzed using novel exposure estimates (as attempted in Section II.2 of this HEED using airport visibility to estimate ambient fine particle concentrations). In addition, existing health surveys such as HIS and NHANES (National Health and Nutrition Examination Surveys) should be expanded to better accommodate analysis for air pollution effects. Further, various exposure-averaging times should be examined in order to address questions regarding response times associated with observed biological effects of air pollution. Particular attention should also be paid to improving exposure estimation by incorporating available personal monitoring data and exposure modeling techniques. Finally, associations obtained between air pollution exposures and different measures of human morbidity should be compared in terms of their significance and biological plausibility.

For time-series analysis, we need an improved model of the effects of confounding variables (such as temperature) on acute mortality and morbidity. This also suggests the need to develop a physiologically based model of acute mortality in time-series studies.

Based upon our results from cross-sectional mortality analyses (which indicate the importance of fine aerosol fraction), ambient measurement of fine particle should be expanded. Moreover, future work should explore the sources and composition of fine particles to examine their respective importance in the interpretation of epidemiologic data bases.

Future bioassay studies should address the question of biological significance of assays with respect to human disease (both neoplastic and non-neoplastic). Basic research into the physio-chemical mechanisms of carcinogenesis may eventually provide a model that, in conjunction with bioassays, will be quite useful to risk assessment.

Future research should also be directed toward the refinement of present bioassay technology, especially those utilizing the comparative potency approach (which necessitates the use of multiple systems and compounds). For instance, approaches such as those used in the EPA's cancer bioassay studies may be improved upon by expanding the potency sets to include the much larger group of known animal carcinogens. However, relationships between assays still need to be determined for a greater data base to account for interlab and intersample variability. The effects of differences in chemical composition on assay results also need further clarification. It seems probable that certain assays will be effective as predictors of carcinogenic potency for certain chemical classes. Finally, questions of bioavailability must also be addressed in assessing mutagenic potential of urban aerosols.

I. Introduction

This report is the second generic Health and Environmental Effects Document (HEED) on airborne particles. The 1983 HEED provides results to date of continuing analyses of the nature, magnitude and uncertainty of potential health impacts of airborne particles.

The scope of this HEED includes those particles which are most commonly associated with general types of fossil fuel energy technologies. Particle types considered in the toxicity assessments included: fine, inhalable and total suspended particles; sulfates; nitrates; various trace metals; particles from coal, oil and gasoline combustion; and, diesel particles. Characterizations of potential health effects resulting from exposures to airborne particles primarily have been developed from the analysis of toxicologic and epidemiologic data utilizing ambient air pollution measurements. To a large extent, predictions of population exposures to particles were derived from the EPA's Storage and Retrievel of Aerometric Data System (SAROAD) and Inhalable Particles (IP) network data bases. Characterizations of ambient particle concentrations and apportionments of typical sources of airborne particles have been discussed in various sections of this report (e.g., II.2, II.4 and III.1) as well as in Appendix I.

Section II presents epidemiologic assessments of the health effects of human exposures to particulate matter. In Section II.1, we included an updated review and a preliminary re-analysis of previously reported morbidity data bases. Using the 1979 Health Interview Survey (HIS) data base of the National Center for Health Statistics, in Section II.2 we present investigations into the association between fine particle pollution and human morbidity. In Section II.3, we devoted most of our efforts to describing the results from our re-analysis of 14 years of daily mortality and air pollution data collected in New York City. Section II.4 includes the assessments derived from our cross-sectional analysis component of our epidemiologic investigations. This analysis searched for relationships between geographic differences in fine particle, total suspended particulate matter, inhalable particle and sulfate concentrations in the U.S. and geographic differences in mortality rates. Further details on epidemiologic investigations regarding mortality and morbidity effects of air pollution can be found in Appendix II.

Analyses of the toxicity of airborne particles (presented in Section III and Appendix III) concentrated on the evaluation of neoplastic and non-neoplastic health risks of particles. In Section III.1, we developed estimates of the carcinogenic risks posed by various sources of airborne particles, including those derived from coal, oil, wood, diesel, and leaded and unleaded gasoline combustion. In Section III.2.1, we evaluated bioassays relevant to non-neoplastic lung disease using *in vitro* and *in vivo* studies of metals including Cd^{2+}, VO_3^-, Ni^{2+}, Cr^{3+} and Mn^{2+}. Our toxicologic review of acid sulfates (presented in Section

III.2.2) focused on the effects of sulfuric acid exposures on mucociliary clearance and respiratory mechanics. Potential implications of these lung function changes to human chronic bronchitis is also included in Section III.2.2. Finally, in Section III.2.3, we reviewed the available literature on human and animal health effects of nitrates.

Our assessments in this HEED are concluded in Section IV with a summary of the principal conclusions and research needs indentified during our analysis of health risks resulting from exposures to ambient particles. The reader is referred to the three Appendices accompanying this report for details on specific points.

II. Epidemiologic Assessments of Health Effects of Exposures to Ambient Particulate Matter

In Section IV of the 1982 HEED on airborne particles, we provided epdemiologic assessments regarding the nature and the extent of association between air pollution and population health effects. In this year's HEED, we attempted to expand our epidemiologic studies on the morbidity and mortality effects of particle air pollution in to order to: (1) explore the likely range of air pollution effects on alternative health outcome and exposure variables; and,(2) characterize the uncertainties and sensitivities of results to choice of data base and models used.

The morbidity effects component of our investigations included both an updated review of the epidemiologic literature on morbidity effects of human exposures to ambient particulate matter and new analyses of available morbidity data. Our review this year encompassed several new studies, most of which were made available to us after the development of the 1982 HEED. We also conducted new analyses using morbidity data from the 1979 National Center for Health Statistics (NCHS) Health Interview Survey (HIS). The principal health outcome variables included in this preliminary analysis were total Restricted-Activity Days (RAD) and total Work-Loss Days (WLD). This work focused mainly on examining the extent of the realtionships between fine particle pollution and human morbidity measured by either RADs or WLDs.

To estimate the magnitude of possible mortality risks associated with particle exposures, we concentrated our recent efforts on studies of daily time-series and annual cross-sectional mortality data bases. In particular, we re-examined the 1963-1976 New York City daily mortality and air pollution series to develop estimates of daily mortality risk coefficients. Under a separate analysis, we also studied the implications of using alternative exposure indices in cross-sectional studies of air pollution and total mortality. Using a methodology similar to the one employed in the 1982 HEED, we analyzed 1960 and 1980 cross-sectional data bases, along with information from the EPA'S 1979-1981 Inhalable Particle (IP) network data base.

In the remainder of this section, we discuss the results of our epidemiologic assessments regarding morbidity and mortality effects of air pollution. Further details on our epidemiologic studies can be found in Appendix II of this report.

II.1 Review of Evidence from Observational Epidemiology: Morbidity Effects of Particle Pollution

Introduction

This section updates the initial assessment of morbidity consequences of particle exposure included in the 1982 HEED. We have also reviewed the morbidity analysis from an independent risk evaluation (Manuel et al., 1983) that was designed to deter-

mine the benefits associated with alternative standards for particulate matter.

In developing this HEED, most of our efforts in quantitative analysis have been directed toward mortality as an outcome. However, if mortality is plausibly an outcome of human exposure to particulate air pollution, there should be a relationship between this form of air pollution and non-fatal disease outcomes. Unfortunately, ascertaining whether particulate pollution at current U.S. concentrations is linked to morbidity is hampered by an extremely limited data base. We have identified several reasons for this limitation, including:

- Morbidity outcomes are measured with less regularity and precision when compared with the relatively complete vital statistics available for mortality. This severely limits the opportunity to conduct aggregate-level, cross-sectional investigations of morbidity outcomes.

- Many morbidity outcomes (e.g., lung function) require the investigator to make direct measurements on study subjects. Also, most observational studies have involved relatively few subjects and, therefore, do not have the statistical power to detect slight changes in nonspecific disease outcomes. Unfortunately, this is exactly the type of effect we would hypothesize to result from particulate exposure at current levels.

- The majority of studies were conducted at particulate-matter concentrations exceeding levels of concern for standard-setting and risk evaluations (i.e., years ago and/or at very polluted sites).

- Most experimenters do not design their studies to develope quantitative dose-response information. Therefore, many studies which suggest a health effect from particulate matter are not useful for quantitative interpretations.

Interpretation of the morbidity studies must be qualified similarly to all non-experimental epidemiologic studies. The individual epidemiologic studies of morbidity can demonstrate an association between particulate matter and ill health, but they cannot prove the causality of that association. The morbidity studies, however, do have one major design advantage over the aggregate-level studies that use vital statistics information: the individual-level analysis often employed in these studies permits more careful control of personal factors (e.g., smoking and occupation) which might otherwise act as confounding items in an aggregate-level study.

Results from Review of Morbidity Literature

Studies of the morbidity effects of chronic exposure to particulate matter have shown upper and lower respiratory symptoms (including bronchitis) and reduced pulmonary function to be associated with particle [in Total Suspended Particulate Matter (TSP) equivalents] concentration in excess of approximately 180 ug/m^3 (Ware et al., 1981). No evidence exists in these data to suggest an effect threshold. The observational studies on short-term particle exposure are more sparse, and most of these studies address TSP levels in excess of 1000 ug/m^3 (24-hour average). Those which have studied effects at lower concentrations (Martin, 1964; and Lawther et al, 1958 and 1970) suggest increased hospital admissions for cardiac or respiratory illness (with TSP at 600 ug/m^3 in association with SO_2 at 400 ug/m^3) and worsening of health status among bronchitics (with TSP at 350 ug/m^3 in combination with SO_2 at 500 ug/m^3). As is the case in chronic exposures, these studies do not suggest an effect threshold.

Initial Results from Assessment of Morbidity Effects

In a preliminary attempt to derive simple linear coefficients for morbidity, we selected several highly regarded studies that provided quantitative estimates for air pollution concentration and morbidity outcomes. Only the study of hospital visits addresses a concentration range for particles that is relevant to current air pollution levels in the U.S. The other studies address relatively high particulate levels, and one must extrapolate beyond the range of observed concentrations in these studies to conduct a useful risk assessment. This approach must obviously be taken with caution as very little evidence exists to indicate whether or not the relationships observed at higher particle concentrations hold at lower concentrations. With these qualifications, coefficients were derived and are presented in Table II.1.

The coefficients shown in Table II.1 are left in the original air pollutant form [i.e., Smoke using OECD calibration, British Smoke (BS) or (TSP)], but nonetheless present a biologically consistent impression with the coefficients typically derived for mortality. The right-hand column of Table II.1 indicates the range over which health effects were observed in each of the studies. Air pollution is only responsible for a portion of this effect, since the intercept for the health effect is generally greater than zero. This column is included because any extrapolation outside the effects range will produce an uncertain error.

In Table II.1, we also present results from the Mathtech analysis for their linear functional form (Manuel et al., 1983). In Appendix II.1, we discuss the two functional forms used by Mathtech in their analysis of morbidity outcomes and describe our reasons for selecting the linear forms as most justifiable and parsimonious. The additional studies relied upon by Mathtech are

Table II.1 Assessment of Morbidity Response Rates

Type of Health Response		Estimated Exposure-Response Slope (cases/year/100,000 per $\mu g/m^3$)	Pollution Range That Estimate is Based Upon ($\mu g/m^3$)**	Pollutant Measured in Study	Range of Total Health Effects Observed in Study***
Childhood lower respiratory infection		60±*	BS (97-301) SO_2 (123-275)	BS	23-36% reporting symptoms
Bronchitis in Males (smokers and nonsmokers)		100-170±*	BS (90-170)	Smoke (OECD calibration)	4-27% reporting symptoms
Bronchitis in Females (smokers and nonsmokers)		0-10±*			2-10% reporting symptoms
Acute Respiratory Disease (Manuel et al., 1983)+	age 0-24yrs 25-54yrs 55+yrs	540±* 100±* 120±*	TSP (0-200)	TSP	- -
Excess Emergency Room Visits++ for Respiratory Disease		13±**	TSP (14-696)	TSP	24.5 ± 9.3 daily visits
Excess Total Emergency Room Visits++		20±*	SO_2 (4-369)		94.3 ± 14.2 daily visits
Excess Emergency Room Visits for Respiratory Disease++		8.2±*			

* Standard errors can not be estimated from these studies in a straightforward manner. Errors from sampling considerations are under investigation by us; however, larger errors will result from nonsampling considerations. In our opinion, the errors should be considered to be half as large as estimates.

** Based upon annual average concentrations with exception of emergency-room-visit study that was based upon 24-hour averaging period.

*** This column represents the inclusive range over which health effects were observed in each of the studies. A portion of these effects will be due to factors other than air pollution.

\+ Based on data of Saric et al., 1981. Assuming, conservatively, that TSP level is 0 in clean city.

++ These coefficients are based upon regression results for which TSP explained only approximately 1 percent of the variance in hospital emergency room visits (Samet et al., 1981). The 13 and 20 rates can be computed by assuming a population base of 20,000 for the hospital. The value of 8.2 is based on estimates of Manuel et al., 1983, assuming population base of 31,000 and compares with our coefficient of 13 for excess emergency room visits for respiratory disease.

consistent with the results obtained in the preliminary analysis (Table II.1).

It should be mentioned that the range of coefficients shown in Table II.1 must logically include 0 because of the extrapolation below concentrations observed in the studies. Furthermore, in addition to this major extrapolation problem, there are other important contributors to the uncertainties of the morbidity risk estimates. These can be categorized into sampling and non-sampling errors.

Sampling errors refer to the lack of precision of a sample result. If a sample were to be collected without sampling error, then one could reproduce from the sample the results which would have been obtained if the entire population had been included. To the extent that this is not true, sampling error exists. Non-sampling errors include a variety of factors that influence the uncertainty of the estimated particle air pollution/morbidity relationships. They include: confounding factors (e.g., cigarette smoking, socio-economic status, occupational exposures, race, prior exposures and residence); collinearities with other pollutants (e.g., particles and sulfur dioxide); changing measures of particle pollution that are not extirely comparable [e.g., British Smoke or Coefficient of Haze (COH) versus TSP]; oversimplifications in estimating personal exposures from data collected at fixed-site monitors; and, biases due to historical and across-community differences in particle and source composition.

These and other caveats (see, for example, Section II.4 and Appendix II of this HEED; and, Section IV of the 1982 HEED) should always be considered when morbidity risk estimates are used. In particular, if these coefficients are applied to aerosols having a different makeup than the ones they have been based upon, the results may be quite misleading. In conclusion, due to potential error contributions by the factors noted above, the standard errors of the estimates should be considered half as large as the estimates themselves. Since further efforts to quantify some of these errors are currently underway, thevalues presented in this section should be considered as tentative.

II.2 Fine Particle Pollution and Human Morbidity

As described previously, published literature on observational epidemiology does not provide information on the nature and the extent of the relationship between human morbidity effects and population exposures to respirable particles. The major problem in determining fine particle/morbidity relationships has been the limitation of the available aerometric data bases characterizing ambient concentrations of respirable or fine particles in the U.S. However, for the purposes of air pollution health effects investigations, most of the health studies conducted in this country also lack the desired number of pertinent health, behavioral, socio-economic and demographic variables which have been used in the surveys administered to large populations. Faced with these serious limitations, we elected the option of using a comprehensive national health data base, the 1979 National Center for Health Statistics (NCHS) Health Interview Survey (HIS).

In order to examine the possible effects of particle air pollution on the morbidity measures obtained from the HIS, we developed estimates of fine particle mass exposures. These estimates were derived from established relationships between fine mass, from the EPA's IP Network data, and relative humidity-corrected aerosol extinction coefficients, from airport visibility observations. In addition to the daily estimates of fine particle mass concentrations averaged over each two-week survey period, a number of other weather and socio-economic controlling variables were developed.

The essential features of the data bases used and the results from the preliminary analysis are summarized below. Further discussion regarding this analysis can be found in Appendix II.2.

Description of the National Health Interview Survey

The health data utilized in this report were gathered during the 1979 National Health Interview Survey. This survey is a national multi-stage probability sample of approximately 100,000 individuals. From information gathered in interviews, the survey attempted to describe the social, demographic and economic aspects of illness, disability and the use of medical services. The survey has been conducted continuously since 1957, and is currently managed by the Census Bureau for the NCHS. The health concepts employed by the NCHS differ somewhat from those used in scientific and medical studies.

According to the NCHS, morbidity is considered to be departure from a state of physical or mental well-being resulting from disease or injury of which the affected individual is aware. Illness, however, is considered only one form of evidence of the existence of a morbidity condition, since a morbidity condition may lead to other types of actions such as the

restricting of usual activities, bed disability, work loss, the seeking of medical advice or the taking of medicines.

An acute condition according to the NCHS (1975) is defined as a condition which had its onset during the two weeks immediately preceding the interview week and which involved either medical attention or restricted activity during that two-week period. Acute condition groups include: infective and parasitic diseases, respiratory conditions (e.g., influenza, pneumonia and bronchitis), digestive system conditions, injuries, and other conditions such as diseases of the ear and skin, as well as headaches. By contrast, a morbidity condition is considered to be chronic if (1) the condition is described by the respondent as having been first noticed more than three months before the week of the interview, or (2) it is one of the conditions listed in Table 1, Appendix II. Chronic conditions include, among others: asthma, emphysema, chronic bronchitis, and heart and mental conditions.

The survey also collected a variety of economic and demographic information, as described in various NCHS publications. The 1979 questionnaire included supplements on smoking habits for adults and residential mobility. The smoking supplement was given to one-third of the sample, but unfortunately was not given to all adults in a household, thereby precluding an assessment of passive smoking effects for most of the sample. (Children in homes with a single adult may be an exception.)

