50-400/40101

NRC STAFF EXHIBIT 2

8-2
10/82

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

HEALTH AND ENVIRONMENTAL EFFECTS DOCUMENT

1982

Prepared by:

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

October 1982

Prepared for:

Health and Environmental Risk Analysis Program
U.S. Department of Energy
Agreement No. DE-AC02-81EV10731

HERAP
Health and Environmental
Risk Analysis Program

NUCLEAR REGULATORY COMMISSION

Docket No. 50-400 401 OL Official Exh. No. 2

In the matter of Shearon Harris

Staff	✓	IDENTIFIED	✓
Applicant		RECEIVED	✓
Intervenor		REJECTED	
Comm Off			
Contractor		DATE	6/15/84
Other		Witness	
Reporter	Ley		

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

HEALTH AND ENVIRONMENTAL EFFECTS DOCUMENT

1982

Prepared by:

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

Assessments performed under the direction of:

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

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

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

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

Principal authors of the report:

H. Ozkaynak, Ph.D. (Project Manager), A.J. Warren, Ph.D.,
T.D. Tosteson, M.S., J.S. Evans, Sc.D.,
G.D. Thurston, M.S., and S.D. Colome, Sc.D.

October 1982

Prepared for:

Health and Environmental Risk Analysis Program
U.S. Department of Energy
Agreement No. DE-AC02-81EV10731

ACKNOWLEDGEMENT

This HEED, "Analysis of Health Effects Resulting from Population Exposures to Ambient Particulate Matter" is based upon the contributions of the staff, consultants and co-principal investigators of the study on Health Effects of Exposures to Airborne Particles which is administered by the Eneregy and Environmental Policy Center at Harvard University, John F. Kennedy School of Government. The results of our study are contained both in the interim and annual progress reports previously submitted to HERAP of DOE and in the three Appendices submitted along with this HEED.

We appreciate and acknowledge the technical contributions of the following senior technical staff, advisors and consultants to the project.

B.D. Beck, Ph.D. - Harvard School of Public Health
J.D. Brain, Sc.D. - Harvard School of Public Health
J.M. Daisey, Ph.D. - Institute of Environmental Medicine, NYU
R.J. Ferek, Ph.D. - Florida State University
R.G. Isaacs, M.A. - AER, Inc.
N.M. Laird, Ph.D. - Harvard School of Public Health
D.T. Mage, Ph.D. - U.S. Environmental Protection Agency and Harvard University
B.L. Murphy, Ph.D. - TRC, Inc.
M.B. Schenker, M.D. - Harvard Medical School
J.H. Ware, Ph.D. - Harvard School of Public Health

We appreciate the critiques performed by our outside advisors as well as the comments provided to us be Dr. Nathaniel Barr and his staff at DOE. In May of 1982 the following advisors to the study convened in Cambridge, MA, for a two day review meeting.

Dr. Leonard Hamilton - Brookhaven National Laboratory
Dr. Donald Hornig - Harvard School of Public Health
Dr. Rudolf Husar - Washington University
Dr. Morton Lippmann - Institute of Environmental Medicine, NYU
Dr. Michael McElroy - Division of Applied Sciences, Harvard University
Dr. Alan Moghissi - U.S. Environmental Protection Agency
Dr. James Whittenberger - University of California, Irvine
Dr. Gerald Wogan - Massachusetts Institute of Technology

TABLE OF CONTENTS

Executive Summary

In the following report, we assess the human health effects resulting from exposure to airborne particles. The purpose of this Health and Environmental Effects Document (HEED) is to provide results to-date of continuing anlayses of the nature, magnitude and uncertainty of potential health impacts of airborne particles.

In this first generic HEED on airborne particles, assessments are derived from the review and analysis of data from epidemiological and toxicological studies. Particles evaluated include: total suspended particles, sulfates, nitrates, B(a)P, diesel particles, certain trace metals, and natural dusts. Health and environmental effects due to viable particles and asbestos are not addressed in this report. The health outcomes considered are mortality, morbidity, and experimental measures of toxicity and carcinogenicity relevant to human disease.

The key findings from our assessments are summarized below. We should state here, however, that in the majority of cases there are large uncertainties and qualitative statements associated with our estimates, reflecting the often tentative nature of the current state of knowledge.

Our HEED concludes with the identification of: limitations, gaps in knowledge, and research needs in the area of health risks from population exposure to ambient particles.

Assessment of Exposures

- The variable composition of particles by size and source were characterized by the following observations:
  - The smaller size particles have been linked to combustion sources, either as direct emissions or as secondary aerosols formed from gas-to-particle reactions or condensation of vapors.
  - The main anthropogenic sources of fine particles were associated with stationary fuel combustion, transportation sources (automobiles, mostly), and industrial processes.
  - Sulfates, nitrates, and ammonium ions, organic compounds and most volatile metals have been shown to be in the fine particle (FP, <2.5 μm) or respirable particle (RSP, <10 μm) size range. These fractions have also been shown to contain the acidic particles in addition to other toxic components of airborne particles.
  - Elements and compounds from the earth's crust (Cu, Si, Fe) were identified with larger sized particles (5 to 50 μm). These particles are predominantly generated by grinding, abrasion, and erosion and their air quality impacts are mostly localized.
- The principal health implications of the variable particle size and composition can be described by the following observations:

- Our assessment of recent data on aerosol acidity indicated that sulfate aerosols usually contain significant amounts of sulfuric acid which is known to cause human health effects (see also discussion below on sulfates). The average sulfuric acid fraction of total sulfate is typically 20 to 45% of the total with a standard error of the same magnitude as the estimates. Furthermore, data suggest that:

  (a) Most of the acidity is associated with high ambient sulfate concentrations during which ambient sulfuric acid concentrations can exceed 25 $\mu g/m^3$, which is about 3 times the typical ambient sulfate levels.