Preliminary Analysis Using 1979 HIS Files, EPA's IP Network Data Base and Historic Airport Visibility Records.

The health outcome variables considered in our analysis were:

(1) total Restricted-Activity Days (RAD);
(2) total Work-Loss Days (WLD);
(3) acute respiratory condition incidence; and,
(4) RADs due to acute respiratory conditions.

The two principal disability terms that we have used as health outcome variables were RAD and WLD.

A restricted-activity day according to the NCHS (1975) is a day on which a person cuts down on his usual activities for the whole of that day because of an illness or an injury.

A work-loss day according to the NCHS (1975) is a day on which a person did not work at his job or business for at least half of his normal workday because of a specific illness or injury. In the Health Interview Survey, the number of days lost from work is determined only for persons 17 years of age and over who reported that at any time during the 2-week period covered by the interview they either worked at a job or had a business.

From the 1979 HIS files, we have constructed two data sets for analysis. Table 2 in Appendix II.2 provides a list of the variables selected and a brief description of these variables. Prior to the modeling of the four health variables, we (1) attempted to determine those behavioral and demographic factors having the greatest influence on the observed disability rates; and (2) obtained estimates of daily fine particle concentrations representative of population exposures in the Standard Metropolitan Statistical Areas (SMSA) studied. We briefly describe below the approaches used in these preliminary investigations prior to analyzing fine particle/morbidity associations.

Demographic and Behavioral Health Determinants

Due to the extemely skewed nature of the survey data on the morbidity outcomes (which were mostly zero) in the analysis undertaken, the health outcome variables were treated as dichotomous rather than continuous variables. Thus, greater than or equal to one RADs or WLDs were all grouped together in the category of "effects" versus the category of "no effects". Furthermore, due to computational and aerometric data base concerns, only the 12 SMSAs (representing 3,431 individuals) identified in Figure II.1 were used in our initial analysis. The cities were chosen after consideration of the availability of air pollution data on fine and coarse particles. The correlations between the dichotomized morbidity variables and other demographic, socioeconomic and behavioral factors were then analyzed to determine the factors having the greatest influence on the observed rates.

All of the health measures show a strong seasonal pattern, as illustrated in Figure 3 of Appendix II.2. Fall and winter quarters show the highest rates. Not surprisingly, estimated fine mass exposures also demonstrate seasonality (fine mass concentrations are higher in the summer months than in other months of the year).

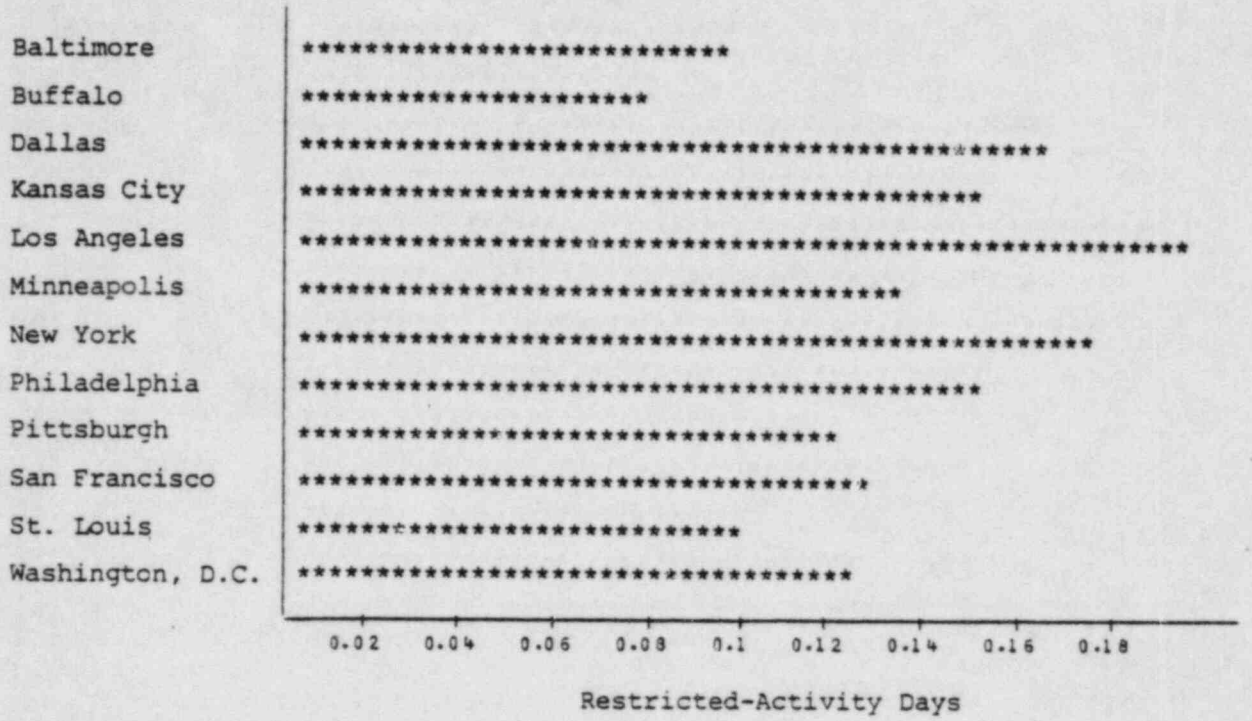
As displayed in Figure II.1, all rates show noticeable inter-city variability. Los Angeles is consistently among the cities showing higher incidence rate of RAD and WLDs. WLD and RADs appear to have a similar pattern, as do incidence due to acute respiratory condition and RAD due to respiratory conditions (c.f. Appendix II.2).

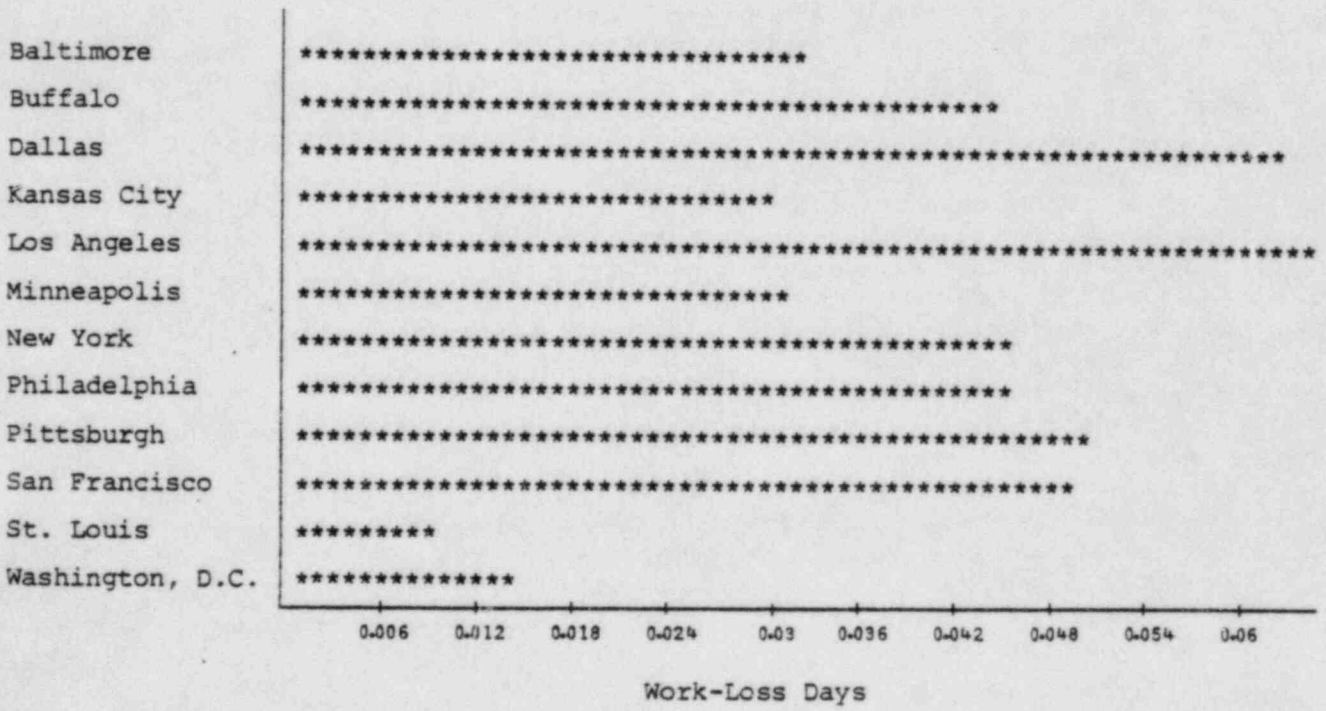
One of the most potent predictors of RAD and WLD is the presence of existing limitation due to chronic conditions. As indicated in Figure 8, Appendix II.2, almost half of all individuals reporting restricted activity also have a limiting chronic condition. However, for the incidence of restricted activity due to acute respiratory conditions, the limited and non-limited groups exhibit greater similarity and low incidence rate (around 0.04).

Economic factors and age clearly play a role in restricted-activity and work-loss days. The analysis discussed in Appendix II.2 indicates opposite trends for RAD and WLD over the three

Figure II.1

Proportion of Sample
Reporting RAD and WLD by City





categories of income. This may occur as a result of the higher levels of unemployment in the lower income categories, and because RAD data was collected from both working and non-working populations. Occupational status may affect rates of WLD. Individuals classified by census occupation categories above 400 (blue-collar workers, farm workers and service workers) were noted to have a much higher rate of WLD, perhaps due to injuries or job-related financial compensatory effects. In contrast, the opposite trend, which was not immediately apparent, was shown for RADs (c.f. Appendix II.2). Age is also an important determinant. As shown in Figure 12, Appendix II.2, the incidence of restricted activity increases with age while WLD rates decrease with age.

We expected that smoking status would be an important factor for all of the health outcome rates. In fact, as shown in Figure 13, Appendix II.2, the apparent effects were rather small, particularly for the respiratory condition measures.

Marital status and sex also appear to be influential factors. Single adults, either divorced or never married, tend to have higher rates of health effects than married adults. Rates also vary according to sex, as shown in Figure 15, Appendix II.2. In every case, women reported a greater incidence of health effects than men.

In summary, this initial analysis showed that the health effects rates derived from the HIS data are strongly influenced by demographic factors, as well as personal and seasonal factors. Since these variables may also be correlated with the exposure variables of concern, in the subsequent analysis of the morbidity effects of air pollution utilizing the 1979 NCHS/HIS records, we explored the extent of the influence of these potential confounding variables on the modeled effects.

Daily Fine Particle Exposure Estimates Derived from Airport Visibility Observations

Since the Health Interview Survey data was reported for individuals during specific two-week periods, it was necessary to develop mean Fine Particle (FP) exposure estimates for these specific periods. At the time of the HIS work, little or no FP mass data were being collected at these 12 SMSAs. Typically, for example, sulfate data collected by the National Aerometric Surveillance (NASN) stations have been limited to one-every-sixth-day measurements. However, by using FP and visibility data collected in these SMSAs during 1980 and 1981, combined with airport visibility records during the same periods, it was possible to develop site-specific and daily estimates of FP exposures which were then averaged for each two-week period. This was so because there is a roughly linear relationship between fine particle concentrations and inverse visual range, with visual range decreasing as particle mass concentrations increase [see, for example, U.S. EPA (1979a), Latimer et al. (1978); Waggoner and Weiss (1980); and Trijonis and Yuan (1978)].

The FP-visibility relationship is founded upon the principle that fine particles absorb and scatter light, causing an extinction of light and loss of visual contrast (reduction in visual range, V_r). The extinction coefficient can be estimated from visibility via the Koschmieder Formula:

$$B_{ext}\ (km^{-1}) = 3.91/V_r\ (km)$$

A summary of the site-by-site FP/B_{ext} relationships utilized in this analysis is shown in Table II.2. Details of their development may be found in Appendix I.2. Applying these formulae (developed from 1980-1981 data) to the visibility data recorded during the 1979 HIS study allowed for the estimation of average FP mass exposures in each SMSA during the individual periods of interest.

Estimation of Morbidity Effects
of Air Pollution, Weather and Other Factors

Given the nature of our exposure measure (i.e., airport observations of visibility which integrate pollution levels over a wide distance), we decided to aggregate central and non-central city data. Furthermore, since the reported incidence levels for the acute respiratory conditions and the restricted activity due to acute respiratory conditions were relatively low, we decided to limit our final analysis to the study of the associations between fine particle exposures and RAD or WLD.

For our initial modeling, we used Ordinary Least Squares (OLS) to estimate the regression of the dichotomous variables on air pollution and demographic variables. This method yields unbiased estimators of coefficients of a linear model for the incidence probabilities and their standard errors. However, the distributional assumptions associated with ordinary p-values are not satisfied, and these must be viewed with more than usual skepticism.

Table II.3 shows the results for RAD and WLD. The same sites of demographic variables were included in each fit for purposes of comparison. Two coefficients for fine mass are estimated--one for the limited group (defined in terms of chronic limitation) and one for the non-limited group. As expected from our previous graphical analysis (see Figure 17, Appendix II.2), the sign of the coefficient switches to negative for the non-limited group. The coefficients may be interpreted as the change in the probability of an occurrence of a health effect in a two-week period. For instance, an increase of 10 ug/m^3 average fine mass concentration would be expected to increase the probability of a restricted-activity day in a two-week period by 0.056. If we assume that the probabilities in successive periods are independent, then we can use the laws of probability to calculate occurrence probabilities for periods greater than two weeks. Under the independence of events assumption, an increase of

Table II.2

Light Extinction-Particle Mass Relationships at 12 U.S. Cities

	SMSA	SAROAD Site Code	Total Number of Obs.	Mean B_{ext} (km^{-1})	Mean FP Mass (M_f) ($\mu g/m^3$)	$M_f = K[B_{ext}]^{**}$ Coefficient K ($km\text{-}\mu g/m^3$)	$B_{ext} = K_0 + K_1[M_f] + K_2[M_c]^{**}$ Coefficients K_0 (km^{-1})	K_1 (m^2/g)	K_2 (m^2/g)
1.	Los Angeles, CA	054180103	104	0.333 ± .034	26.9 ± 1.9	69.8 ± 4.2	0.16 ± .07	8.6 ± 1.5	-2.6* ± 2.9
2.	San Francisco, CA	056300003	119	0.204 ± .016	14.4 ± 1.1	62.4 ± 3.0	0.06 ± .03	10.4 ± 0.9	2.9* ± 1.6
3.	Washington, D.C.	090020017	94	0.194 ± .008	26.1 ± 1.6	138.0 ± 8.0	0.15 ± .02	2.3 ± 0.6	-0.1* ± 0.8
4.	Baltimore, MD	210120009	76	0.231 ± .016	24.3 ± 1.5	90.5 ± 6.7	0.18 ± .05	5.4 ± 1.7	-3.2* ± 2.4
5.	Minneapolis, MN	242260051	111	0.228 ± .036	16.7 ± 0.8	65.4 ± 4.6	0.05* ± .08	14.2 ± 2.7	-2.8* ± 1.4
6.	St. Louis, MO	260030001	47	0.286 ± .020	21.1 ± 1.4	69.5 ± 3.9	0.12 ± .04	8.0 ± 1.6	0.1* ± 1.4
7.	Kansas City, MO	262380002	75	0.248 ± .015	19.1 ± 1.1	68.8 ± 4.3	0.20 ± .04	6.3 ± 1.5	-2.0* ± 1.1
8.	Buffalo, NY	330660003	114	0.276 ± .014	40.0 ± 2.0	124.0 ± 7.0	0.19 ± .03	2.4 ± 0.6	0.6* ± 0.9
9.	New York, NY	334680005	50	0.263 ± .017	22.0 ± 1.4	82.4 ± 3.7	0.08 ± .03	8.2 ± 1.3	0.0* ± 1.3
10.	Pittsburgh, PA	390100068	77	0.290 ± .019	23.0 ± 1.5	71.2 ± 4.0	0.13 ± .04	7.7 ± 1.3	-0.4* ± 1.2
11.	Philadelphia, PA	397140036	67	0.213 ± .015	24.2 ± 1.3	93.9 ± 3.4	0.07 ± .03	7.0 ± 0.8	1.6* ± 1.6
12.	Dallas, TX	451310050	97	0.233 ± .009	19.1 ± 0.9	78.3 ± 3.5	0.15 ± .02	4.2 ± 0.9	0.7* ± 0.7

*Not statistically significant at $p = .05$

**Regressions based upon a selected subset of entire data set (see Appendix I).

Table II.3

Results from OLS Regressions
for Restricted-Activity Days and Work-Loss Days

	Restricted-Activity Days		Work-Loss Days	
Variables*	Estimate (Standard Error) X 1000	Significance Level (P-value)	Estimate (Standard Error) X 1000	Significance Level (P-value)
Age	-0.74 (0.36)	0.042	-0.95 (0.22)	0.0001
Noon temperature	0.001 (0.72)	0.79	0.25 (0.45)	0.57
Hours of precipitation	12.65 (12.9)	0.69	7.29 (7.97)	0.36
Fine mass: with chronic condition	5.59 (1.81)	0.002	1.78 (1.12)	0.11
Without chronic condition	-0.95 (0.89)	0.28	-0.76 (0.55)	0.17

*Model used in regression analysis also included categorical variables on the following: income, city, sex, city residence, employment, smoking status, quarter of the year, chronic conditions, marital status, health status, and blue-collar occupation. These variables represented fixed effects that could not be estimated directly.