  (b) Exposure hazard is thus related to frequency of acid sulfate episodes.

  (c) Statistical analyses, conventionally performed using annual average sulfate concentrations as the measure of exposure, will not resolve questions on acute or chronic exposure/response relationships.

- Particles with sizes ranging from 0.1 to 1 μm in diameter were noted to have the longest residence times in the atmosphere, thereby posing the greatest potential for causing public health impacts over large areas.

- Since the majority of the larger or coarse particles (>10 μm) were shown to be predominantly deposited in the nasopharynx, unlike the particles of respirable size which penetrate to the ciliated regions of the bronchi and the alveolar air spaces, it was concluded that for toxicity and risk assessment, respirable or inhalable particles (IP) should be preferred over TSP.

. For the study of population health risks in the U.S., airborne particle concentrations were quantified by region and city size. These analyses pointed out that:

  - In general, IP is about 65% $\pm$ 10% and FP is about 30% $\pm$ 10% of the measured TSP ($\pm$ representing one standard deviation).

  - As summarized in Table II-3, p. 18, typical mean concentrations of TSP, sulfates ($SO_4^=$), benzo(a)pyrene (B(a)P), Iron (Fe), and Manganese (Mn), based on SAROAD data for 1970, 1974, and 1976, are roughly: $SO_4^=$, 9-13 $\mu g/m^3$; TSP, 60-90 $\mu g/m^3$; B(a)P, 1-2 ng/m^3; Fe, 1 $\mu g/m^3$; and Mn, 0.02-0.07 $\mu g/m^3$. The actual concentrations of the pollutants at a given time, however, can be within $\pm$ a factor of ~5 from these quoted values.

  - The median exposure levels for the U.S. population were determined to be: 10.6 $\mu g/m^3$ for $SO_4^=$, 65 $\mu g/m^3$ for TSP, 1.4 ng/m^3 for B(a)P, 1 $\mu g/m^3$ for Fe, and 0.04 $\mu g/m^3$ for Mn (based on SAROAD data for 1970, 1974, and 1976 and 1970 census data). Cumulative population exposures are displayed in Figure II-1, p.17.

. Scoping studies examining the indoor-outdoor particle relationships have led to the following observations:

  - Indoor particulate levels are significantly higher for homes with one or more smokers than where there are no smokers. Furthermore, the impact of each smoker is to add around 20 $\mu g/m^3$

of RSP to the average exposure. In most cities in the U.S. this exposure level is comparable to or greater than the outdoor RSP concentrations. Typical indoor RSP concentration averages across six U.S. cities were: $24 \pm 11 \mu g/m^3$ with no smokers, $37 \pm 15 \mu g/m^3$ with one smoker, and $70 \pm 43 \mu g/m^3$ with two or more smokers, with corresponding outdoor concentrations being around $21 \pm 12 \mu g/m^3$ (Spengler et al., 1981)

- Using tracer chemicals and elements for outdoor particulate matter, indications are that, typically, 70% of the outdoor RSP penetrates indoors. In well-sealed homes and during winter conditions, effective penetration drops to 30 to 50%.

Toxicological Analyses

Since epidemiological studies have not identified specific components of particulates responsible for various deleterious health effects, the health effects literature on animal and human studies has been reviewed to provide specific and relative toxicity information for different types of particles.

A. Metals. Many trace metals are associated with airborne particles derived from a variety of sources. Metals can produce a variety of toxic effects, including cancer. The effects of inhaled metals are not limited to the lung but may also occur in a variety of target organs.

- As a preliminary screen for toxic effects of metals associated with particles, we have compared their U.S. ambient concentrations to threshold limit values (TLVs) set for occupational exposures. Our conclusions were:
  - For most metals, the typical ambient concentrations are at least 3 orders of magnitude lower than the reported TLVs.
  - Lead concentrations in some cities are only about 2 orders of magnitude lower than the TLV and thus close to the National Ambient Air Quality Standard, which is 1/100 the TLV.
  - We conclude that the levels more than 3 orders of magnitude lower than the TLVs are generally not hazardous except perhaps in certain regions near emission sources where short-term peaks may be much higher.
  - For carcinogenic metals there is not thought to be a threshold and thus no safe level since total exposure to carcinogens determines the risk. We suggest careful evaluation of metal carcinogens, even when present at concentrations 3 orders of magnitude below the TLV.
- In an assessment of the toxicity of several metals in the *in vitro* macrophage viability assay, we have utilized concentration data from human lungs to estimate the *in vivo* dose to macrophages. The toxic effects, ranked by the fraction of the EC_{50} dose (the concentration at which there is a 50% change in viability) received per macrophage, were found to be in this order: Cd > Ni > Cr > Mn. If we assumed instead that the dose of each metal to a macrophage is the same fraction of ambient levels, then the order of toxic effects would be Mn > Cd > Ni > Cr. This analysis shows the importance of utilized dose rather than ambient levels of pollutants.

B. Sulfates. Although a number of studies have been done on sulfates, it is difficult to draw definitive conclusions from the myriad of experiments using different species, different dosage schedules, and different endpoints, having varying degrees of relevance to human health effects. The nature and extent of effects observed can be summarized as follows:

- Morphological changes have been observed after short exposures to concentrations of sulfuric acid about 3-4 orders of magnitude higher than ambient sulfate concentrations. In humans, Leikauf (1981) reported decreased clearance after a 1-hour exposure to 1000 $\mu g/m^3$ sulfuric acid. Morphological effects have generally not been observed after long-term exposures to concentrations ranging from the highest urban average to about 100 times that value.
- Exceptions to these are the studies by Alarie et al. (1973) which showed morphological effects in cynomologus monkeys exposed for 78 weeks to 380 $\mu g/m^3$ sulfuric acid (a concentration about 5 times the highest urban average for sulfate that we report) and the recent work by Schlesinger et al. (1982). Schlesigner et al. (1982) demonstrated that daily 1 hour exposures of rabbits to 250 $\mu g/m^3$ of sulfuric acid (more than 5-10 times the ambient levels of aerosol acidity) over a four week period produced proliferation of airway secretions in the middle to small airways and epithelium thickening in these same airways. There is also evidence in donkey for reduced clearance after exposure to 100 $\mu g/m^3$ of sulfuric acid for 1 hour per day for a few weeks.

C. Natural Dusts. Because of their coarseness and generally low toxicity, natural dusts are not likely to produce significant health effects at the ambient concentrations at which they generally occur.

D. Nitrates. Although nitrates comprise a significant portion of airborne particulates by mass concentration, their health effects have not been well-studied. There are no definite indications of strong health effects of nitrates at ambient concentrations, but there are not enough data to conclude they have no toxic effects. Due to scarcity of data, we suggest in the interim the use of toxicity data on other acid aerosols, such as sulfuric acid, in the assessment of the range of potential health effects resulting from exposures to ambient nitrates or nitric acid.

E. Diesel Emission Particles. Experiments in which animals have been exposed to high concentrations of diesel exhaust (1-3 orders of magnitude higher than levels projected for the year 2000) have shown some effects on lung morphology and physiology. The occurrence of such effects in humans at much lower levels of exposure seems unlikely.

Organic carcinogens are adsorbed to diesel particles, and Cuddihy et al. (1981) have utilized bioassay and epidemiological data to estimate risk factors of 0.007 to 0.3 lung cancers per 100,000 people per $\mu g/m^3$ lifetime exposure to diesel particulates.

F. B(a)P. Because the concentration of B(a)P has been measured in air samples for a reasonable period of time, it has been used as a crude indicator of the carcinogenicity of a mixture. Wilson et al. (1980), for example, have

derived an estimate of 0.2-1.0 cancers per 100,000 people per ng/m^3 B(a)P from epidemiological studies. We have concluded from our assessments that the risk of cancer due to B(a)P exposures is bounded by 0 and 4 cancers per 100,000 people per ng/m^3 B(a)P.

As a means to assess B(a)P as a surrogate for the carcinogenicity of a variety of emissions, we have compared the percentage spread for bioassay activity relative to organic content and relative to B(a)P (see Table III-2, p.34). In 4 assays, the spread is greater for organics, while in 3 assays the spread is greater for B(a)P. These results suggest that B(a)P is not a better indicator of biological activity of a variety of combustion emissions samples than total organic content is.

Epidemiological Assessments

Mortality Studies

In Section IV and in Tables IV-1 (p.39) and IV-2 (p.40) of this HEED, we report in detail the findings from the re-analyses of the evidence from cross-sectional mortality studies. The key conclusions, estimates, uncertainties and statements of qualifications are summarized below:

- We believe, in general, that for quantifying the magnitude of the effects of airborne particles, total respirable particles would be an intuitively plausible surrogate. However, in the absence of good concentration data on respirable particles or acid aerosols, we currently have no alternative but to suggest the continued use of sulfates as a surrogate, with caution.
- Although the results from our re-analyses of the cross-sectional mortality studies are typically consistent with the sulfate damage coefficient suggested by Wilson et al. (1980), we have produced coefficient estimates which vary by a factor of almost five, and estimates of the standard errors of these coefficients which vary by a factor of nearly two and a half. As we have emphasized in the following analysis, the uncertainty surrounding the mortality risk coefficients is large — so large that the true mortality risk might in fact be somewhere between zero and a large number such as 10 deaths/yr/10^5 persons per $\mu g/m^3$ of sulfate.
- For the purposes of obtaining rough bounding estimates we have provided (see Tables IV.1 and IV.2, pp.39 and 40) mortality risk coefficients (β) along with their respective coefficients of variation (CV) to characterize the extent of typical uncertainties. These estimates include results from regressions on single pollutants (i.e., $SO_4^=$, TSP, B(a)P, Mn, or Fe) as well as estimates from joint regressions consisting of more than one pollutant (for example, $SO_4^=$ and TSP combined).
- Except for the estimates of the mean sulfate coefficient (a typical estimate, for example, is $\beta_{SO_4^=} = 3.72$ deaths/yr/10^5 persons/ $\mu g/m^3$, with $CV_{SO_4^=} = 51\%$) most of the risk estimates obtained contain significant errors represented by large coefficients of variation (essentially greater than 100%). It is especially difficult to interpret the species-specific risk estimates derived from joint regressions, since there are strong covariances among the concentrations of pollutants

considered and the estimated risk coefficients for these pollutants.

- The damage coefficient estimates derived from cross-sectional mortality studies were not inconsistent with the time-series mortality coefficients which range from 0.033 to 0.531 deaths/year per 10^5 persons per $\mu g/m^3$ of TSP (the associated coefficients of variation ranged from 20 to 80%).
- Typically, time-series mortality studies have shown lags between exposure and death of no more than 3 to 5 days.

Since the coefficients from cross-sectional mortality studies are often used to estimate the risk of mortality associated with exposure to particulate air pollution, we must emphasize the large uncertainties surrounding these damage coefficients. Furthermore, due to the severe limitations of these studies and the lack of substantiated biological causality at ambient concentrations in their interpretation, the true mortality risk might in fact by zero. We are reluctant, therefore, to suggest any application of the damage coefficients derived from such studies without specifying a large number of precautions and caveats. For example, our review of DOE technology HEEDs indicated that damage coefficients derived from cross-sectional studies have been used, often without adequate attention to the specifics of the application and the uncertainties involved, in predicting mortality risks. While the estimated damage coefficients may be used with some confidence to predict the impact of small changes in particulate concentrations in areas with exposure near those typical of the SMSAs involved in these studies, we emphasize that proper application of these coefficients will require:

- Specifying the types of pollutants to be analyzed so that a proper set of damage coefficients and standard errors can be selected.
- Checking whether the relative proportion of predicted ambient concentrations of these pollutants and various other organic compounds are similar to those measured in most statistical studies characterizing the health effects of air pollution.
- Making sure that the projected emissions are not released into an environment which has low background concentrations of the key pollutants analyzed.