N = 3,431 R^2 = 0.14

1 ug/m^3 of the fine particle mass concentration over a year's period will translate into an increase in the RAD probability by 0.14. But, an increase of 20 ug/m^3 (over the mean of the baseline level) of fine particle mass concentration may result in an additional 95 percent chance in experiencing one or more restricted-activity days during the year due to (fine particle) air pollution.

In an additional analysis, we fit the model for restricted-activity days using logistic regression. In this model, the occurrence probability is modeled with the logistic function, and the coefficients, therefore, may not be compared directly. In this analysis, we excluded cases with no reported chronic limitation. Table II.4 compares the coefficients (a linearized coefficient is shown for the logistic regression). As can be seen, the coefficients and p-values agree fairly well.

Discussion of Results

The preliminary results reported in this HEED regarding the use of the (1979) NCHS/HIS morbidity files and estimated fine particle mass, to our knowledge, are the first of such studies in open literature. We are, however, aware of the ongoing work (which is similar in character to ours) by P. Portney and his colleagues at Resources for the Future. Since the results from their work are not yet available, we can only compare our results to those of B. Ostro (1983 a,b) and Crocker et al. (1979). These investigations, however, have studied the morbidity effects of air pollution using the 1976 NCHS/HIS and SAROAD (the Storage Retrieval of Aerometric Data system) (TSP, SO_4, etc.) air pollution files. Overall, our results seem to be consistent with those of Ostro, although our exposure measure is quite different (two-week average fine mass versus annual average TSP or sulfate). Assuming an average fine mass to TSP ratio of 0.4 (1982 HEED), our estimates can be "scaled" to the same units as Ostro's. With this approach, our estimate of 1.78×10^{-3} incremental WLD probability estimate converts to 7.5×10^{-4}, which is about half of Ostro's estimate (0.0013 - 0.0017) as presented in Ostro (1983b). Given the fact that our estimated significance level is around 10 percent, this cannot be interpreted as a different result, since Ostro's estimates will most likely be within the estimated confidence intervals.

Another way of (at least, empirically) comparing our findings is to translate our estimated coefficients into measures of elasticity (a method especially popular among economists). Simply put, the elasticity indicates the percentage of change of a dependent health outcome variable which is associated with a one-percent change in air pollution, and thus provides an index of relative effects. Fine mass coefficients (for the limited group) from Table II.3 were scaled by mean pollution over mean effects to develope Table II.5 presenting estimated air pollution/effect elasticity coefficients. Employing work-loss days as an example, Table II.5 suggests that a one-percent reduction in FP concentrations would reduce work-loss thedays of the

Table II.4

Comparison of Logistic Regression and OLS*

Model	Coefficient and Standard Error	p-value
Linear	0.0065 (0.0032)	0.042
Logistic	0.0072 (0.0035)	0.042

*Restricted-Activity Days excluding cases with no reported chronic limitation.

Table II.5

Estimated Elasticities for the Outcome Variables

Outcome	Mean Fine Mass $\mu g/m^3$	Mean Outcome	Estimated Elasticity
Restricted-Activity Days	18.75	0.149	0.70
	18.75	0.403*	0.26
Work-Loss Days	18.75	0.046	0.73
	18.75	0.072*	0.46

* Represents averages for the chronically limited group.

limited group by half a percent. These results and elasticities are comparable to those given in Ostro (1983a).

Perhaps the most important difference, or an issue of further concern, is the negative sign of the sulfate damage coefficient reported by Ostro versus the positive fine mass coefficients obtained in our study. One obvious reason, of course, is the use of a single-particle exposure measure in our work versus the multiple-particle exposure measure employed by Ostro. However, it should also be mentioned that in our analysis we were able to use daily estimates of fine particle mass to predict average FP concentrations corresponding to the individual-specific two-week recall periods. In contrast, Ostro's annual average sulfate estimates were based on the limited (every sixth day) EPA/NASN sulfate measurements. Nevertheless, since sulfates and fine mass are typically highly correlated, caution is advised in the use of our current estimates until joint regressions investigate collinear effects of various particle and gaseous pollutants have been completed. Presently, our results tend to suggest morbidity effects of fine mass air pollution at the significance levels of $p = 0.1$ or less. The most significant effect ($p = 0.002$) is for the restricted-activity day outcomes for the chronically limited group. However, it must be stressed that, for all the non- (chronically) limited groups, the fine mass effects were non-significant and negative, suggesting that the association of morbidity outcomes only for the sensitive population.

Our results can be summarized in terms of possible ranges (or 95 percent confidence levels) of incremental risk for the population subgroups with chronic limitations, as follows:

(1) for restricted-activity day outcome:

0 - 0.01 per ug/m^3 FP
per 2-week exposure period

(2) for work-loss day outcome:

0 - 0.004 per ug/m^3 FP
per 2-week exposure period

These ranges are based on the limited OLS and logistic model runs reported in the text and should be considered tentative, since further model refinements are presently being considered.

In summary, we are aware of the following factors contributing to the overall uncertainty in our results. Only one measure of pollution has been considered. This is a problem in two ways. First, although we have found a strong relationship between fine mass and visibility, a similar relationship may also hold between estimated fine particle concentrations and other pollutants such as sulfates or ozone. Second, even if we were using fine mass directly, we would still have to consider the confounding effects of other air pollutants as well as passive

smoking. The matching of health responses to air pollution and meteorological observations are expected to introduce additional uncertainties. Since we only know the week of the interview, the assigned exposure does not conform exactly to the two-week recall period. In addition, the adequacy of monitoring data as a measure of personal exposure is, as always, highly questionable. Finally, the problems of missing data and the possibility of reporting biases require further investigation. So far in our analysis, we have classified the missing values in the unknown category.

II.3 Investigations of the Mortality Effects of Air Pollution Using Time-Series Studies

In this section, we present the main results of our continuing examination of time-series epidemiologic methods. Our primary emphasis was on analyses useful for interpretation of results from recent time-series mortality studies (Schimmel, 1978; Mazumdar, Schimmel and Higgins, 1982; Mazumdar and Sussman, 1983). These recent studies have examined the air pollution/mortality association in New York City, London and Pittsburgh, together representing the main body of results currently available. In order to provide background for the analyses that follow, we first review some of the special features and challenges of observational (as opposed to experimental) time-series mortality studies.

Introduction

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/or cloud the interpretation of the results obtained. One issue is that of "temporal confounding" (i.e., the potential existence of variables, either measured or not, which are correlated in time with air pollution and exert influence on mortality independently of air pollution). Ignoring such variables in the analysis might lead to over-estimates of pollution effects. Temporal confounding has been thought of by most investigators as falling into two categories or components: low frequency and high frequency.

The low-frequency component is the shared seasonal cycle of daily mortality and air pollution. In the typical time-series approach, this annual correlation is assumed to reflect confounding by unmeasured variables, and an attempt is made to remove its influence prior to the analysis. This is often done by re-expressing the variables to be analyzed as residuals from their 15-day moving averages. This approach has the effect of "filtering out" (removing) certain low-frequency components in the data.

After the variables have been filtered, the remaining "high frequency" residuals are used in regression analysis. At this stage, consideration is given to which variables, other than pollution, should be included as explanatory variables. Temperature is one such variable. It is known, for example, that death rates are elevated during summer heat waves. Other more moderate temperature excursions might also be influential. Of course, variations in temperature and other weather variables are closely linked to variations in air pollution concentrations. This is true both for seasonal trends (low frequency) and for day-to-day variations (high frequency). Thus, weather is a potential confounder of the air pollution/mortality association. Since the low-frequency components in the variables (including weather) have already been removed through filtering, what remains is just

the "high frequency" confounding. Most time-series investigations have included weather variables (after appropriate filtering) in their regressions. For example, Schimmel (1978) included nine functions of temperature as explanatory variables in his regressions.

It is important to recognize that these concepts of temporal confounding are difficult to disentangle. Our conceptual model of the system studied suggests that the potential for confounding exists, but tells us little about its exact nature. Without such information, the choice of a method used to control for temporal confounding introduces a certain amount of uncertainty. The results of the modeling process, quantitative estimates of the influence of daily air pollution on mortality, carry with them this source of potential error. Clearly, too little control could lead to over-estimates of pollution effects, while too much control could lead to under-estimates. However, 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.

Another issue which clouds 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 Inhalable Particle (IP) 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 more 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 stated in our 1982 HEED (Appendix II.3), the relationship of filter soiling measures (COH and BS) to measures of mass concentration varies over both location and time. [A recent study of one summer in Detroit (Wolff et al, 1983) found that COH was closely related to elemental carbon content of the aerosol.]

Sensitivity Analysis of New York City Air Pollution/Mortality Results

As previously mentioned, the lack of theoretical underpinning of the temporal confounding hypothesis leads to uncertainty in choosing methods for its control. In this section, we summarize results from our time-series investigations which tested the sensitivities of results and uncertainties to a range of plausible modeling choices.

Description of Data

The data used in the sensitivity analysis is a subset of the New York City data set obtained from Dr. Herbert Schimmel (see Schimmel, 1978). It consists 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. The means and standard

deviations of these variables are given in Table II.6. Through the middle of 1975, the pollution data were collected at the East 121st Street "laborabory" station in Manhattan. The last year and a half's data were collected at the Roosevelt Island station, with correction factors applied to adjust for the generally lower concentrations at that site. This correction was made using an approach developed by Schimmel. To further conform to Schimmel's preliminary data manipulations, the mortality and pollution data were initially "indexed" by dividing each daily value by a centered 365-day moving average. The indexed variables have means of approximately one and lack long-term (cycles greater than one year) trends.

Sensitivity to Alternative Filters

This anlysis consisted of estimating regression coefficients for COH and SO_2 after all variables were preprocessed with one of several filters (see Table II.7); regression results with no filtering are presented first. The first set of three filters consisted of taking residuals from 7-, 15- or 21-day moving averages of the data. These three filters remove primarily low-frequency components from the data. Shorter moving averages cut more severely into the high-frequency components than do longer ones. (Inthe limit, taking residuals from a "one day" moving average removes all variation from the data.) The regression coefficients were found to increase with the length of the moving average, suggesting that the mortality/air pollution association increases as a wider band of high frequencies are allowed to remain in the data (see Appendix II.3). 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 (1/frequency) lengths, measured in days. For example, the ideal 2-4 filter removed all cycles with periods of greater than 4 days. It should be noted that the shortest period that can be evaluated in data measured daily is two days. The three ideal filters focused on high-frequency bands of varying widths. Qualitatively, this was the same as the three moving averages, but we gained a clearer sense of which frequencies were removed from the data. The results were also in qualitative agreement with pollution coefficients increasing as band width increases.

Overall, the regression coefficients for COH ranged from 1.2 to 5.4 daily deaths per unit COH. The lower value was obtained when only periods of 2 to 4 days were evaluated. The higher 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. Since these six filters represent a range of reasonable approaches to removing low-frequency confounding from the analysis, the range of coefficients derived from them is also expected to provide the relevant sensitivity measure.

Table II.6

Means and Standard Deviations (SD)
of Principle Variables in Analysis

	Mean	S.D.
Mortality*	182	25.9
COH	1.96	0.965
SO_2 (PPM)	0.103	0.098
Temperature (^{o}F)	54.5	17.5

* The sum of respiratory, heart disease, other circulatory and cancer mortality. See Schimmel 1978, p. 1073 for corresponding ICD codes.

Table II.7

Regressions Using Different Filters

[All regressions include SO_2 same-day temperature, and day-of-week dummy variables. Coefficients represent number of daily deaths per unit COH. (Mean COH = 1.96)]

Filter*	Coefficient	Statistical Error
none	5.40	0.46
7-day MA	1.40	0.46
15-day MA	1.76	0.46
21-day MA	1.97	0.46
Ideal 2-4	1.20	0.71
Ideal 2-7	1.21	0.56
Ideal 2-14	1.38	0.49

*See text for description of filters used.

MA stands for moving average.

Analysisof New York City Time-Series Results Using Different Temperature Corrections

In this set of analyses, variables representing various functions of weather were introduced into the regressions. For practical reasons, the weather vector was approximated by average daily temperature. Throughout the analyses, variables were initially filtered by taking residuals from their 15-day moving average. The COH regression coefficients presented in Table II.8 are from models with no temperature variables, with same-day temperature, with same-day temperature by month, with Schimmel's nine-temperature variables, and with Schimmel's nine-temperature variables by month (the latter results were taken from Schimmel, 1978). The regression coefficients decrease from 3.1 to 1.3 (daily deaths per unit COH) as more elaborate temperature variables are introduced. Such behavior is not too surprising since filtered COH and filtered temperature are moderately correlated (r = .34). Current understanding of the independent physiologic effects of temperature on mortality, which might guide the choice of appropriate temperature specification, is unfortunately limited. However, it is worth noting that, for the range of temperature specification from "same day" to "nine by month," the COH coefficient ranges only from 1.8 to 1.3. Thus, the uncertainty in results due to this factor is not large.

Summary and Discussion

For a reasonable range of preliminary data filters meant to control for low-frequency (seasonal) confounding, estimated coefficients from a model relating daily mortality to COH range from 1.2 to 2.0 deaths per day per unit COH. Similarly, a reasonable range of variations in the specification of temperature resulted in coefficients rangingfrom 1.3 to 1.8 deaths per unit COH. These results can be re-expressed as risk coefficients by dividing by the mean New York City population for the period 1963-1976, estimated to be 9.8 million persons. This operation yields a range of risk coefficients from 0.01 to 0.02 deaths per day per unit COH per 100,000 persons. If the statistical uncertainties as quantified by the standard errors are added, then the range of risk coefficients we obtained can be said to extend from just below zero to about 0.03 deaths per day per unit COH per 100,000 persons.

For purposes of comparison with mortality risk coefficients derived from cross-sectional studies, these daily risks can be converted into annual risks. If we assume daily probabilities are independent, we can then use the binomial expression to estimate an annual risk coefficient from the daily probabilities. However, for low-probability events, such as those we are considering, this is equivalent to simply multiplying the daily risk by 365. Annual risk due to pollution at its mean is obtained by multiplying by the mean COH level for the period of study (i.e., 1.96).

It should be noted that the coefficient range given above is probably too narrow for characterizing our uncertainty of the

Table II.8

Regressions Using Different Temperature Variables

[All variables were first filtered using 15-day MA deviation filter. Regressions include SO_2 variable and day-of-week dummer variables. Coefficients represent number of daily deaths per unit COH. (Mean COH = 1.96)]

Temperature Variables	Coefficient	Statistical Error
none	3.09	0.44
same day	1.76	0.45
same day, by month	1.88	0.44
Schimmel's nine*	1.45	0.46
Schimmels' nine, by month**	1.26	0.42

*Including:
1) Same-day temperature
2) Previous-day temperature
3) Average of second and third lags
4) Average of fourth to sixth lags
5) Average of seventh to thirteenth lags
6) The square of the positive deviation of same-day temperature from its expected temperature (where expected temperature = least squares fit of sine wave to 14 years of data)
7) Same as 6 for negative deviations
8) The square of the positive deviation of the average of same-day and previous-day from their expected value
9) Same as 8 for negative deviations

**Taken from Schimmel, 1978. No day-of-week dummy variables.

relationship between daily mortality and COH in New York City. Several sources of potential error were not explicitly considered in our analysis, including: (1) population exposure misclassification resulting from utilization of pollution data from one fixed ambient monitoring site; (2) the imperfect relationship between the exposure metric, COH, and a more biologically optimal metric such as respirable particle mass concentration; and, (3) too little diversity in the range of models we fitted. Regarding the latter point, we chose to analyze a range of models that, in our opinion, spanned the approximate extent of current modeling uncertainties.

There are also more subtle reasons why our range of coefficients does not include the full range of results reported in earlier analyses of this data set (see Schimmel and Greenburg, 1972; Schimmel and Murawski, 1976; and the 1982 HEED, Appendix 3, pg. 89). One reason is that we haven't performed separate analyses of subsets of the data set (e.g., jackknife analysis). Early analyses of the New York City data were, by necessity, performed on various early segments of the full 14-year data set for which air pollution effects tended to be larger than those in later periods. Further, a simplifying feature of our sensitivity analysis was the use of a design in which model variations of one type (for example, filtering) were performed while keeping the other model variable fixed. This reduced computation complexity and simplified presentation of results, but also understated the variability that would have been obtained had a full matrix of model variations been tested. Lastly, we made no attempt to evaluate the delay (or lag) structure of air pollution-mortality associations. We expect this to lead to an underestimate of total pollution effects. Schimmel (1978) found, for example, that total air pollution effects, when summed over coefficient estimates for same-day and up to four-day lags of pollution were about 60 percent higher than effects computed from a simple same-day pollution coefficient.

Finally, the results quoted herein apply directly only for the mix of sources and time pattern of concentrations observed in New York City between 1963 and 1976. The general applicability of these results will not be certain until validation studies in several other cities with different pollution characteristics and weather patterns are undertaken.

A Test of the Time-Series Methodology Using Simulation of Los Angeles Data

Various investigators have conducted studies combining filtering and regression to investigate the relationship between daily mortality and air pollution (e.g., Schimmel, 1978; Mazumdar, Schimmel and Higgins, 1982). In the previous section, we investigated the sensitivity of regression results to filter variations and alternative regression specifications using New York City data. The purpose of this section was to investigate the behavior of analysis in cases where the "true" results were known in advance. Based upon actual mortality, air pollution and

weather data from Los Angeles County, simulated mortality series with pollution effects (as similar as possible to the actual mortality) were generated. These pollution effects were then "back calculated" using typical time-series methods (see Schimmel, 1978).

The data set for the simulation study was based upon data from Los Angeles County for the period 1973 to 1977 and including:

(1) Total daily mortality.