Even when all these conditions are met and proper confidence intervals specified, the risk analyst should still mention all the caveats that question the causality and the utility of these estimates. Basically, the risk coefficients from cross-sectional mortality studies are crude, appropriate only for development of rough bounding estimates. Nonetheless, they are the only tools readily available to the air pollution risk analyst today.

For assessing benefits and risks associated with mitigative measures to reduce pollutant emissions (mostly SO_2) and economic incentives for pollution reduction, we suggest again the continued use of sulfates as a surrogate, although we advise caution. Most importantly we discourage the use of sulfate as a surrogate in cases where the sulfur emissions are reduced in greater proportions than the particulates or the trace metals. In circumstances such as these, we believe that the use of respirable particles as

surrogates may be more advisable. Additionally, in assessing risks from trace metal exposures, it is expected that occupationally derived TLVs or MEG-MATE values would be adequate. Finally, we suggest a continuation of the policy of assessing the carcinogenic effects of polycyclic aromatic hydrocarbons separately on the basis of occupational epidemiology and animal studies, rather than on the basis of the very imprecise coefficient estimates derived from cross-sectional mortality studies.

Morbidity Studies

Review of morbidity literature performed along with other epidemiological evaluations indicated that:

- Studies of the morbidity effects of chronic exposure to particulate matter have shown upper and lower respiratory symptoms and reduced pulmonary function to be associated with annual average particle (TSP equivalent) concentration in excess of approximately 180 $\mu g/m^3$ (Ware et al., 1981)
- The observational studies on short-term particle exposure are more sparse and most of these studies address TSP levels in excess of 1000 $\mu g/m^3$ (24-hour average). These few studies suggest increased hospital admissions for cardiac or respiratory illness (TSP at 600 $\mu g/m^3$ in association with SO_2 at 400 $\mu g/m^3$) and worsening of health status among bronchitics (TSP at 350 $\mu g/m^3$ in combination with SO_2 at 500 $\mu g/m^3$) (Ware et al., 1981). As is the case in chronic exposures, these studies do not suggest an effect threshold.
- No evidence exists in these data to suggest an effect threshold.
- In a preliminary attempt to derive simple linear coefficients for morbidity, a selected set of studies reporting air pollution concentration and morbidity outcomes were analyzed. Based on assumptions and qualifications that were discussed on p. 46, morbidity coefficients were derived and presented in Table IV.3, p. 47. It should be mentioned here, however, that all of the caveats for use of mortality coefficients must be imposed on the morbidity estimates. Furthermore, our efforts on this question are preliminary and these values should be considered as tentative.

In general, interpretation of the morbidity studies must also be qualified similarly to the mortality studies and, in fact, to all nonexperimental epidemiological studies. As we mentioned above for mortality studies, the individual epidemiological studies for morbidity can also demonstrate an association between particulate matter and ill health but they cannot prove the causality of that association.

Research Needs

During our analysis of the health effects resulting form exposure to ambient particles, we have identified several areas for future research that will help reduce some of the uncertainties reported in this HEED. The following is a list of the research areas discussed in Section V, p.49 of the report.

Recommended Research Areas Pertaining to Particle Toxicity and Exposure Analysis

- Evaluation of the relative toxicity of particles by jointly utilizing: the *in vitro* and animal bioassays; toxicity of samples of ambient particles from as many cities and rural areas as possible; and detailed occupational data. The approach recommended above is similar to one being utilized by EPA in their evaluation of the carcinogenicity of diesel emission particles. What is now needed is an expanded analysis including a much greater variety of types of emissions and evaluation of toxicity for chronic lung diseases as well as cancer.
- Defining the origin and composition of particles for the purpose of characterizing historic exposures to fine, respirable, and total suspended particles. This information is needed to reduce uncertainties associated with the estimation of population exposures to various toxicants.
- Collection of more data on nitrates and acid aerosols, in particular, on the sulfuric acid fraction of sulfates, in order to understand the extent of exposures and observed effects due to nitrates, and sulfates in ambient air.
- Collection and analysis of more data to determine the extent and nature of personal exposures to respirable particles.

Recommended Research Directions to Improve Risk Assessments Based on Epidemiological Evaluations

- Better quantification, through experimental and epidemiological studies, of the possible role of particle exposures in: altering short and long-term measures of lung function; and affecting predisposition to diseases in later years.
- Health effects modeling activities, especially in the areas of lung deposition, lung function decline, and relating morbidity with mortality risk.
- New cross-sectional investigations with new data and exposure variables that are more pertinent to effects investigated.
- Expanding time-series studies to include more biologically plausible air pollution indices.
- Additional observational morbidity studies designed to provide quantitative risk (or dose-response) estimates.

I. Introduction

This report is an assessment of the effects of airborne particles on human health. It represents approximately one year of study and is the first generic Health and Environmental Effects Document (HEED) on airborne particles. More specifically, this HEED provides results to-date of continuing analyses of the nature, magnitude and uncertainty of potential health impacts of airborne particles common to a number of emerging energy technologies.

The scope of this HEED is to consider those particles that are most commonly associated with general types of fossil fuel energy technologies. Particles included in the toxicity assessment include: sulfates, nitrates, particles containing high levels of organic compounds (diesel particles and other combustion products), and certain trace metals and natural dusts. The discussions presented in this HEED also include health effects and characterizations derived from consideration of known size distribution of airborne particles such as respirable, inhalable and total suspended particles. Health and environmental effects due to viable particles and asbestos are not included in this document, nor have we yet evaluated in detail the data from the occupational studies. Prior to discussing the likely toxic effects of particles, this HEED first addresses various questions regarding the nature and extent of human exposures to various particle species. Typical sources of ambient particles, their concentrations in the air and the size and location of populations exposed to different levels of these pollutants are also quantified.