(2) Daily average particulate level in KM units from one station. KM is a reflectance measure of the particles' blackness. It is proportional to the quantity of elemental carbon in the atmosphere (Cass, 1983).

(3) Daily maximum temperature, minimum temperature and relative humidity.

(4) Indicator variables for day of week.

Simulated mortality data were generated (see Appendix II.3) based on assumed dose-response relationships for air pollution effects. The first case simulated was that of no pollution effects. In 500 simulations, the estimated linear regression coefficient was not significantly different from zero, suggesting that the procedure gives a reasonably unbiased estimate of B, the constant of proportionality relating KM to daily deaths. Next, various simulations were run with linear pollution effects. Again, the estimated results were reasonably unbiased with approximately the same variance as in the no-effects case. Using this information, we computed the probability of rejecting the hypothesis of no pollution effects for different values of B. Results are given in Table II.9.

Table II.9

Probability, P, of rejecting the hypothesis of no pollution effects given various "true" effects B (deaths per day per unit KM).

B	P
0.0	.05
0.5	.33
0.7	.51
1.4	.95
1.6	.99

These results may be more easily interpreted if we consider "effects at the mean," i.e., the product of B and the mean pollution level, KM = 2.9. For example, an air pollution effect that

would produce (an average) 0.7 X 2.9 = 2 deaths per day in Los Angeles could be detected 50 percent of the time. To be detected 95 percent of the time, the mean effect would have to be twice as large, or 4 deaths per day.

The 1975 population of Los Angeles County is estimated to have been 7.26×10^6 persons.* Dividing through by this figure, the numbers in the above table can be converted to risk estimates. Thus, our simulation results indicate that, in a series of length such as 1826 days with a mean pollution level of 2.9 KM, the lowest slope of a proportional dose-response curve which could be detected 95 percent of the time would be 1.9×10^{-7} deaths/person/day per KM.

The results given above provide information about the ability of typical time-series regression methods to detect air pollution/mortality effects. We don't consider these results to be directly applicable to the New York City analysis, because of several unique features of the simulation analysis. We note, however, that the risk coefficient that could be detected 95 percent of the time, when expressed at the mean exposure ($1.9 \times 10^{-7} \times 2.9$ KM = 5.5×10^{-7} deaths/person/day), is about three to five times larger than those we estimated for New York. The exact interpretation of this result must await further analyses aimed at both replicating the simulation using New York City data and estimating effects in the real Los Angeles data set. However, if these results prove to be comparable, then it would appear that the air pollution health effects indicated by the New York time series are below or near the level at which mortality effects might typically be detectable by such techniques.

*Obtained by linear interpolation of 1970 and 1980 Census figures (7.04×10^6 and 7.48×10^6, respectively).

II.4 An Analysis of Cross-Sectional Mortality Data Incorporating Fine and Inhalable Particle Mass Indices

Introduction

In prior cross-sectional analyses of the health effects of particle mass and sulfate air pollution, it has been found that these pollutants are contributors to mortality, even after socio-economic control variables are considered (e.g., see analyses by Evans et al, 1982). Such past work has employed Total Suspended Particulate Matter (TSP) and Total Suspended Particulate Sulfates (TSP $SO_4^=$), as these were the particle measures available for the 1960 and 1969 total mortality data sets considered. However, it is now thought that it is primarily the Inhalable Particles (IP) (d_a < 15um) and (especially) Fine Particles (FP) (d_a < 2.5um), that may affect mortality. It is this subset of TSP which can enter the body and is expected to have the greatest human health implications.

It is the purpose of this work to test the hypothesis that the air pollution health effects estimate derived from cross-sectional analyses will be found to be both more reliable (i.e., regression coefficient more significant) and of larger magnitude (i.e., greater mean effect), if the exposure estimates are improved. This hypothesis is based upon the statistical fact that if there is error in a predictor variable (x) in a regression, then the coefficient for that x must be biased downward (e.g., see Snedecor and Cochran, 1967). Since TSP measures are, at best, indirect indicators of true human exposures to particles, the past use of TSP indices can be expected to have introduced error (and bias) into the mortality modeling process. We wish to now test whether or not employing size-fractionated particle mass concentrations (which should more accurately represent variations in human particle exposures) enhances the statistical reliability and the magnitude of estimated particle air pollution health effects.

Method

In this work, the Lave and Seskin 1960 cross-sectional mortality data set [previously analyzed by this study (Evans et al, 1982] is first reexamined in light of recent data regarding the relationships between TSP, TSP $SO_4^=$, FP and IP (Trijonis, 1983). The TSP and sulfate data reported for each of 98 Standard Metropolitan Statistical Areas (SMSA) are employed in formulae developed by Trijonis (1983) primarily from the IP aerosol sampling network (Watson et al., 1981). These formulas were derived on a regional basis by Trijonis (see Figure II.2), and allow an estimation of FP and IP mass concentrations from historic TSP mass and sulfate data (see Table II.10). These estimates of each SMSA's mean FP and IP concentration can therefore be readily substituted into the previously developed 98 SMSA 1960 cross-sectional mortality regressions. This allows a preliminary test of the hypothesis that improved particle exposure

Table II.10

Regional Equations for the Estimation of FP and IP Mass from TSP and Sulfate Data*

REGION	EQUATIONS
Cal - San Francisco	FP = 1.1 ($SO_4^=$) + .20 (TSP - 1.4 $SO_4^=$)
	IP = 1.2 ($SO_4^=$) + .50 (TSP - 1.4 $SO_4^=$)
Cal - Central Valley	FP = 1.1 ($SO_4^=$) + .18 (TSP - 1.4 $SO_4^=$)
	IP = 1.2 ($SO_4^=$) + .49 (TSP - 1.4 $SO_4^=$)
Cal - Los Angeles	FP = 1.1 ($SO_4^=$) + .23 (TSP - 1.4 $SO_4^=$)
	IP = 1.2 ($SO_4^=$) + .64 (TSP - 1.4 $SO_4^=$)
Pacific Northwest	FP = 1.1 ($SO_4^=$) + .15 (TSP - 1.4 $SO_4^=$)
	IP = 1.2 ($SO_4^=$) + .52 (TSP - 1.4 $SO_4^=$)
Arid Southwest	FP = 1.1 ($SO_4^=$) + .17 (TSP - 1.4 $SO_4^=$)
	IP = 1.2 ($SO_4^=$) + .56 (TSP - 1.4 $SO_4^=$)
North Central	FP = 1.1 ($SO_4^=$) + .14 (TSP - 1.4 $SO_4^=$)
	IP = 1.2 ($SO_4^=$) + .48 (TSP - 1.4 $SO_4^=$)
Northeast	FP = 1.1 ($SO_4^=$) + .23 (TSP - 1.4 $SO_4^=$)
	IP = 1.2 ($SO_4^=$) + .60 (TSP - 1.4 $SO_4^=$)
Southeast	FP = 1.1 ($SO_4^=$) + .18 (TSP - 1.4 $SO_4^=$)
	IP = 1.2 ($SO_4^=$) + .50 (TSP - 1.4 $SO_4^=$)

*Listed equations are those derived via regression from 1979-1981 inhalable particle data for each region (Trijonis, 1983).

estimates should increase the statistical reliability and magnitude of the estimated air pollution mortality effects.

Figure II.2 Sites and Regions Utilized to Develop Regional FP and IP Estimation Formulae. (S denotes suburban locations, N denotes nonurban locations, and sites not marked by a letter are metropolitan locations.
Source: Trijonis (1983)

As a further test of the above-stated hypothesis, the 1960 mortality analyses were repeated using 1980 Census and 1979 mortality data (the most recent available) for some 30 SMSAs for which direct IP and FP measurements were made during 1979-1980. Although only a subset of the original 98 SMSAs can be considered, this test does provide an independent and direct means by which to check the 1960 results.

Results

TableII.11 presents an intercomparison of mortality regressions in which various particle measures are separately added to a base model (described in detail in the 1982 HEED on Airborne Particles) containing the following socio-economic control variables for each SMSA: percentage of population over 65, population median age, percentage of non-white population, population density, percentage of college educated, smoking index, and percentage of poor in the population. For the 1960 data, both the TSP mass and TSP sulfate variables approached statistical significance at the 95 percent confidence level (Models 1 and 2). However, when the Trijonis formulae were applied to the 98 SMSAs (Models 2 and 3), the resulting estimates of IP and FP yielded a noticeable improvement in the significance of the particle measures in predicting mortality, and a 50 percent rise in the mortality effect at the mean.

Table II.11

Intercomparison of Cross-Sectional Total Mortality Regressions for Alternative Particle Pollution Measures

		1960 Data Analysis (n = 98 SMSAs)				1980 Data Analysis† (n = 30 SMSAs)
Model No. (i)	Particle Pollution Variables Added to the Base Model*	Reg. Coefficient (b_i) [deaths/year per 10^5 people per $\mu g/m^3$]	Coefficient p-value	Mean Value of Variable ($\bar{x}_i$) [$\mu g/m^3$]	Ratio of Pollutant Mean Effect ($b_i \bar{x}_i$) to the Mean Effect Calculated for Sulfates	Ratio of Pollutant Mean Effect ($b_i \bar{x}_i$) to the Mean Effect Calculated for Sulfates /p-value of b_i
1	Sulfates	2.6	.064	10	1.0	1.0 /p = .001
2	TSP	0.31	.052	121	1.4	0.05/p = .88
3	IP	0.58**	.029	70	1.5	0.8 /p = .06
4	FP	1.3**	.029	31	1.5	1.3 /p = .002

*Base Model includes an intercept, percent of population $\geq$ 65, median age, percent college educated, smoking index, and percent poor in each SMSA (for details, see Appendix 3 of 1982 HEED).

TSP = Total Suspended Particulate Matter.

IP = Inhalable Particle Mass ($d_a < 15\,\mu m$).

FP = Fine Particle Mass ($d_a < 2.5\,\mu m$).

**For 1960, IP and FP were estimated based on known relationships to SO_4 and TSP (Trijonis, 1983).

†See Appendix II for complete presentation of 30 SMSA Analysis of the 1980 data set.

Table II.11 also contains summary information from the 1980 (30 SMSA) analysis.* It is interesting to note that the TSP coefficient is no longer a significant predictor of mortality, that IP approaches significance, and that sulfate and FP remain highly significant. In terms of the mean mortality effect implied by the particle coefficient, it can be seen that FP retains its greater magnitude of effect (relative to sulfates), while IP and (especially) TSP do not.

Conclusions

Based upon the 1960 and 1980 analyses, it is concluded that the use of a FP mass measure in cross-sectional mortality analyses does indeed result in a more significant and larger magnitude health effect than previous measures employed in such analyses. This agrees with both physiological and statistical expectations.

The TSP measure would have appeared to have been a reasonable choice of exposure variable based upon the 1960 analysis alone, but the 1980 data indicated that this relationship was not consistent. For 1960, TSP was found to yield a larger and (slightly) more statistically significant effect than sulfates, but in the 1980 mortality regression TSP was not at all significant. Based upon these conflicting results, the use of TSP for the estimation of particle health effects is not recommended.

The commonly employed TSP sulfate measure was found to be a consistently significant predictor in both the 1960 and 1980 analyses, indicating it to be a useful measure in the absence of FP measurements. This is not surprising in that the conditions conducive to the formation of sulfates are also conducive to the formation of other fine particle constituents, such as secondary carbonaceous material and nitrate aerosols. Thus, sulfates are often highly correlated with fine particle mass concentrations. However, it should be noted that the FP mean effect ranged from 30 to 50 percent higher than the sulfate mean effect. This indicates that the use of sulfate as a surrogate for all constituents of the FP mass, while useful, introduces additional error into the estimation of exposure, and thus may cause underestimation of actual mortality health effects of particle air pollution. As a result, it is recommended that, until a 98 SMSA 1980 analysis is completed, the FP coefficient shown in TableII.11 (1.3 deaths/year per 10^5 people per ug/m^3) be employed in the assessment of the health effects of air pollution, with the 1960 sulfate coefficient (2.6 deaths/year per 10^5 people per ug/m^3) being employed when estimates of FP impacts are unavailable.

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*Complete details of the 30 SMSA methodology and results can be found in Appendix II.

When applying the coefficients noted above, consideration must be given to the composition of the aerosol mixture involved. For example, if a sulfate coefficient were to be applied to a case in which sulfates are present in substantially lesser or greater than usual proportions (e.g., relative to organic particles or trace metals), then the results would be misleading. It can be expected that the use of the entire fine particle mass should be less sensitive to errors introduced by compositional variation from case to case. Also, it should be kept in mind that the FP coefficient is most representative for an "average" urban aerosol composition and will, to some extent, be subject to the biases noted for sulfates when applied to aerosols having a makeup very difference from the mean composition. It may be that this problem can be addressed through the development of coefficients for each of the numerous aerosol components (e.g., auto particles, soil particles, oil combustion particles, etc.). However, until aerosol component-specific coefficients are developed, the use of fine particle coefficient (rather than a TSP or sulfate coefficient) appears to provide the more acceptable alternative for risk analysis at this time.

Although the use of a fine particle mortality coefficient should provide an improvement over previously used cross-sectional indices of particle air pollution, we must emphasize the large uncertainties surrounding any such damage coefficient. Indeed, despite the fact that the coefficient is statistically greater than zero, uncertainties not considered by such analyses (e.g., errors in the measurement of the exposure variable) make it possible that the mortality risk might in fact be zero. Such coefficients have, in the past, been applied without adequate attention to their actual applicability to the situation and the uncertainties involved. We refer readers to the coefficient limitations noted in Section IV and the Summary of the 1982 HEED. Improper application of cross-sectional coefficients may lead to erroneous conclusions regarding health risks.

Probably the most important conclusion to be drawn from this analysis is that making refinements in the estimation of human exposures to air pollution does indeed enhance our ability to quantify the health effects of these exposures. The use of FP is an improvement in that it represents the breathable mass fraction, which is also less subject to errors introduced by the siting of specific monitors (because it is less spacially variable). It is important to note, however, that further improvements can and should be made in pollution exposure estimates. These include the estimation of variations in personal exposure (due to influences such as indoor air pollution), as well as in individual dosages, given similar exposures. It seems clear that, as the estimates of exposure and dosage are refined, our ability to detect and to be confident in our estimates of the human health effects of air pollution will improve.

III. Toxic Effects of Airborne Particles

The 1982 HEED on airborne particles summarized the literature on animal and human studies relevant to the component-specific toxicities of airborne particles. Toxicity data on metals, sulfates, nitrates, natural dusts, diesel particles and B(a)P were reviewed. Our second year toxicity evaluations have concentrated on the evaluation and ranking of health risks based upon *in vitro* and *in vivo* bioassays. In particular, mutagenicity, carcinogenicity, and animal bioassays on non-neoplastic particle toxicity effects were analyzed. In addition to these assessments (those derived from bioassay and relative potency evaluations), we have extended our review of the toxicity of airborne acid sulfates and nitrates, which in our 1982 HEED were identified to be among the most significant factors in the interpretation of observational and epidemiologic data on population exposures to ambient particles.

In this section, carcinogenic and noncarcinogenic effects and risks associated with particle exposures will be described.

III.1 Carcinogenic Effects of Particulate Matter: Review of Evidence from Bioassay Experiments

The main objective of our work in this area was the estimation and comparison of the carcinogenic potencies of various particle types (diesel, coal fly ash, woodstove, oil, gasoline engine emissions, etc.). Another important goal of this component of our research was the identification of the sources of uncertainty involved and the estimation of their magnitude. As discussed further in the Appendices to this and the previous HEED on airborne particles, we have evaluated three broad categories of studies relevant to accomplishing this task. They are:

(1) Epidemiologic/occupational studies (see Appendix II).

(2) Animal studies (see 1982 HEED Appendix 2).

(3) Short-term bioassays (see Appendix III.1 and 1982 HEED Appendix 2).

Strengths and weaknesses, with respect to the quantification and ranking of particle potencies, were identified in each of three categories. In brief, they are as follows:

(1) Epidemiologic studies
   a) high degree of relevance; but,
   b) studies often lack estimates on many complex particles or components of airborne particles.

(2) Animal studies
   a) extrapolations between species are difficult and controversial;
   b) again, definitive data lacking.

(3) Short-term bioassays
   a) techniques for extrapolation are not yet established; however,
   b) considerable data bases to support risk analytic studies are available.

Subsequent to our initial scoping efforts, we decided to concentrate on bioassays, mainly because of the availability of data allowing for correlation between in vitro and human carcinogenicity results. Looking further at our options, we focused on Ames bioassay data since this data base was the most extensive and among the most standardized.

Activities in this area have been divided into three phases. In the first phase (contained in the 1982 HEED), the biological validity and quantitative shortcomings of short-term bioassays were reviewed. In light of the inadequacy of traditional surrogates for carcinogenicity such as the B(a)P content of complex mixtures, a proposal was developed for utilizing potencies from short-term bioassays directly in our risk assessment of airborne particles.

In the second phase, a number of projects have been undertaken in an effort to provide a human risk interpretation of the quantitative results of several bioassay systems. The progress of these is summarized below. (Further details may be found in Appendix III.1)

In the third and final stage of the project, published bioassay results pertinent to urban aerosols and combustion emissions are presented and interpreted using the results of the previous phases.

Toxicity Ranking of Particles by Using Potencies Estimated from Short-Term Bioassays

Rationale and Method

One approach which is useful in ongoing assessments of carcinogenic risk involves comparisons through a ranking scheme. These rankings can be formulatd by weighting various types of evidence which relate to human carcinogenic potential. In the past, emphasis has focused on ranking compounds as to the likelihood of their being carcinogens. More recently, attention has shifted toward attempts to go beyond mere determinations of carcinogenic potential. Such efforts seek to estimate the relative carcinogenic potencies of these substances.

Many investigations have approached this problem through comparisons of activities in different short-term bioassays and animal model systems (Albert et al., 1982;DuMouchel and Harris, 1983; Cuddihy et al., 1981). For complex mixtures, the relative concentrations of surrogate substances which exhibit carcinogenic acitivity, such as B(a)P, have also been used (Cuddihy et al.,

1980). The limitations of this latter approach are discussed in more detail in the 1982 HEED.

These comparisons can provide a rank ordering of potencies within certain well-defined tests or between disparate tests. A consistent response within a system which is believed to closely mimic the in vivo situation in humans would provide the best evidence of human cancer risk. Although it seems reasonable to assume that short-term assays using whole animal systems (skin painting) or eukaryotic cell lines are more representative of humans than prokaryotic bacterial systems, the relationships between these systems are not clear. Thus, it does not appear advisable at this time to completely discount the results from any of these tests when attempting to rank the potencies of suspect carcinogens. Consistent responses, or rankings, across disparate systems should provide the analyst with an increased degree of confidence in any proposed ranks. For pollutants tested in only a few or even one test system, confidence in the rank potencies cannot be great.

As a first step, potency rankings provide comparative information while avoiding a direct quantitative calculation of the magnitudes of risk involved. Of course, quantitative estimates can also be used as the basis for a ranking scheme. However, the numbers generated often assume a greater importance and degree of validity than is justified or intended. Still, rank estimates may prove useful in determining the value or urgency of research or control efforts among different pollution sources (Holmberg, 1983). They may also be used to follow the effects upon genotoxic emissions subsequent to various alterations in combustion conditions or pollution control technology. Yet even here, an implicit assumption must be made that the respective tests are in fact relevant as predictors of human health risk. Therefore, the presentation and use of such data requires caution. Many factors must be considered, including: fundamental assumptions and non-quantifiable sources of uncertainty, which are often unstated; differences in the extent and magnitudes of exposure; comparability of data; and, issues which are less scientific in nature relating to questions of equity and differential assumption of risks or hypothetical risks.

Sources of Uncertainty and Data Base Considerations

Comparisons of both a qualitative and quantitative nature are best made when the various samples are treated within the same experiment (Claxton and Huisingh, 1979). Our attempts to extend a comparative potency analysis to additional particles has necessitated the use of results from many experiments and a number of separate investigations. Although consistency between and within laboratories can be demonstrated for a number of assays, many sources of uncertainty exist which have not yet been adequately quantified. These include factors integral to the assays themselves, as well as other variations in sampling, extraction, etc. Variations in these factors is likely to be greater between laboratories than within, and for certain assays

as compared to others which have a more standarized protocol. However, restricting an analysis to only those studies where multiple sources have been compared within the same laboratory would drastically limit an already meager data set and, as importantly, discount differences occurring within an emission category. For this reason we have considered all data available, despite having been reported by a number of laboratories using varying analysis techniques.

Many of the following comparisons are taken from data presentedin Appendix III.1. Due to inconsistencies in experimental methods and data presentation, extensive comparisons between different particle types has proven difficult. Throughout the analysis certain assumptions have been necessitated. These are explicitly stated when made. Data from specific research groups covering different particles and combined data from several groups are used.

Diesel and Gasoline Engine Emissions

The data base on autobmobile-related mutagencity is fairly extensive, with Ames data available for many makes, models and operating conditions. While there are problems with direct comparison of these data (see 1982 HEED, Appendix II), the comparability of the data on these sources is enhanced because of the fairly standardized protocols used.

Combustion Products

Numerous difficulties exist in the interpretation of data from coal and oil combustion. Compared to the case for diesels, few studies have been performed on these sources, limiting the useful data base. The data available is also confounded by a number of factors. Many of these have been reviewed by G. Fischer (1983). Briefly, these problems relate to the following: the toxicity of the fly ash samples to the bacterial strains; inconsistencies in the mode and location of sampling, especially with respect to the location of the samples in the effluent stream; and variations in the combustion conditions, fuel sources and engineering design of the units tested. Finally, a variety of solvents have been used to extract fly ash.

Many of these same difficulties apply to the other combustion emissions for which we have data. Thus, appropriate data is available from only a limited number of studies. For these reasons, variation in mutagenic output between different combustion units, or between laboratories, cannot be estimated.

Comparison of Potency Rankings

The potencies of particles emitted by sources are dependent upon the character and quantity of that emission. Exposures will be determined by the proportion of deposited particles which is available for biological uptake or surface interactions with given cell populations. This is roughly approximated by organic

solvent extracts, a likely upper-bound estimate. Moreover, the quantity of deposited particles will be a function of particulate mass emissions. Thus, carcinogenic risk posed by various particles will be a function of the total exposure to active carcinogens sorbed to or comprising the particles, and the specific activity of these compounds.

Variations in any of these three parameters--potency, percent extractable mass and total particle mass--will alter overall risk comparisons. Thus, the choice of potency units (activity per mass of particles, per mass of extracts, per vehicle mile, etc.) will have profound effects on comparative ranks. This point is illustrated in Table III.1, where Ames rankings shift depending upon the units used. (Further illustration of this matter appears in Appendix III.1, Table 1.)

Ultimately, comparisons must be made in units which are appropriate for a given category of emissions. For automotive emissions, the units of activity/mile traveled seem appropriate. Other technologies may be more appropriately compared using activity per unit of energy utilized to achieve a given end result. Finally, intercomparison between different particle types requires a consistent unit of measurement. In this case, activity/unit of particle mass seems appropriate, and is also of obvious utility in extensions to ambient exposures. Investigators reporting biological activity should attempt to measure and present data allowing for conversions between as many units as possible and include, at a minimum, information on particle emission rates for determination of activity per particle mass. Often this has not been the case, resulting in substantial quantities of relevant, but non-comparable, data. Because of this, our quantitative attempts to compare particle potencies have been limited to the most commonly used units, activity/ug extracted organics. These estimates are therefore difficult to relate to reported ambient concentrations of various particles, which are almost universally reported in terms of total particulate mass. In the following, we summarize the comparative potency data on emissions from automobiles, woodstoves, residential heaters, and oil and coal combustion.

Automobile Emissions

A number of trends were noted in comparisons between particle types tested in a number of assays (Albert et al., 1982). Available data indicate that cigarette smoke condensate consistently ranks low in many assays (Table III.2). Assay results also suggest that fundamental differences exist between the active components of automobile emissions and the particle types for which human epidemiologic data are available. These latter samples rank high in the eukaryotic test systems with S9 metabolic activation in the Mouse Lymphma (ML) assay, but rank consistently lower in the Ames test and ML assay without activation. This clearly indicates that more of the activity in these samples is due to activatable mutagens rather than direct-acting compounds which contribute a large portion of the activity of diesel

Table III.1

Ames Ranking, Standardized to Nissan Value*

	MA⁻			MA⁺		
Vehicle	Rev/ug Extract	Rev mg/ Part.	Rev/ Mile	Rev/ug Extract	Rev mg/ Part.	Rev/ Mile
Caterpillar	.03	.11	--	.01	.05	--
Nissan	1.00	1.00	1.00	1.00	1.00	1.00
Oldsmobile	.19	.41	.65	.10	.21	.34
Volkswagon Rabbit	.33	.69	.37	.25	.56	.31
Gas Unleaded	.14	.76	.01	.10	.54	.009
Gas Leaded	1.04	2.48	.37	.80	1.93	.27

*Data from Albert et al. (1982)

Table III.2

Ranking of Particulate Extract Potencies Standardized to Coke Oven Topside*

Human Lung Cancer	Coke Oven Topside (1) > Roofing Tar (.39) >> Cigarette Smoke Condensate (.0024)
Mouse Skin Tumor Initiation	Coke Oven Main (1.5), Topside (1) > Nissan (.28), Roofing Tar (.20), Olds (.15), VW Rabbit (.11), Mustang II (.08) >> CSC (.0011), Caterpillar (neg.)
Mutation in L5178Y Mouse Lymphoma Cells ($S9^+$)	Coke Oven Main (2.2), Roofing Tar (1.4) > Coke Oven Topside (1) > Nissan (.24), Olds (.11), VW Rabbit (.06), Mustang II (.09), CSC (.06) > Caterpillar (.005)
Mutation in L5178Y Mouse Lymphoma Cells ($S9^-$)	Nissan (5.9) > Olds (1.7), VW Rabbit (1.4) > Coke Oven Topside (1) > Roofing Tar (.55), CSC (.55), Coke Oven Main (.54), Mustang II (.54), Caterpillar (.35)
Ames ($S9^+$) TA98	Nissan (12) > Coke Oven Main (6.1) > Mustang II (3.12), VW Rabbit (2.76), Olds (1.32) > Coke Oven Topside (1), Roofing Tar (.78), CSC (.52) > Caterpillar (.05)
Ames ($S9^-$) TA98	Nissan (16) > VW Rabbit (5.5), Olds (3.1), Mustang II (2.3), Coke Oven Topside (1) > Caterpillar (.54) > Coke Oven Main (.16) >> Roofing Tar (0), CSC (0)

*Data from Albert et al. (1982)

particles. However, it must be kept in mind that rankings can be altered through choice of potency measures, mainly being influenced by the percentage extractable from the particles (compare Table III.2 and Table 2 in Appendix III.1). (For example, a large difference in relative potencies--84 times greater--is apparent with coke oven main samples compared with topside samples.)

Table III.1 and Table 3 in Appendix III.1 present Ames rankings standardized for comparative purposes to the Nissan diesel engine values on a mileage basis. Although the relative potencies of the diesel emission vary somewhat, they are generally within a factor of 3. On the other hand, the gasoline catalyst engine (Mustang II) tested is one to two orders of magnitude lower. This consistency between assays strengthens the hypothesis that diesel engines constitute a greater human health hazard than gasoline catalyst vehicles.

Woodstove and Residential Oil Furnace

The total mutagenic output of woodstoves for two fuel types (oak and pine) appear considerably greater than that of residential heaters (Table III.3). This data is in general agreement with activities presented by Viau et al. (1982) for forest-fire polluted air (see Appendix III.1). Although the extracted organics from the two oil furnaces exhibit greater activity, the woodstoves emit considerably more organic mass. Therefore, the emission rates largely determine the potency rank when based upon activity per unit of heat generated.

These findings can be extended one step further through comparison with another data set presented by Claxton and Huisingh (1979). In this paper, the authors compare residential heater emissions with a number of particulate categories discussed previously. On an extract basis, the residential heater exhibited approximately one half the activity of the gasoline catalyst of the Mustang II. These results are summarized in Table 4, Appendix III.1. Again, however, the data presented do not allow for the expression of these results in terms of activity per mass, making potency comparisons in terms of overall particle output impossible.

Coal and Oil Combustion

Commercial coal and oil combustion fly ash have also been compared, although only to a limited extent. Alfheim et al. (1983) compared the mutagenic output from three oil-fired and four coal-fired burners (Table 5, Appendix III.1). One of the oil burners showed a mutagenic activity of about 500 rev/mJ and samples from an FBC had an activity of 58,000 rev/mJ. The activities in the other plants were considerably lower, ranging from <50 - <80 rev/mJ (Alfheim, 1983). Ahlberg et al. (1983) tested emission from an oil-fired plant and a coal plant and found the mutagenicity of the emissions to be below the detection limit of the assay for most samples. Data on the highest responses recor-

Table III.3

Rank Potencies of Residential Health Units[a,b,c]

Rev/Joule[d]:	Woodstove Oak Fuel	>	Woodstove Pine Fuel	>>	Modified Commercial Furnace	>	Residential Oil Furnace
	(900)		(169)		(7.6)		(1)
Rev/ug Extract:	Modified Commercial Furnace	>	Residential Oil Furnace	>	Woodstove Pine Fuel	>	Woodstove Oak Fuel
	(2.5)		(1)		(.65)		(.45)

[a]Lewtas (1981)

[b]TA 98, DCM extracts

[c]Results standardized to residental furnace results

[d]$S9^+$, $S9^-$ results - .15 rev/ug (oak), .29 rev/ug (pine)

Table III.4

Mutagenicity from Experimental AFBC[a,b]

Rev/mg Ash TA 98, $S9^-$	Ba_y Filter Samples (mean ± standard deviation)	High Volume Filter[c] (mean ± standard deviation)	High volume Cascade Impactor (mean ± standard deviation)
	(2.9 ± 3.7)	(3.7 ± 2.9)	5 ± 5.4

[a]Source: Clark and Hobbs (1980)

[b]DCM extracts, 6 sets of operating conditions, samples 6A-E

[c]calculated from single doses

[d]calculated from mutagenicity of smallest size fraction

ded indicate little difference between these plants (Table 6, Appendix III.1). Samples of Fluidized Bed Combustion (FBC) and conventional coal combustion fly ash tested by Mumford and Lewtas (1982) suggest that FBC emissions may exhibit more Ames activity (Table 7, Appendix III.1). However, conversion to units of rev/energy released is not possible for this paper. Results from Clark et al. (1980) are in agreement with this finding on a rev/extract basis, but suggest the opposite relationship for rev/particle mass (Table 8, Appendix III.1).

It is apparent from the studies noted above that combustion conditions are important determinants of mutagenic output. The FBC tested by Alfheim was operating at a very inefficient level; Kubitschek and Williams (1980) found greatly increased mutagenic activities during start-up versus steady-state operations in another FBC (Table 9, Appendix III.1). Therefore, the differences noted in results between this source and others may be due to inefficient combustion occurring in these smaller, experimental plants, and not due to any intrinsic differences in the emissions. The comparative differences in results between these investigators are summarized in Table III.4. The wide range in sampling techniques, locations and solvents used seriously complicates attempts at potency ranking. However, it appears safe to conclude that inefficient combustion conditions will significantly increase mutagenic outputs.

Projection of Human Cancer Risks Utilizing Potencies from Short-Term Bioassays

The following summary presents an attempt to determine quantitative assessments of the comparative risks posed to human populations by various particles. First, a discussion of a general potency model is presented, followed by the estimation of potency conversion factors and associated uncertainties for the various assays considered.

Initially, Ames potencies for the various particles are obtained from results reported in the literature. Using these figures and a proposed model based upon a relative potency hypothesis, 95 percent confidence intervals are calculated for increments in relative human cancer risk attributable to each emission category. The uncertainties involved are great and are not fully captured in our variance estimates. Therefore, these results should not be considered as reliable best estimates of the range of risks posed. However, their calculation serves a useful purpose in demonstrating the complexity of such a process. The results may also be used for general comparisons between particle types. Better estimates await a more extensive data base in more bioassays, and a better understanding of the relationships between bioassays and carcinogenic potency.

Calculation of Extrapolation Factors and Errors for Short-Term Bioassays

In 1979, the EPA initiated a program to evaluate the population lung cancer risk attributable to the increased use of light-duty diesel engines (U.S. EPA, 1979). Their novel approach involved the simultaneous application of several bioassays to diesel emissions and three organic combustion products for which enough reliable epidemiologic evidence exists to establish exposure response relationships. By assuming that the relative potency of a substance is preserved over species, it is possible to use the EPA data base to derive human potencies for diesel emissions (Albert et al., 1982). By implication, their method allows the calculation of multiplicative factors relating bioassay and human potencies. In this section, we utilize a model proposed by DuMouchel and Harris (1983) to estimate extrapolation factors and a measure of the uncertainty incurred by their use.

Methods

The procedure used is based upon the models shown in Figure III.1. As DuMouchel and Harris pointed out, the constant relative potency assumption implies that any dose-exposure response slope may be represented as the product of a particle-specific factor and an assay-specific factor. This model preserves the constant potency ratio for any two particles between assays and for any two assays between particles. In addition, it provides a method for utilizing the multiple assay results contained in the EPA data base.

Figure III.1

Model Specification

(Source: DuMouchel and Harris, 1982)

$$Y_{ij} = \alpha_i \beta_j \delta_{ij} \epsilon_{ij}$$

Y_{ij} = Dose/exposure response slope in the ith assay for the jth particle extract.

α_i = The constant assay factor, unknown.

β_j = The constant particle factor , unknown.

δ_{ij} = The random deviation from the model, ln (δ_{ij}) assumed $N(0,\sigma^2)$, σ^2 unknown.

ϵ_{ij} = The random experimental error, ln (ϵ_{ij}) assumed $N(0,c_{ij}^2)$, c_{ij}^2 known.

Inadequacies in relative potency assumption are modeled by a stochastic disturbance, represented by δ_{ij} terms in Figure III.1. These are assumed to be interchangeable assay/particle combinations in the sense that the absolute deviations in different cells are equally informative about the expected deviation in a new, untested cell. The precision of each slope is included explicitly in the model in order to distinguish between the error made in assuming constant relative potencies and the precision of individual studies.

In our analysis, we deviate from the model only in the specification of σ^2, the variance δ_{ij}. Instead of a single σ^2, we allow for an arbitrary partition of the cells into groups with a common variance for δ_{ij}. Thus, we estimate several values, σ_k^2.

DuMouchel and Harris used a variety of methods for estimating the critical parameters in their model. However, we have adopted only the Maximum Likelihood (ML) methods. Computations are performed using the EM algorithm for mixed random and fixed effect models (Laird, 1982). A Restricted Maximum Likelihood estimator (REML) approach (Harville, 1977) was used in estimating variance components to compensate for bias in the ordinary ML estimators.

Estimated Extrapolation Factors and Errors

In a preliminary analysis, we calibrated the model separately for each assay against the human data. Almost all of the assays fail to accurately predict the human data. The most common cause of error is an over-prediction of the CSC (Cigarette Smoke Condensate) coefficient. The skin tumor initiation assay stands out as the best predictor and the sister chromatid exchange as the worst (Figure 1, Appendix III.1).