Characterizations of the nature and magnitude of the health effects resulting from exposures to airborne particles reported in this document have followed primarily from the analysis of experimental-toxicological data and epidemiological-vital statistic data utilizing ambient air pollution measurements.

We have utilized two approaches in our analysis of the toxicity of airborne particles. Our first approach consisted of a general review of health effects of airborne particles and of their chemical constituents. The second approach involved determining the relative toxicity of particles in bioassays relevant to neoplastic and non-neoplastic diseases. Non-neoplastic effects of particles were evaluated using *in vitro* macrophage and infectivity bioassays. Under neoplastic effects, we have also performed an initial assessment of the carcinogenicity of various combustion emission particles (mostly diesel emissions) using results from short-term bioassays to determine the magnitude of error involved in using B(a)P as a surrogate for predicting the carcinogenic effects.

In the epidemiological phase of our research, we have devoted most of our efforts to the analysis of cross-sectional mortality studies, in which geographic differences in air pollution levels are related to geographic differences in mortality rates. For the purposes of checking the consistency of results from cross-sectional mortality studies, we have also conducted preliminary analyses of the time-series mortality studies, in which changes in the daily levels of air pollution are related to changes in the daily number of deaths in a single large metropolitan area

such as New York City or London. Non-mortality effects of air pollution (morbidity effects, changes in physiological signs, etc.) are also summarized in this report. The primary purpose of these epidemiological investigations has been to characterize the uncertainties associated with the selection and the use of species-specific damage coefficients in projecting population risks.

Our assessments in this HEED are concluded with the identification of: limitations, gaps in knowledge, and research needs associated with the analysis of health risks resulting from population exposures to ambient particles. Finally, we suggest improvements in the methods of analysis which will reduce the uncertainties that currently exist.

In the remainder of this document, we present the key findings from our assessments. The reader is referred to the three Appendices accompanying this report for details on specific points.

II. Exposures to Particles

An individual's total exposure to particles is the integration of a number of exposures in different environments. These can be divided into indoor and outdoor environments, where indoor exposures often have additional sources of particles (e.g., cigarette smoking) superimposed upon the entering ambient air. Since the observed population in an epidemiological study provides information on the effect of total personal exposures to pollutants, an understanding of these variations in human exposures is important to any assessment of the health effects of particulate pollution.

One factor which has an important influence on the response of an individual to a given total exposure to (particulate) pollutants is the amount, or dose, of the pollutant actually inhaled during a given time period. Furthermore, the retention properties of particles in the human lung after inhalation are quite complicated, since the clearance of different types of particles from various lung compartments varies from individual to individual. For example, solubility and physical characteristics of various particles result in differences in the observed clearance half-lives. Also, small percentage differences in clearance half-lives can result in large percentage differences in retained material. Therefore, clearance may be the more important parameter for studies of chronic health effects and deposition may be the more important parameter for studies of acute health effects (Mage, 1982). This situation can be even more complicated because of gas-particle interactions. (Section III and Appendix 2 provide further information on the toxicity of various particles and the mechanisms of particulate deposition in the lung.)

It is evident that there is a need for the description and characterization of particles according to their potential for adverse health effects and toxicity. Particle size, chemical composition, ambient concentrations and human activity patterns determine population exposures to particles and thus to associated potential health effects. In the following section, key factors influencing estimates of particulate exposure are briefly discussed. (See Appendix 1 for further information.)

Sources and Physical and Chemical Characteristics of Particles

Ambient airborne particles arise both naturally and anthropogenically. Natural sources include windblown soil, seaspray, volcanic activity, and forest fires; manmade sources include industry, utility emissions, agriculture, construction sites, and automobile traffic. Primary particles describe those emitted directly from a source; secondary particles are those which form in ambient air and the atmosphere as a result of condensation and chemical reactions. Geography, topography, seasonal and meteorological conditions greatly influence particle composition and size distribution. These factors are also known to influence potential effects of particles to human health.

Particle distributions are typically characterized by a coarse and a fine mode, described by the aerodynamic diameter of the particle. The coarse

mode is often defined as particles ranging in aerodynamic diameter (d_a) from 2.5 to 100 μm, while the fine fraction is defined as those particles below 2.5 μm. Ambient aerosol mass is distributed somewhat evenly between the fine and coarse modes (fine being 1/3 to 1/2 of the total mass and coarse being the remainder). Particle number, however, tends to decrease as particle size increases.

The composition of particles varies by size. Fine particles (FP) tend to come from combustion sources, either as direct emissions or as secondary aerosols (e.g., sulfates and nitrates) formed from gas-to-particle reactions or condensation of vapors. The main anthropogenic sources of fine particles are stationary fuel combustion, transportation sources (primarily automotive), and industrial process emissions. Sulfates, nitrates and ammonium ions, organic compounds and most volatile metals are found in this fine particle size range. The more volatile metallic elements, including arsenic, antimony, cadmium, lead, selenium and thallium, are vaporized during combustion. They are subsequently concentrated upon fine particles during cooling and condensation because these particles have a higher surface to volume ratio than coarse particles (Natusch et al., 1974).

Sulfur compounds represent a major portion of the fine mass at most U.S. sites. Over 90 percent of ambient sulfur is contained in the fine fraction, and this sulfur represents an average 35 percent of the total fine mass (AER, 1981). Aerosol acidity has been found to correlate well with sulfate concentrations (Ferek, 1982), causing the fine mass to be the acidic fraction. The average sulfuric acid fraction of total sulfate is typically 20 to 45 percent (with a standard error of the same magnitude as the estimate). Furthermore, data indicate that there are cases of sulfate episodes during which sulfuric acid concentrations have exceeded 25 $\mu g/m^3$ or about 3 times the typical ambient sulfate levels in the U.S. From the perspective of health effects, these occasional peaks in aerosol acidity may be significant. However, the analysis conventionally performed using annual average sulfate concentrations as the measure of exposures will not resolve questions on acute or chronic exposure/response relationships.