Since the evidence seemed to suggest differences in the degree of fit between assays, we estimated a different variance component for each assay. Because the human and tumor incidence data agreed so well and because of the sparse skin cancer data, we pooled all of the *in vivo* tests in this analysis. The variance components, σ_k^2, may be thought of as measuring the degree to which each assay diverges from the constant relative potency model.

In Appendix III.1, we also contrast the estimated variances (expressed as coefficients of variation) computed using all the data and multiple components with the single component estimates. (The latter estimates are measures of how well each assay agrees with the human data, whereas the former are measures of how well each assay agrees with the other assays.) Especially, we found that the relative potencies in the human data run counter to the trend found in the majority of assays (Figure 2, Appendix III.1. Furthermore, even precise knowledge of the common relative potency does not completely determine the human response. In fact, if this battery of assays adequately characterized the

common relative potency, the actual human potency may differ by a factor of 10. (See also Figure 3, Appendix III.6.)

Table III.5 provides extrapolation factors for each of the five assays. The coefficient of variation is an estimate of the error encountered in using the assay to predict an emission's relative potency. For instance, for the Ames test, a confidence interval of which a standard deviation wide on the log scale would include values of a factor of 2 higher than the predicted relative potency.

Quantification of Risks and Uncertainties

It should be stated at the onset that the calculations that follow include many uncertainties (mostly experimental), some of which are not quantifiable at this time. The Ames potency values which have been determined for the various particle types are derived from results from many labs. This provides an empirical picture of the stability of these estimates as compared to estimates from a single lab or a limited number of vehicles. Thus, some inter-vehicle differences and inter-lab variability are captured in these results. However, a similar approach has not proven feasible for the known carcinogens that are used in comparative potency determinations, since fewer of the samples have been testd. We do not know if the fundamental relationships (variability in response as it relates to predictive value) between assays are a function of the laboratories carrying out the assays. If this is the case, then scaling factors and variance components of our comparative potency model would require modification. Thus, even our estimations of the variances cannot be viewed as conservative; a greater degree of variability would be likely.

Table III.6 summarizes the Ames TA 98 potencies for several emission sources, as determined from a number of published studies. Due to limitations in the data base, several estimates are based upon the results of only one or two investigators. In these cases, the highest Coefficient of Variation (CV) value, determined from the diesel category (the largest data base), was used as an approximate value. Given the overwhelming contribution of the model variances, this appears to be a reasonable determination.

These values were used to estimate increments in relative risk of human lung cancer following the analytical method outlined previously. Results are summarized in Table III.7 and Figure 4 in Appendix III.1, where estimated risks and 95 percent confidence intervals surrounding them are presented. As can be seen, the uncertainty involved in these estimates is considerable, spanning several orders of magnitude. Again, it must be noted that all sources of uncertainty have not been adequately accounted for in this analysis, due primarily to the limitations and/or sparseness of the data base. It should also be emphasized that these estimates are based upon using only the Ames data and may differ markedly if alternative bioassays are used in pre-

Table III.5

Bioassay Extrapolation Factors and Errors

Assay	Units	Factor	Extrapolation Error	
			Coefficient of Variation	Log Variance
Enhancement of viral transformation	$\frac{\text{RR* per } 10^4\ \mu g/m^3 \text{ extractable organics - years}}{\text{foci}/10^6 \text{ surv. cells}/\mu g/ml}$	6.6	2.4	1.5
Mutation in L5178Y mouse lymphoma cells (+MA)	$\frac{\text{RR per } 10^4\ \mu g/m^3 \text{ extractable organics - years}}{\text{TK mutants}/10^6 \text{ surv. cells}/\mu g/ml}$	0.26	2.6	1.6
SCE in CHO cells (+MA)	$\frac{\text{RR per } 10^4\ \mu g/m^3 \text{ extractable organics - years}}{\text{SCE/cell}/\mu g/ml}$	15.3	1.2	0.60
Ames, TA 98 (+MA)	$\frac{\text{RR per } 10^4\ \mu g/m^3 \text{ extractable organics - years}}{\text{Revertants}/\mu g}$	0.29	1.1	0.56
Ames, TA 98 (-MA)	$\frac{\text{RR per } 10^4\ \mu g/m^3 \text{ extractable organics - years}}{\text{Revertants}/\mu g}$	1.14	5.6	3.6
Skin tumor initiation	$\frac{\text{RR per } 10^4\ \mu g/m^3 \text{ extractable organics - years}}{\text{Papillomas/mouse at 1 mg}}$	3.4	5.9	3.7

*Human Relative Risk of Lung Cancer

Table III.6

Ames TA 98, S9⁻ Potencies

	Mean (Rev/µg Extract)	Standard Deviation (Rev/µg Extract)	Coefficient of Variation
Light-duty[a] diesel	12.45	12.47	1.002
Catalyst[b] spark engine	11.1	4.4	.40
Non-catalyst[c] spark engine	8.5 (high estimate)[c] .7 (low estimate)[d]	-- --	1.002[k] 1.002[k]
Woodstove[e]	1.1	.28	1.002[k]
Residential[f] heater	.905	--	1.002[k]
Fluidized[g] bed coal	10.15	--	1.002[k]
Conventional[h] coal	2.04	--	1.002[k]
Oil[i]	6.1[j]	--	1.002[k]

[a]Results from Hyde et al. (1982), Pitts et al. (1982), Pederson and Siak (1981), Dukovich (1981), and Clark et al. (1982).

[b]Lang (1981), Pierson (1983), Clark et al. (1982), Claxton and Kohan (1981), Dukovich (1981).

[c]Lang et al. (1981).

[d]Wang, Rappaport et al. (1978).

[e]Lewtas et al. (1982).

[f]Claxton and Huisingh (1979).

[g]Mumford and Lewtas (1982), Clark et al. (1981b).

[h]Clark et al.(1981), Mumford and Lewtas (1982).

[i]Alfheim et al. (1983).

[j]Acetone extract.

[k]Limited sample size, coefficient of variation taken as maximum obtained in all categories.

Table III.7

Increment in Relative Risk of Lung Cancer per $\mu g/m^3$ extractable organics - years*

		95% Confidence Interal	Estimate
Light-duty diesel		$(5.4 \times 10^{-6} - .37)$	1.4×10^{-3}
Catalyst spark engine		$(6 \times 10^{-6} - .28)$	1.3×10^{-3}
Non-catalyst spark engine	high:	$(3.7 \times 10^{-6} - .25)$	9.7×10^{-4}
	low:	$(3 \times 10^{-7} - .02)$	7.9×10^{-5}
Woodstove		$(4.8 \times 10^{-7} - .033)$	1.25×10^{-4}
Residental heater		$(4 \times 10^{-7} - .027)$	1.02×10^{-4}
FBC		$(4.4 \times 10^{-6} - .301)$	1.15×10^{-3}
Conventional coal		$(1.3 \times 10^{-6} - .087)$	3.3×10^{-4}
Oil		$(2.6 \times 10^{-6} - .18)$	6.9×10^{-4}

*Estimates based upon Ames data shown in Table III.6

dicting incremental relative risk cancer (e.g., for light-duty diesel).

Unfortunately, the values presented in Table III.7 do not tell us much about the actual contributions to risk by each particle category. The extension of the analysis to comparisons of actual exposures experienced by the population as a whole is difficult. Rough interconversions between the units of activity (extract activity and whole particle activity) are possible, based upon the approximate percentage of particle mass that is extractable for each category of particles. Likewise, estimates of exposures can be generated based upon ambient monitoring and source apportionment techniques. Data on particulate exposures were collected for various sections of the country (c.f. Appendix I.1) in an attempt to tie such information to our bioassay results, thereby providing a regional estimate of excess risk attributable to each particle source type. Unfortunately, the available data were not in a form compatible with our biassay results, being expressed in terms of TSP or other measures of particle mass, and not including consistent apportionment for the particles for which we generated risk estimates. It is also obvious that interconversion of these units would introduce considerable additional uncertainty (extractable organic fraction is not a stable characteristic within a particle category). Additionally, the present exposure apportionments were also highly uncertain. Because of these new uncertainties and the already large degree of variability in the risk estimate, it was decided not to combine these data sets until further refinements are achieved. The estimated risk coefficients do, however, suggest that with the current state of knowledge attention should be given to sources which emit the greatest mass of extractable organics, especially those sorbed to particles in the inhalable size range. Aside from their greater potential for depositing in the lung, the smaller size particles appear to contribute the largest quantity of mutagenic activity, probably due to their larger surface area and, thus, sorbtive capacity.

Conclusions

The comparative potency approach holds much promise for delineating the range of potential human cancer risks resulting from exposures to complex particle mixtures. However, at this time, it appears premature to use data generated from short-term bioassays for anything more than general comparisons.

Before applying these factors, the risk analyst should be aware that the following assumptions have been made:

- all exposure response relationships are linear;
- interactive effects are ignored;
- all coefficients are in terms of DCM (dichloro-methane) extractable organics, and DCM is assumed to extract all activity; use of these coefficients in actual ambient

exposure-risk determinations is difficult since data on such exposures are usually available only in terms of particle mass; and,

- experimental and extrapolation errors are random and lognormal.

The constant relative potency model must be recognized as an intentional oversimplication of the complex and inevitably nonlinear relationship between currently available short-term tests and human risk. However, if we assume that no additional human data becomes available, future research will have to be directed primarily toward improving bioassay technology. Approaches such as the EPA study may be improved upon by expanding the potency set to include the much larger group of known animal carcinogenics. Eventually, basic research into the physiological mechanisms of carcinogenesis may provide a model that, in conjunction with bioassays, will provide useful risk assessments. Therefore, we believe that in the interim, the "correlation" studies are perhaps the best available technology.

III.2.1 Non-Neoplastic Toxicity of Particles and Their Significance to Human Health: Metals

Animal bioassays have been employed in the study of chemical species which are components of particles (e.g., metals, sulfates, hydrocarbons), specific emission sources (e.g., coal combustion products, automobile exhaust), and certain composite aerosols (Arizona road dust). In this component of the study, we have evaluated bioassays relevant to non-neoplastic lung disease. We believe that this approach will help in understanding the toxicity of ambient particulate matter in terms of disease outcome, while identifying those components most likely to cause lung damage.

There are many methods available to assess the toxicity of particles and their components. These tests range from *in vitro* measures of pulmonary macrophage function (phagocytosis, viability, etc.) to measure of lung function in whole animals and histopathological studies of lungs from exposed animals. We have focused on five main categories of bioassays. This choice was based on the relevance of the assays to lung damage and the number and types of toxic agents studied using the different assays. The remainder of this section (as well as Appendix III.2) discusses these assays in further detail. It also presents toxicity rankings and related information on various metals (which are common constituents of airborne particulate matter) in *in vivo* and *in vitro* systems. The bioassay data are then compared to human data on ambient exposures and occupational threshold limit values for the metals considered.

Bioassays for Mucociliary Function

Previous research regarding *in vitro* macrophage bioassays and infectivity models (see Appendix II, 1982 HEED) considered the toxic effects of particles on the alveolar regions of the lungs. These effects were relevant to inflammatory changes, susceptibility to infection, fibrosis and emphysema. The response to particles deposited in the airways must also be considered when estimating health effects from exposure to air pollution particles. This is especially important for particles in the 5 to 10 um range, since a significant portion of these particles will be deposited in the tracheobronchial region. In this work, we have, therefore, evaluated bioassays that measure the effects of particles (or components of particles) on the mucociliary layer of the conducting airways. These measures include measures of function (ciliary beat frequency, electrical conduction, particle clearance), histopathological changes (necrosis of cilia, desquamation of epithelial cells), and biochemical indicators (quantity and quality of glycoprotein secretion, intracellular levels).

Mucociliary bioassays have now been used to evaluate metals with respect to toxicity ranking. Interestingly, some of the toxicity ranks were the same order as those observed in *in vitro* macrophage and infectivity models (e.g., Cd > Cu > Ni). This

suggests that the mechanism of damage may be similar for the different cell types. Further indication that these effects may be mediated through common mechanisms can be derived from studies of antagonism and modifying factors. As was observed with *in vitro* studies of macrophage viability, there were antagonistic interactions among different metals for mucociliary effects. For example, Cu suppressed the toxicity of Cd, and Ni suppressed the toxicity of Cu. A plausible mechanism for the antagonism is competition for binding sites and subsequent cellular uptake. These observations suggest that calculations of total toxicity based on individual metal contents could be overestimates when many different metals are present.

The effects of metals on the mucociliary layer were usually reversible. A noticeable enhancement of recovery, when allowed, occurred *in vivo* versus *in vitro*, suggesting an influence of other cell types and humoral factors on the repair process. Rapid clearance rates of particles from the tracheobronchial region were probably also involved in the reversal of the toxic effects. These studies suggest that acute effects may be more important than chronic effects with respect to mucociliary injury. However, it must be realized that the longest exposure was two weeks, and chronic studies are thus necessary. Furthermore, observations also suggest that the airway epithelium may be very sensitive to the effects of toxic agents. Since many of these effects are relatively severe (albeit reversible), they must be considered as important health effects when evaluating the toxicity of particulates. Further details on the bioassays for mucociliary function are presented in Appendix III.2 to the HEED. A description of other assays considered can be found in Appendix 2 of the 1982 HEED.)

Ranking Ambient Particulates

Having identified relevant bioassay systems, we have attempted to establish a hierarchy of toxicity for various components of air pollution through a toxicologic ranking protocol. The following section describes some of the assumptions and methods used and the principal findings to date (more detailed discussions are presented in Appendix III.2).

Our preliminary linear regression studies of dose-response relationships on *in vitro* macrophage tests provided the estimated concentrations required to reduce the effect level to 50 percent of the maximum observed value over background (EC_{50}). We then established a relative toxicity ranking of the five metals from these data (see Appendix III.2). By combining these toxicity ranks with compositional data of air pollution particulates, we also attempted to assess the toxicity of defined urban aerosols (in terms of metal-based components) that appear most likely to cause harm. This aspect of our assessments is summarized below.

Comparison of Bioassay Toxicity Levels to Human Exposures

It is difficult to extrapolate from concentrations of samples tested in *in vitro* macrophage bioassays to levels that would be encountered by macrophages in human lungs. In the whole lung, serum components and surfactant will coat particles, and that may affect their toxicity. Furthermore, the macrophage population of the lungs is in a dynamic state; macrophages killed by toxic particles will be replaced by new macrophages recruited into the lungs. Thus, it is difficult to assess how a dose of aerosol received by macrophages *in vitro* compares to the same dose received by macrophages within the lungs.

While realizing these uncertainties, a comparison of *in vivo* and *in vitro* levels of certain metals and the results are presented in Table III.8. The values used for metals in human lungs (Schroeder, 1970) are maximum observed values, and thus represent a worst-case estimate. The concentrations of the various metals in a human lung are determined by assuming that 1 g of tissue occupies 1 ml volume and the average weight of the lungs of an adult male is 953 g (Diem and Lentner, 1973). Thus, the maximum ug/lung is divided by 953 to obtain ug/ml "*in vivo*". This assumes that the metal is evenly distributed in the lungs, which is probably not true. Heterogenicity of fly ash particles results in some macrophages receiving very high doses of certain metals (Hayes et al, 1980). Many chronic pulmonary diseases are initiated (or at least aggravated) by the inhalation of toxic particles, yet little is known about how particles deposit in lungs that are abnormal.

TableIII.8 shows that the average metal concentration in human lungs is 0.6 to 6 percent of the *in vitro* EC_{50} concentration. Since the human values chosen represent the maximum levels observed, it would appear from these calculations that the levels of these metals may not be high enough to cause direct and measurable macrophage effects. However, for non-cancer health effects, such as changes in susceptibility to infection and respiratory function, damage to the respiratory system may not be apparent below certain threshold exposure levels, but might increase sharply above those values.

Although Threshold Limit Values (TLV) should not be considered as absolute thresholds, they are believed to represent exposure levels below which significant health effects are not likely to occur. One can estimate the amount of Cd deposited in the lungs of a normal 70 kg man, breathing approximately 1.1×10^4 liters of air/day, assuming a 20 percent alveolar deposition. If the average air concentration is 0.002 ug/m^3, 0.0044 ug Cd will be deposited per day, and in one year 1.61 ug will be deposited. Once deposited, Cd is very efficiently retained in the body and very small quantities are excreted. If one assumes the biological half-time (clearance) for Cd in the lung is six months, 0.81 ug will be present at the end of one year. Usiug the calculations described above, this would mean an average Cd concentration of 0.85×10^{-3} ug/ml or 0.008 percent of *in vitro*

Table III.8 Comparison of Levels of Metals *In Vitro*, *In Vivo* and in Ambient Air

Metal	In Vitro: Bioassay	In Vitro: µg/macrophage[a]	In Vivo (MAN): Maximum µg/lung[b]	In Vivo (MAN): µg/macrophage[c]	Fraction of EC_{50} dose received by macrophages	Average in community air (µg/m³)[d]	Maximum in community air (µg/m³)[b]	TLV (µg/m³)[e]
	Viability (EC_{50})							
Cd^{2+}	11.1 µg/ml	1.1×10^{-6}	930	4.0×10^{-8}	0.04	.002	0.35	50
VO_3^-	11.9 "	1.2×10^{-6}	680	3.0×10^{-8}	0.03	<.003-0.90	1.4	50
Ni^{2+}	245 "	24.5×10^{-6}	8000	3.5×10^{-7}	0.01	.032	0.69	100
Cr^{3+}	285 "	28.5×10^{-6}	2000	9.0×10^{-8}	0.003	.015	0.35	500
Mn^{2+}	290 "	29.0×10^{-6}	1700	7.0×10^{-8}	0.002	.100	10	5000
	Phagocytosis (EC_{50})							
Cd^{2+}	9.0 µg/ml	0.9×10^{-6}	930	4.0×10^{-8}	0.04			
VO_3^-	1.5 "	0.2×10^{-6}	680	3.0×10^{-8}	0.15			
Ni^{2+}	59.0 "	5.9×10^{-6}	8000	3.5×10^{-8}	0.006			
Cr^{3+}	15.8 "	1.6×10^{-6}	2000	9.0×10^{-8}	0.06			
Mn^{2+}	14.3 "	1.4×10^{-6}	1700	7.4×10^{-8}	0.05			
	Acid Phosphatase (EC_{50})							
Cd^{2+}	23.6 µg/ml	2.4×10^{-6}	930	4.0×10^{-8}	0.02			
VO_3^-	4.5 "	0.5×10^{-6}	680	3.0×10^{-8}	0.06			
Ni^{2+}	224.0 "	22.4×10^{-6}	8000	3.5×10^{-8}	0.002			
Cr^{3+}	227.0 "	27.7×10^{-6}	2000	9.0×10^{-8}	0.003			
Mn^{2+}	239.0 "	23.9×10^{-6}	1700	7.0×10^{-8}	0.003			

[a] Obtained by assuming 10% of metal is taken up macrophages after 20 hours *in vitro*.