Particulate Organic Matter (POM) represents an important portion of the fine fraction aerosol, averaging roughly 10% of the fine mass. POM is derived from both natural (e.g. plants and animals) and anthropogenic (e.g. combustion) sources. Many of the organic compounds present in airborne particles have been found to be carcinogenic in animal studies (NAS, 1972).

Physical removal processes at work in the atmosphere interact so that the net removal efficiency is lowest in the particle size range of 0.1 to 1 μm in diameter. This size range has appropriately been named the accumulation mode. While fine particle concentrations may be higher in the immediate vicinity of sources than in the surrounding areas, fine fraction aerosol concentrations in general tend to be regionally uniform. This fine mass uniformity is due in part to the sizable fraction of the fine particle mass made up by secondary aerosols, which have no individual point sources, per se, although they do have long residence times in the atmosphere. The widespread nature, long residence times, and toxic composition of fine aerosols cause them to have the greatest potential for public health impacts.

Larger sized particles (5 to 50 μm) are predominantly the results of fugitive (i.e., not ducted) emissions. These anthropogenic sources, such as agriculture, construction, transportation, and mining, add to the natural sources such as windblown soil and seaspray. Industrial operations with uncontrolled combustion, grinding and pulverizing operations, and slag or storage piles will certainly influence particle mass concentrations by the emission of coarse particles. Their impacts will be localized, however, because of the short residence time of coarse particles in the atmosphere. Similarly, locally elevated Total Suspended Particulate Matter (TSP) concentrations are experienced near roadways and in arid or agricultural areas. Due to the crustal nature of particles found in the coarse fraction, these particles are rich in elements such as Al, Si, Fe, Mn, and Ca.

The characteristics of particles found in an indoor environment may differ greatly from those found immediately outdoors. Differences are caused by a number of factors, including the nature of the indoor sources of particles. Research has shown that smoking, cooking, and the use of fireplace and wood-burning stoves are sources of indoor particles that are also rich in organic compounds (see Appendix 1, Sec. II). Aside from indoor sources, fine particles generated outdoors can penetrate quite readily around doors and windows (WHO, 1982). The differences between indoor and outdoor particles will depend a great deal on the ventilation system (which varies from building to building), the rate of filtration/ventilation (which often varies with season), and the rate of emission of particles indoors. Using tracer chemicals and elements for outdoor particulate matter, indications are that, typically, 70 percent of outdoor respirable suspended particles (RSP) (d_a < 3.5 μm) penetrates indoors. In well sealed homes and during winter conditions, effective penetration drops to 30 to 50 percent.

Particle Measurement and Exposure Assessment

Unlike the particles of respirable size which penetrate to the ciliated regions of the bronchi and the alveolar air spaces, larger or coarse particles (> 5 μm) are predominantly deposited in the nasopharynx. Although these deposited particles can enter the bloodstream from the gastrointestinal tract, these particles do not penetrate into the lungs. Thus, a better measure for lung disease risk calculations of the particle mass is considered to be the IP fraction of the TSP (having an aerodynamic diameter less than about 10 to 15 μm) (Miller et al., 1979), or the RSP fraction of the TSP. Recognition of the need for size fractionization of samples has led to measurements of the particles in different size ranges. The particles sampled have been called by various names such as inhalable particles, IP (≤ 15 μm), respirable particles*, RSP, and total thoracic deposition particles**, TTP (≤ 10 μm). The particles of utmost importance physiologically are those penetrating beyond the nasopharynx compartment (corresponding to the established medical description of the upper respiratory tract). It is probable that these respirable particles are related to the mortality and morbidity due to respiratory disease that has been associated with air pollution episodes in the past.

---

* By ACGIH (1976) definition, a RSP sampler collects none of the particles > 10 μm, 50% of the 3.5 μm particles and 90% of the 1 μm particles.

** EPA (1982)

Particle Concentration

In the U.S., levels of TSP were historically much higher than they are today. Overall trends in TSP concentrations have been downward (mostly due to instituted control measures and changes in the choice of industrial fuels). Comparing 1958 and 1974 data for 5 industrial cities, for example, the mean TSP levels decreased from a range of 140-170 $\mu g/m^3$ in 1958 to 80-100 $\mu g/m^3$ in 1974 and to around 60 $\mu g/m^3$ in 1977. The emphasis on particle removal efficiency based on mass has led primarily to the collection of large particles (NRC, 1979). In 1978, the approximately 4000 TSP monitoring sites reporting valid annual averages had a median concentration of 60 $\mu g/m^3$. There are systematic differences in TSP concentrations by site locations. Rural sites tended to be lower (10-40 $\mu g/m^3$) than urban areas which have TSP concentrations ranging from 50-150 $\mu g/m^3$. Levels of TSP tend to be higher in the eastern U.S. than in other non-arid regions by 20-40 $\mu g/m^3$. This is in part due to the larger contribution of fine aerosol mass (predominantly sulfates).

Table II-1 summarizes the recent results of measurements from U.S. EPA's IP network by region of the country. In general, Inhalable Particles (IP) (d_a < 15 μm) average 65 percent (± 10%)* and FP about 30 percent (± 10%) of the measured TSP.