[b] From Schroeder (1970).

[c] Obtained by dividing by 23×10^9, the average number of macrophages/lung (Crapo et al., 1982).

[d] From Graham et al. (1975).

[e] From ACGIH, Threshold Limit Values (TLV), 1981.

EC_{50} as determined by the bioassay for macrophage viability, 0.009 percent by phagocytosis and .004 percent by acid phosphatase. A similar calculation has been made by Medinsky et al. (1981), who concluded that the levels of H_2SeO_3 encountered by macrophages in human lungs were only 0.001 percent of the levels necessary to demonstrate toxicity in vitro. It must be realized, however, that in vitro tests of macrophage function (e.g., viability, phagocytosis) may be relatively insensitive.

As always, the validity of extrapolating the harmful effects of controlled animal exposure studies to risk in human populations is difficult. Not only are the levels greater than encountered in urban air, but differences in animals and man in regard to pulmonary anatomy, physiology and biochemistry make caution necessary. For example, compared to man, the mouse has a pulmonary ventilation approximately 10 times greater when expressed as liters of air per minute per kilogram body weight. As a result, the mouse will receive a higher dose of metal per gram of lung for any given concentration and duration of exposure. However, theoretical and experimental work has also shown that collection efficiency of inspired particles is similar in a variety of animal species and humans. Thus, an approximation of the toxicity of the various metals in man can be attempted by extrapolating from the mouse infectivity data presented in Table III.9. In this calculation, the average deposition in man was determined using the average concentration in community air, and assuming there is no clearance. Even after these conservative assumptions are made, extrapolated ED_{20} levels (the dose levels required to induce 20 percent of the maximum mortality above background following a bacterial or viral challenge) seem to be an order of magnitude below the predicted deposition rates of metals in human lung.

In conclusion, it can be stated that no reliable scientific data exist which directly demonstrates effects in humans as a result of chronic or long-term exposure to these various metals at levels found in the ambient air. Health effects other than the induction of cancer have, typically, not been addressed due to a lack of quantitative information. As an initial step in evaluating the available data, a review of the pertinent data used in the documentation of the Threshold Limit Values for the five metals reported is included in Appendix III.2 of this HEED. Unfortunately, for the most part, these lack needed numerical data. However, there is an extensive data base which demonstrates that serious biological effects have been observed in a variety of animal bioassays as a result of short-term exposures to these various metals at concentrations above those found in ambient air. The importance of these effects and the similarities of the biological systems between animals and humans suggest that long-term chronic exposure to humans may result in an as yet unquantifiable risk to human health.

Table III.9

Comparison of Bioassay Infectivity Data in Mouse and Man

	MOUSE	MAN				
	ED_{20} µg/lung	Maximum µg/lung[a]	Extrapolated µg/lung[b]	µg/macrophage[c]	Average in community air (µg/m^3)	Average deposition µg/year
Cd^{2+}	.17	930	81	0.4×10^{-8}	.002	1.61
VO_3^-	.66	680	315	1.4×10^{-8}	<.003 - 0.90	<2.4-723
Ni^{2+}	.63	8000	300	1.3×10^{-8}	.032	25.7
Mn^{2+}	1.4	1700	670	2.9×10^{-8}	.100	80.3

[a]From Schroeder (1970)

[b]Obtained by comparing the pulmonary ventilation of mouse and man.

[c]Obtained by dividing by 23×10^9, the average number of macrophages/lung (Crapo et al., 1982)

[d]From Graham et al. (1975)

III.2.2 Non-Neoplastic Toxicity of Particles and Their Significance to Human Health: Acid Sulfates

In the 1982 HEED on airborne particles, we briefly reviewed the nature and extent of toxic effects of exposures to sulfuric acid in terms of morphological effects and pulmonary function changes. In this HEED, we provide a more detailed description of the effects of sulfuric oxide aerosols on the mucociliary clearance functions and the possible implications of these changes for lung disease. A brief summary of the reported effects of nitrate aerosols on respiratory disease is also provided later in Section III.2.3. The information provided in the following two sections has been derived from the assessments provided by Dr. Morton Lippmann of the New York University Institute of Environmental Medicine (Lippmann, 1983a,b).

Introduction

For many years, standard tests of respiratory mechanical function have been used as criteria of irritancy potential of airborne particles. These tests were developed to assess the ability of the lungs to provide adequate ventilation of alveoli (which, of course, is the lung's prime function). However, it does not follow that the production of reversible mechanical changes is the only effect of importance following pollutant exposure. Indeed, questions of the sensitivity and significance of such changes have not been adequately resolved, and it is important to determine whether alterations in other lung defenses occur either before respiratory function tests become abnormal, or in the absence of changes. Another critical component of the defense system is mucociliary clearance from the tracheobronchial tree. Therefore, in the following we summarize recent knowledge of the effects of airborne sulfate particles on physiological parameters.

Effects of Acid Sulfate Aerosols on Mucociliary Clearance Function: Results from Recent Studies

Mucociliary clearance is the main route by which particles and dissolved gases are removed from the conducting airways, and is a route of removal for macrophages from alveolar regions. Derangement of clearance may be involved in the development of chronic bronchitis or mucus hypersecretion (Hilding, 1965; Kilburn,1968; Albert et al., 1973; Wanner, 1977; Fishman, 1980) and may also be a factor in the pathogenesis of bronchogenic cancer (Schlesinger and Lippmann, 1978; Menkes et al., 1979). Noninvasive measurements of clearance can be made following the inhalation of radioactively tagged, insoluble tracer microspheres, by measuring thoracic retention at various times following the brief inhalation using external *in vivo* measurements with collimated scintillation detectors.

A series of studies of the effects of H_2SO_4 (sulfuric acid) on mucociliary clearance in humans was performed at NYU Institute of Environmental Medicine by Leikauf (1981). The subjects were

either exposed on four different days for one hour each day via nasal mask to submicrometer droplets of H_2SO_4 or to a distilled water aerosol. The acid exposures, in random sequence, were at 100, 300 and 1000 ug/m^3. The following generalizations were made from the results of the various tests. The one-hour exposure to 100 ug/m^3 had no effect on tracheal mucus transport, but accelerated clearance in the large proximal airways and slowed clearance from the small distal airways. At 1000 ug/m^3, tracheal transport was still unaffected, but both proximal and distal airway clearance was depressed. Thus, it appears that the lowest H_2SO_4 exposure level produced a small, stimulatory dose to mucociliary transport in the larger airways, while at the same time the dose to the smaller conducting airways was large enough to depress mucociliary transport in that region. Thus, single one-hour exposures to submicrometer sulfuric acid aerosol did not significantly change any index of respiratory mechanics in nonsmoking volunteers, but did markedly alter mucociliary clearance. However, very recent clinical evidence suggests that sulfuric acid when inhaled at concentrations of 100 ug/m^3 (near ambient levels) can induce reversible pulmonary functional changes in adolescent asthmatics (see Koenig et al. 1983).

Recently, Schlesinger et al. (1982) developed an animal model using the rabbit for further tests on the effects of irritants on clearance and other lung defense functions. They have used this model for studies of the effects of single one-hour exposures to a variety of sulfur oxide aerosols and for a study of the effect of daily one-hour exposures to H_2SO_4. In tests involving repeated one-hour exposures for five days/week, for four weeks, there was an examination of both mucociliary clearance changes during, and for two weeks after, the exposures, and of changes in the bronchial epithelium as measured following sacrifice at two weeks after the last exposure. Three groups of animals were exposed at a concentration of H_2SO_4 of either 250 or 500 ug/m^3. One group (Series 1) received 250 ug/m^3 via an oral tube; one (Series 2) received 250 ug/m^3 via nasal mask, and one 500 ug/m^3 via nasal mask (Series 3). In all H_2SO_4 exposure series, clearance times were significantly reduced from pre-exposure values on specific individual days during the course of the acid exposures, with the greatest number of such days occurring during the 500 ug/m^3 exposures. In addition, for the acid-exposed animals, the relative number of airways in each classification group indicated an increase in Epithelial Secretory Cells (ESC).

The results of the single exposures of rabbits indicated that H_2SO_4 was the most potent of the major ambient sulfur oxide aerosols [i.e., H_2SO_4, NH_4HSO_4 (ammonium bisulfate) and $(NH_4)_2SO_4$ (ammonium sulfate)], in producing changes in the rate of tracheobronchial mucociliary clearance. Ammonium bisulfate was the only other of these three chemical species which produced a significant change in clearance rate. However, since it requires twice as much NH_4HSO_4 as H_2SO_4 to produce the same $[H^+]$ in solution, then, stoichiometrically, approximately 1700 ug/m^3 of NH_4HSO_4 would be comparable, in terms of $[H^+]$, to approximately

850 ug/m^3 of H_2SO_4. The change in clearance which would be predicted to occur at this latter concentration of H_2SO_4 is similar to that which was observed at the former concentration of NH_4HSO_4. As a result these studies strongly suggest a relation between the hydrogen ion concentration ($[H^+]$) and extent of clearance alteration.

In summary, the sulfur oxide having the greatest effect on both respiratory mechanics and mucociliary clearance function is H_2SO_4, and the effects appear to be related to the concentration of hydrogen ion deposition on the airways. For both responses, the effects produced by single exposures appear to be transient. Of the two responses, the more sensitive one is mucociliary clearance, and the sensitivity is greater by about a factor of 10.

Implications of the Effects of H_2SO_4 on Mucociliary Clearance in the Pathogenesis of Chronic Bronchitis (Mucus Hypersecretion)

Chronic bronchitis is a disease of the conducting airways, characterized by persistent excess mucus production (Thurlbeck, 1976; Snider, 1981). In addition, human bronchitis and experimental animals having spontaneous or induced chronic bronchitis show altered mucociliary clearance function (Lourenco, 1969; Camner et al., 1973; Holma, 1967; Iravani and Van As, 1972; Melville et al., 1980). Thus, chronic bronchitis involves dysfunction of the mucociliary system, and altered clearance may be an initial stage in disease progression.

Unfortunately, there are few data concerning the response of the mucociliary clearance system under prolonged insult by potentially harmful pollutants such as H_2SO_4, and direct experimental evidence for a role of H_2SO_4 in the etiology of chronic bronchitis is currently lacking. There is, however, various suggestive evidence which implies an association between exposures to H_2SO_4 and effects on human health. Epidemiologic studies suggest a relationship between sulfur oxide pollution and chronic bronchitis; these surveys, however, did not generally examine either mucociliary clearance dysfunction or H_2SO_4 concentration. In one study, Nobutomo (1978) reported that people from two areas in Japan of differing pollution levels were screened. The greatest differences between the two areas were in the levels of SO_2 and suspended particles. Persistent phlegm was the most common symptom in people from the area with higher pollution levels. In a study in Holland, atmospheres characterized by sulfur oxides and smoke were related by van der Lende et al. (1981) to a higher prevalance of chronic cough and phlegm production. On the other hand, no significant differences in mucociliary clearance were found by Camner and Philipson (1973) in twins, where one twin lived in a rural area and the other in an urban region. Thus, although available evidence suggests that exposures to sulfuric acid may exacerbate disease, it has not been clearly established whether it can initiate it.

The suggestion for a role of H_2SO_4 in the development of chronic bronchitis is given added strength when results of studies of submicrometer H_2SO_4 or whole fresh cigarette smoke exposures, both conducted in the NYU laboratory with donkeys and humans, are compared (Lippmann et al., 1982). Cigarette smoke is an agent known to be involved in the etiology of human chronic bronchitis. The effects of both agents on the mucociliary clearance of tracer particles are essentially the same in terms of: 1) transient acceleration of clearance in low-dose exposures; 2) transient slowing of clearance following high doses; and, 3) alterations in clearance rates persisting for several months following multiple exposures. Thus, although direct evidence for an association between intermittent low-level exposures to H_2SO_4 and chronic bronchitis is lacking, the similarity in response between H_2SO_4 and cigarette smoke exposures suggests that such an association is possible.

Discussion

Since H_2SO_4 produces essentially the same sequence of effects on mucociliary bronchial clearance as cigarette smoke, following both short-term and chronic exposures, it may be capable of contributing to the development of bronchitis. But the question still remains whether variable clearance rates, accelerated clearance, and persistent clearance changes merely predispose to chronic bronchitis, or are the actual initiating events in a pathogenic sequeuce leading to its development. Furthermore, the response of the mucociliary clearance system observed in the rabbits may be adaptive, rather than pathological. Many irritants may stimulate clearance at low doses or after exposure for a short time and then retard it at higher doses, or with prolonged exposures (Wolff etal., 1981). An increase in ESC proportion is consistent with hypersecretion. Thus, low-level exposures may initially increase secretion, which can be coped with and may even be protective. However, pathological changes appear when adaptive capacity is overloaded. Thus, with increasing exposure time and dose, the degree of enhanced secretion may be too great, resulting in overwhelming of clearance, leading to retardation (e.g., as shown in rabbits by Holma, 1971) and eventually bronchitis.

III.2.3 Non-neoplastic Toxicity of Particles and Their Significance to Human Health: Nitrate Aerosols

A re-examination of the literature and an update of our previous review (presented in the 1982 HEED) still indicates that there are limited data linking nitrate aerosol exposures to repiratory disease. In the following, we briefly summarize pertinent literature available, to determine if nitrates in airborne particles contribute to the initiation or exacerbation of respiratory disease.

There are some reports which suggest that nitrates in particles may contribute to the initiation or exacerbation of respi-

ratory disease. Utell et al. (1980) studied the effects on airways of acute exposure to nitrate during uncomplicated influenza A (H_1N_1) infections in 11 previously healthy adults and found significant functional responses associated with exposures to high concentrations of nitrates. Subjects were studied at the time of acute illness and 1, 3 and 6 weeks thereafter. By double-blind randomization, each subject breathed an aerosol of either sodium chloride or sodium nitrate for an initial 16-minute period and then breathed the other aerosol for 16 minutes three hours later. The mass median aerodynamic diameter (MMAD) of the $NaNO_3$ aerosol was 0.49 um; the concentration was 7,000 ug/m^3. Deposition studies showed a mean retention of 45 to 50 percent for both inhaled aerosols. Compared to inhalation of sodium chloride at the time of initial examination and one week later, exposure to sodium nitrate produced significant decreases in specific airway conductance and partial expiratory flows at 40 percent of total lung capacity.

Kleinman et al. (1980) exposed 20 normal and 19 asthmatic volunteers for two hours to 200 ug/m^3 of NH_4NO_3 (ammonium nitrate) having a MMAD of 1.1 um. They found no substantial alterations in pulmonary function or overall reported symptoms attributable to the nitrate aerosol for either group. However, there were some possible meaningful function and symptom increases in some individual members of the group.

In a population study of the effects of particulate air pollution on asthmatics, Perry et al. (1983) recorded symptom scores, peak expiratory flows, and use-as-needed aerosolized bronchodilators for 24 asthmatics in Denver from January through March, 1979. Pollutant variables were 12-hour average concentrations of CO, SO_2, O_3 and particle mass. The particles were collected in two size fractions, i.e., 2.5 to 15 um MMAD (coarse) and less than 2.5 um MMAD (fine), and both fractions were analyzed for total mass, sulfate, and nitrate. Of the environmental variables, only fine particle nitrate concentration was statistically associated with effects, i.e., with increased symptom scores and bronchodilator usage.

The body of literature which suggests that inhalation of NO_2 affects respiratory disease incidence may have some relevance to the issue of possible effects of particulate nitrate. NO_2 penetrates through the upper airways and a significant fraction is deposited on small airways and alveolar surfaces where it hydrolyzes, forming nitrite (NO_2^-) and nitrate (NO_3^-). Thus, if nitrates have the effects suggested in the studies specifically related to nitrates, then exposure to NO_2 may produce similar effects.

Of particular relevance to this discussion are the "gas stove" studies. Melia et al. (1977) reported an increase incidence of cough, bronchitis and "colds going to the chest" in British school children over a wide geographical area when the children lived in homes with gas rather than electric stoves. There were no measurements of NO_2 in these studies, but later

studies by the same group clearly indicated that excess NO_2 was probably present (Melia et al., 1978). Speizer et al. (1980), in their six-cities study, have also shown that there is a greater history of respiratory illness before age two, and decreased Forced Vital Capacity (FVC) and Forced Expiratory Volume (FEV) in one second (FEV_1) in children 6 to 10 years old from homes where gas is used for cooking. Hasselblad et al. (1981) reported a similar association. This finding was age-dependent and changed according to the year studied. However, more recent results of Harvard's six-city study (Ware et al., 1983), in which additional intake cohorts were considered and social class was better characterized, did not show a significant association between gas stoves and respiratory illness before age two. Recent studies in this area by the British group (Melia et al., 1979; Florey, et al., 1979; Goldstein et al., 1979), while not definitive in their demonstration of an effect, suggest a slightly greater relative risk in girls rather than boys. Other studies in Ohio gave negative results (Keller et al., 1979a,b). However, Speizer et al. (1980) noted that correction for parental smoking improved their correlation of lung disease before age two with gas stove use, and they criticized the Keller study for the lack of representative samples as well as small sample sizes.

Respiratory disease illness was also associated with peak exposures to NO_2 in a community health survey in Chattanooga, Tenn. Love et al. (1982) found higher respiratory illness rates in a population periodically exposed to short-term peaks than in others without such peak exposures, even when the long-term average concentrations were nearly the same for both groups. The reduction in excess respiratory disease among the same population in the following year, when the source of the short-term peaks was shut down, was consistent with the hypothesis that peak NO_2 exposures contribute to an elevation in respiratory disease incidence.

Discussion

There are more studies for the effects of NO_2 on humans and animals than for nitrates. However, these are relevant to a consideration of the effects of nitrates, since NO_2 depositing on respiratory epithelium dissolves and forms nitrates. As previously mentioned, the "gas stove" and Chattanooga ambient air NO_2 epidemiologic studies suggest that there may be an excess of respiratory disease associated with NO_2 exposure, and that the effects are more likely associated with periodic peak exposures than with an elevation in the average exposure. Also, animal inhalation studies with NO_2 demonstrate that NO_2 can produce functional decrements and anatomical changes in peripheral airways and airspaces which are consistent with impaired ability to resist lung disease. Thus, while the effects of nitrate aerosols on respiratory disease have not been established, there is a body of epidemiologic and toxicologic data which raises sufficient concern to justify further investigation.

IV. Principal Conclusions and Future Research Needs

PRINCIPAL CONCLUSIONS

The existing epidemiologic literature on the morbidity effects of human exposure to particulate matter was summarized in Section II.1. The major findings were:

- Very few studies have addressed acute health effects of particle pollution below levels of 1000 ug/m^3 (measured in 24-hour average TSP equivalents). Those which have addressed effects at lower concentrations show an increase in hospital admissions for cardiac and respiratory illness, as well as for bronchitis symptoms. Even in these studies the average ambient concentrations of TSP were high relative to current levels in the U.S.

- The available data for short- and long-term exposures to particulate matter do not suggest the existence of effect thresholds. For this reason, simple linear coefficients are derivable which relate particle concentrations to respiratory infections, hospitalization, and symptoms of chronic bronchitis. The cases/year per 10^5 persons per ug/m^3 were estimable for childhood lower respiratory infections (60) and chronic bronchitis (0-170) using the British Smoke measure of particles, and for acute respiratory disease (100-540), excess emergency room visits for respiratory diseases (8-13), and excess total emergency room visits (20) using Total Suspended Particulate Matter data. Standard errors of these estimates are roughly one-half the estimates themselves, indicating a zero risk coefficient to be within the confidence interval of each estimate.

In Section II.2, we reported the results of an original epidemiologic study using the National Health Interview Survey morbidity data and an index of fine particle pollution (based upon airport visibility data). Although this analysis is preliminary and will be continuing during the project's third year, we can report the following findings:

- There is a correlation between fine particle air pollution and human morbidity. This relationship persists even when the analysis is controlled for inter-city and seasonal effects. This fine particle effect is evidenced only among persons reporting periodic limitations due to chronic conditions.

- Of the health measures considered, Restricted-Activity Days (RAD) are the most sensitive to the effects ofair pollution. According to the estimates developed, persons with chronic limitations are expected to experience, in a two-week exposure period, 0 to 0.01 RADs and

0 to 0.004 WLDs per ug/m^3 of average fine particle mass concentration.

Time series of mortality and pollution data were analyzed in Section II.3. Historical Coefficient of Haze (COH) and mortality data collected in New York City (NYC) were analyzed for the years 1963 to 1976. Further, a sensitivity analysis of the time-series approach was also conducted using a simulated pollution and morbiditydata set (generated based upon available Los Angeles County raw data). The major conclusions drawn from these analyses were:

- COH was found to be related to temporal variations in NYC mortality. For a reasonable range of preliminary data filters, estimated coefficients from a model relating daily mortality to COH range from 1.2 to 2.0 deaths per day per unit COH. 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. Re-expressing the results as risk coefficients yielded a range of risk coefficients from 0.01 to 0.02 deaths per day per unit COH per 100,000 persons. The 95 percent confidence interval of the estimates were roughly between 0 and 0.03 deaths per day per unity COH per 10^5 persons. Until validation studies in several other cities with different characterizations and weather patterns are undertaken, the results derived from this analysis apply directly only for the mix of sources and time pattern of concentrations observed in NYC between 1963 and 1976.

- Simulations testing the ability of time-series methods to detect daily mortality effects of air pollution (applicable to Los Angeles) suggested that these methods would typically have a 95 percent chance of detecting a mean daily mortality/exposure coefficient (based upon particle KM measure) of 0.06 deaths/day/10^5 persons.

In Section II.4, we reported results from cross-sectional analyses of total mortality in Standard Metropolitan Statistical Areas (SMSA) across the U.S. In these analyses, a number of particle metrics were considerd, including Total Suspended Particle Matter (TSP), Inhalable Particles (IP), Fine Particles (FP) and sulfates. The following conclusions were made:

- Based upon the 1960 and 1980 SMSA analyses, it is concluded that the use of FP mass measure in cross-sectional mortality analyses results in a more significant and larger magnitude health effect than alternative measures available for such analyses. This agrees with both physiological and statistical expectations.

- For 1960, TSP was found to yield a statistically significant effect ($p < .05$), but in the 1980 mortality regression TSP was not at all significant ($p >> .05$). Based upon these conflicting results, the use of TSP for the estimation of particle health effects is not recommended.

- Using mean exposures and expressing mortality risks in terms of similar units, the NYC time-series analysis indicated less than half the mortality risks predicted by our cross-sectional analysis. Though tentative, this finding is consistent with the expectation that cross-sectional studies may capture more of the chronic health effects of air pollution than would time-series studies (e.g., see Evans et al., 1983).

- Based upon the consistent importance of FP in the mortality regression examined, it is recommended that a FP coefficient of 1.3 deaths/year per 10^5 people per ug/m^3 be employed in the assessment of the health effects of air pollution, with the 1960 sulfate coefficient (2.6 deaths/year per 10^3 people per ug/m^3) being employed when estimates of FP impacts are unavailable.

- Despite the fact that the above-noted coefficients were found to be statistically greater than zero, uncertainties not considered by such analyses (e.g., errors in the measurement of the exposure variables and other non-sampling errors) make it possible that the mortality risk might, in fact, be zero. Such coefficients have in the past been applied without adequate attention to their actual applicability to the situation and the uncertainties involved. Improper application of cross-sectional coefficients may lead to erroneous conclusions regarding health risks.

- Our studies of alternative particle mass measures (i.e., TSP, IP and FP) indicate that refinements in the estimation of human exposures to air pollution (e.g., using fine versus total mass) improve our ability to quantify the health effects of these exposures.

The cancer risks of different types of airborne particles were examined (see Section III.1) using a relative potency model applied to Ames data. The major conclusions were:

- Estimates of the increment in relative risk of lung cancer (in ug/m^3 extractable organics-years) typically ranged from 10^{-4} to 10^{-3} for the sources considered (i.e., light-duty diesel, catalyst spark engine, non-catalyst spark engine, woodstove, residential heater, FBC, and conventional coal and oil combustion). The 95 percent confidence interval of these estimates typically ranged from 10^{-6} to

10^{-1} around each of the particle-specific risk coefficients.

- Due to large uncertainties in predicting incremental relative risk of lung cancer using Ames data, it is not possible to reliably discriminate between the potencies of different types of particles. For this reason, the population risks associated with exposures to various types of ambient particles must, at this time, be ranked on the basis of quantities of extractable (soluble) organics emitted, rather than individual estimates of potencies.

In Section III.2.1, we evaluated the non-neoplastic toxicities of various metals. The major conclusions of this assessment were:

- The rankings of metal toxicities were found to be consistent with their Threshold Limit Values (TLV) (i.e., $Cd^{++} \gtrsim VO_3^- \gtrsim Ni^{2+} \gtrsim Cr^{3+} \gtrsim Mn^{2+}$).

- No reliable scientific data exist which directly demonstrates effects in humans as a result of chronic or long-term exposure to these various metals at the levels found in ambient air.

Literature regarding the human health effects of sulfate aerosols were reviewed in Section III.2.2. Our conclusions were:

- The health effects of sulfate aerosols appear to be related to their acidic strength (i.e., their hydrogen ion concentration).

- Human health effects of short-term exposures to sulfuric acid to have been shown in exercising asthmatics at roughly 100 ug/m^3 approaching peak levels recorded in the ambient environment. These H_2SO_4 levels are much lower than those for which health effects had been seen before.

- Since H_2SO_4 produces essentially the same sequence of effect on mucociliary bronchial clearance as cigarette smoking (following both short-term and chronic exposures), it may be capable of contributing to the development of bronchitis.

The contribution of nitrates to human health effects of particles was examined in Section III.2.3. The major findings were:

- The potential impact of nitrates on human and animal health has received relatively little attention in the scientific literature. However, in the absence of direct evidence regarding nitrate health effects, information can be inferred from exposure studies for

nitrogen dioxide, since the gas dissolves in the respiratory epithelium and forms of nitrates. Thus, there is a body of toxicologic data which raises sufficient concern to justify further investigation of potential nitrate health effects.

FUTURE RESEARCH NEEDS

During our analyses of the health effects of particles, we identified areas of future research which may help reduce some of the uncertainties reported in this HEED. The following is a comprehensive listing of those research needs.

Morbidity Analyses

- For the study of morbidity, existing data bases should receive additional attention. One promising data set comes from the National Health and Nutrition Examination Survey (NHANES). This data base includes direct measures of pulmonary function.

- Ongoing health surveys such as NHANES and HIS should be expanded to better accommodate analysis for air pollution effects. Particular attention should be paid to improving exposure estimation (e.g., to passive smoking) by personal monitoring and the modeling of exposures based upon human activity patterns.

- More prospective health studies to enable characterization of chronic and acute health effect are definitely needed. 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 exposure data.

- Associations obtained between air pollution exposures and different measures of human morbidity should be compared in terms of their significance and biological plausibility.

- Future work should explore the sources and composition of fine particles in order to examine their respective importance in the interpretation of epidemiologic data bases.

Mortality Analyses

With regard to time-series analyses:

- For time-series analysis, we need an improved model of the effects of confounding variables (such as temperature) on mortality and morbidity. This also suggests a need to develop a physiologically-based model of acute mortality in time-series studies.

With regard to cross-sectional analyses:

- For future health studies, we need combinations of both improved exposure and health measures. For example, the use of health surveys or census data would be greatly enhanced by adding measures that would at least partially account for cigarette smoke and indoor exposures.

- The number and types of particle sampling sites in the U.S. should be increased, and the aerosol characterization data should be improved and made more consistent across sites.

- Historical data sets might be re-analyzed using novel exposure estimates. For example, airport visibility, TSP and sulfate measurements might be combined so as to better represent fine particle concentrations.

- Also needed are better estimates of personal exposures to particles, including information on indoor/outdoor exposures by source and chemical composition.

- Various exposure averaging times should be examined. This will partially address questions regarding response time associated with observed biological effects of air pollution.

Toxic Effects of Particles

With regard to mutagenicity and carcinogencity bioassays:

- Research is needed to reduce uncertainty in bioassays for carcinogenicity. Potency derived from *in vitro* tests and animal-to-human extrapolation produce the greatest uncertainty in this type of risk assessment.

- Future bioassay studies should address the question of biological significance of assays with respect to human disease (both neoplastic and non-neoplastic). Basic research into the physio-chemical mechanisms of carcinogenesis may eventually provide a model that, in conjunction with bioassays, will be quite useful to risk assessment.

- Relationships between assays need to be determined under a greater data base to account for inter-lab and inter-sample variability. The effects of differences in chemical composition on assay results also need further clarification.

- Questions of bioavailabity must also be addressed in assessing mutagenic potential of urban aerosols.

With regard to non-neoplastic effects:

- Research should be directed toward an improved understanding of disease progression. More information is needed on the pathogenesis of fibrosis, emphysema, and chronic bronchitis.

- The appropriate application of information on disease processes to specific bioassay studies must be determined. For example, as the mechanism of fibrogenesis becomes better characterized, stage-specific bioassays can be developed.

- The effect of repair and reversibility of injury after particle exposure must also be studied.

- How different agents interact in complex mixtures should also be further evaluated. This is especially important for urban air particles, which are complicated mixtures of aromatic hydrocarbon, metals, silicates, sulfates and other components.

- Bioassays should be better calibrated with both toxic and non-toxic particulates. More organic samples as well as emphysema-producing materials should be employed.

- The role of variation in dose-regimen in determining lung injury must be further assessed. This is especially important in extrapolating from the relatively high-level short-term exposures used in animal studies to the low-level long-term exposures more characteristic of the urban environment.

GLOSSARY OF COMMONLY USED ABBREVIATIONS

B_{ext}	Aerosol extinction coefficient. The fraction of incident light absorbed and scattered by ambient aerosol particles per unit path length. B_{ext} generally is expressed in units of km^{-1}.
BS	British Smoke. An optical aerosol measurement used more commonly in Europe; the reflectance (or darkness) to a standard "British Smoke".
COH	An optical aerosol measurement; the percent transmission of white light through a filter deposit relative to a clean filter. Samples are generally collected (automatically) every 2 hours by tape sampler.
CP	Coarse particle. Particle with aerodynamic diameter between 2.5μm and 15μm.
CV	Coefficient of variation. A dimensionless statistical measure of variation (standard deviation ÷ mean). Useful for comparison of the precision of model results.
D_a	Aerodynamic Diameter. The diameter of a unit density (1 g/cm^3) sphere that has the same settling velocity as the particle.
DCM	Dichloromethane; the solvent most commonly used in mutagenenis bioassays.
EC_{50}	The estimated concentration required to produce an experimental outcome level (which is specific for each bioassay) of half the maximum effect over the background effect.
ED_{20}	For infectivity bioassay: The dose required to induce 20% of the maximum mortality above background.
EM	Algorithm. A method for computing maximum likelihood estimates.
FBC	Fluidized Bed Combustion type coal burning power plant.
FEV	Forced expiratory volume. Volume of air that can be exhaled with maximal effort over a fixed duration (e.g., FEV, over 1 second): measured to indicate changes in lung function.
FP	Fine particle. Particle with aerodynamic diameter smaller than 2.5μm.

FVC	Forced vital capacity. The total volume of air that can be exhaled with maximal effort: measured to indicate changes in lung function.
HIS	National Health Interview Survey. A national study of approximately 100,000 individuals for which information on chronic and acute health conditions was collected. This data base was used in the analysis of FP morbidity effects.
Hi-Vol	High volume sampler; the current EPA reference method for sampling TSP.
IP	Inhalable particle. Particle with aerodynamic diameter smaller than 15μm.
KM	Unit of reflectance in a measurement of blackness of an aerosol filter deposit. The KM measurement is proportional to the sample's elemental carbon content.
MMAD	Mass median aerodynamic diameter. A characteristic parameter which describes a distribution of particles. Half of a distribution's mass is contributed by particles smaller than the MMAD and particles larger than the MMAD.
RAD	Restricted Activity Days. Health variable from HIS data set used in analysis of FP morbidity effects.
Rev/mJ	Revertants/millijoule; a unit of mutagenic activity per unit of energy produced.
RSP	Respirable particle. A particle which can deposit in the alveolar region of the lungs. Measured as a variable fraction of particles smaller than 10μm aerodynamic diameter.
SAROAD	The Storage and Retrieval of Aerometric Data System. A national database of air quality and site information provided by various local, state and federal air pollution agencies. The EPA Inhalable Particle (IP) network data is collected at SAROAD sites.
SMSA	Standard Metropolitan Statistical Area. A geographic area defined by the U.S. Census bureau for heavily populated regions.
S-9	A rat liver homogenate which contains metabolic enzymes that promote bactinal response to mammalian mutageus. Used in Ames test to enhance detection of mutagens.
TA 98	Salmonella Typhimurium (a bacterium) mutant strain used in Ames test.

TLV	Occupational Threshold Limit Value. Airborne concentration of a substance below which nearly all workers may be exposed repeatedly eight hours per day, forty hours per week, without adverse effect, according to ACGIH (American Conference of Governmental Industrial Hygenists).
TSP	Total Suspended Particulate Matter. The fraction of airborne particles collected by high-volume sampler. Generally, only particles smaller than 50um aerodynamic diameter are captured.
V_r	Visibility or visual range. The maximum distance at which an object can be discriminated from its background.
WLD	Work-loss days. Health variable from HIS data set used in analysis of FP morbidity effects.

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U.S. NUCLEAR REGULATORY COMMISSION

EXHIBIT No. 47-135

Applicant ✓ Staff ____ Intervenor ____

Identified ✓ Received ✓ Rejected ____

Date: 5-7-87

Reporter: J BURNS

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