Table II-1. Summary of Inhalable Particle (IP) Network Data**

Region	No. of Observations Sites	IP/TSP	FP/TSP
North Central	9	0.63 ± .08	0.35 ± .10
Northeast	5	0.69 ± .13	0.42 ± .10
South	5	0.59 ± .08	0.33 ± .14
West	7	0.59 ± .15	0.30 ± .07

Table II-2 provides estimates of typical ranges of TSP, IP, and FP as measured in different regions of the country during 1977-81 (Pace et al., 1981). Analyses of temporal trends indicate that maximum seasonal averages for all three particulate indicators occur in the summertime in most places, particularly in the east (Pace et al., 1981). The summertime peaks are most pronounced in the FP fraction and are driven by the sulfate component (Trijonis, 1980; Spengler et al., 1980; Spengler et al., 1982).

Although TSP levels have decreased, concentrations of fine particles appear to have remained unchanged or increased, especially in large cities. As discussed in detail in AER (1981) the net effect of atmospheric transport conversion and deposition processes is that FP, especially secondary aerosols such as sulfates and nitrates, can be transported hundreds of kilometers downwind of the source regions. For sulfates and most pollutants the prevailing transport direction is from the Ohio River Basin area towards the

*± one standard deviation.

**See Appendix 1 for the description of regions and data.

TABLE II-2 CHARACTERIZATION OF PARTICULATE MATTER CONCENTPATIONS FROM SIZE SPECIFIC NETWORKS, 1977-81 (Pace,1981)**

a) LONG-TERM (6-12 MONTHS) AVERAGE	TSP	IP_{15}	FP
EASTERN LOCATIONS			
Undisturbed	30-40	25-35	15-20
Downtown	60-90	40-50	20-30
Industrial	60-110	45-70	25-45
ARID WESTERN LOCATIONS			
Undisturbed	15-20	10-15	3-5
Downtown	75-130	40-70	15-25
WEST COAST			
Los Angeles Area	90-180	50-110	30-40
Pacific Northwest	45-95	20-65	15-25

b) TYPICAL 24-HOUR MAXIMA*	TSP	IP_{15}	FP
EASTERN LOCATIONS			
Undisturbed	60-100	50-100	30-80
Downtown	90-210	75-140	40-90
Industrial	150-360	100-250	50-180
ARID WESTERN LOCATIONS			
Undisturbed	50-100	25-40	10-15
Downtown	125-310	70-180	45-70
WEST COAST			
Los Angeles Area	170-460	150-200	100-110
Pacific Northwest	115-310	50-190	45-90

*60 Samples/Year

** Units: $\mu g/m^3$

northeast U.S. Thus regional assessments of population exposures to secondary and fine aerosols are particularly needed for pollutants released from tall stacks.

Over the last twenty years, sulfate levels in most areas have either increased or remained the same, thus reductions in SO_2 have not brought measurable reductions in $SO_4^=$. (Historic airport visual range observations, which can be used as surrogates for sulfates and/or fine particles when relative humidity is below 65%, also substantiate this observation.) In London, Lawther and Waller (1978) report a reduction of B(a)P concentration between 1935 and 1965, and in U.S. cities there has been a decline from 6 ng/m^3 to 1-2 ng/m^3 since 1959. The nationwide declines in atmospheric concentrations of (benzene) soluble organics and B(a)P are believed to be due largely to reduced use of coal for home heating over this period. However, there has been substantial change in methodology for measuring B(a)P which can in part explain the marked change over the years.

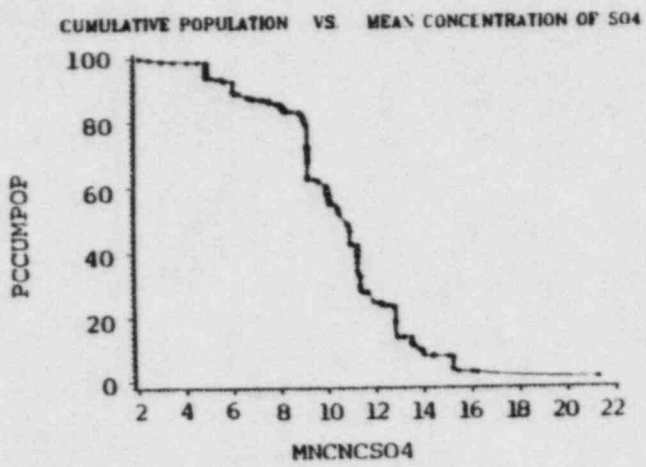
Trends in concentrations of trace metals are a function both of their origin and of the controls placed on their sources. Lead concentrations are down, reflecting the increased use of low-lead and no-lead gasoline. Nickel and vanadium concentrations are down due to reduced amounts in residual oils. Cadmium, iron and manganese concentrations are also down due to industrial control measures. However, titanium concentrations are rising as a result of increased coal use by electric utilities. Finally, regarding increases in NO_x emissions, ambient nitrate levels in both urban and nonurban areas are also found to be increasing.

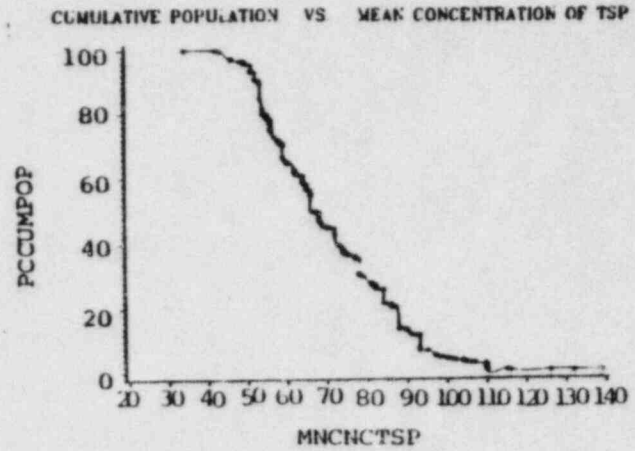
Indoor respirable particle concentrations can achieve concentrations of up to 500 $\mu g/m^3$ (NAS, 1981; WHO, 1982). Indoor levels are significantly higher for homes with one or more smokers than for homes where there are no smokers. Furthermore, the impact of each smoker is to add around 20 $\mu g/m^3$ of RSP to the average exposure (Spengler et al., 1981). In most cities in the U.S. this exposure level is comparable to or greater than the outdoor RSP concentrations. Typical indoor RSP concentrations averaged across six U.S. cities were: 24 ± 11 $\mu g/m^3$ with no smokers, 37 ± 15 $\mu g/m^3$ with one smoker and 70 ± 43 $\mu g/m^3$ with two or more smokers, with corresponding outdoor concentrations around 21 ± 12 $\mu g/m^3$ (Spengler et al., 1981).

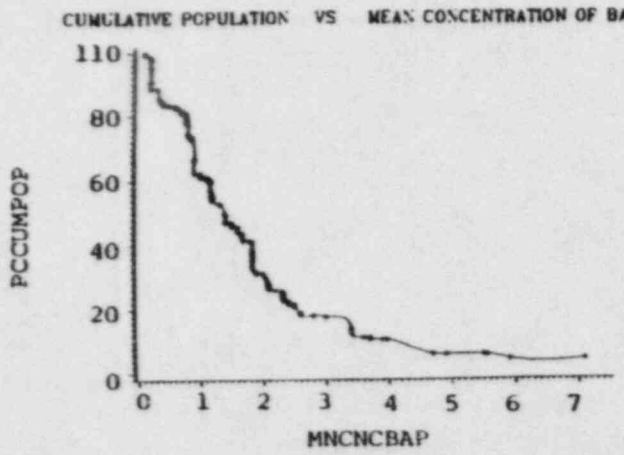
Ranges of Population Exposures

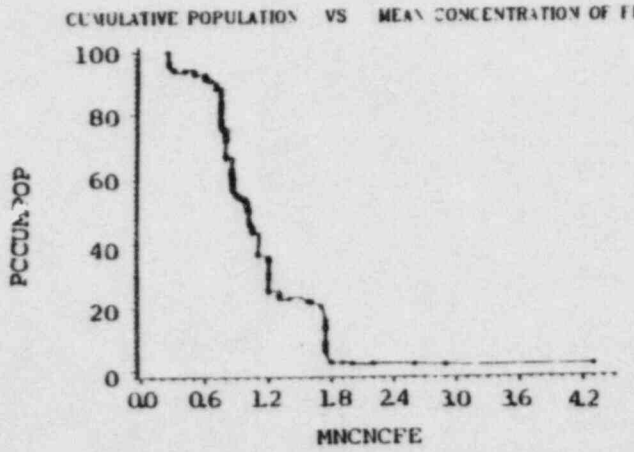
In order to quantify population exposures, outdoor concentrations of TSP, SO_4, B(a)P, Fe, and Mn were obtained or estimated for regions of the country and for populations living in different sized cities. Details are presented in Appendix 1. These are used as first approximations to population exposures; they are only approximations because indoor sources and mobility of populations have not been considered.

Figure II-1 shows cumulative distribution plots for the U.S. population exposed to different B(a)P levels based on 1970 census and 1976 (SAROAD) TSP measurements. According to this figure, more than half of the U.S. population is exposed to (annual average) particle concentrations (TSP) greater than 67 $\mu g/m^3$. More recent data (Watson et al., 1981) indicate that past progress in improving TSP concentrations has slowed, and there


CUMULATIVE POPULATION VS MEAN CONCENTRATION OF SO4
PCCUMPOP
100
80
60
40
20
0
2 4 6 8 10 12 14 16 18 20 22
MNCNCSO4


CUMULATIVE POPULATION VS MEAN CONCENTRATION OF TSP
PCCUMPOP
100
80
60
40
20
0
20 30 40 50 60 70 80 90 100 110 120 130 140
MNCNCTSP


CUMULATIVE POPULATION VS MEAN CONCENTRATION OF BAP
PCCUMPOP
110
80
60
40
20
0
0 1 2 3 4 5 6 7
MNCNCBAP


CUMULATIVE POPULATION VS MEAN CONCENTRATION OF FE
100
80
60
40
20
0
0.0 0.6 1.2 1.8 2.4 3.0 3.6 4.2
MNCNCFE

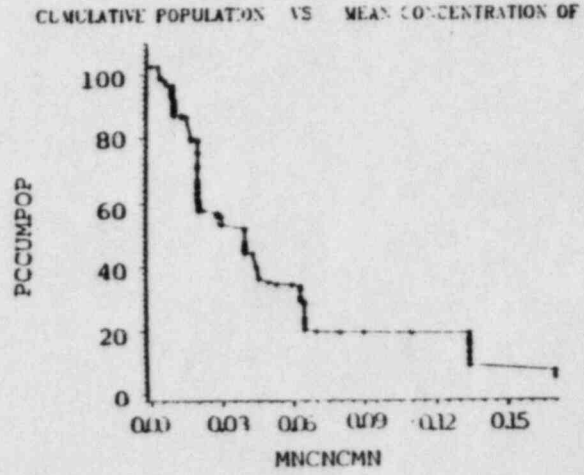

CUMULATIVE POPULATION VS MEAN CONCENTRATION OF MN
PCCUMPOP
100
80
60
40
20
0
0.00 0.03 0.06 0.09 0.12 0.15
MNCNCMN

Figure II-1.

was little change in population exposures to TSP over the last five years of the 1970's.

Figure II-1 also shows the cumulative population (1970 census used) or the percent of the U.S. population exposed to concentrations of $SO_4^=$, B(a)P, Mn, and Fe greater than the levels given. Concentrations are based on SAROAD data for 1974 except for B(a)P which is based on 1970 data. Levels above which 50% of the U.S. population is exposed correspond to: 10.6 $\mu g/m^3$ for $SO_4^=$, 1.4 ng/m^3 for B(a)P, 1 $\mu g/m^3$ for Fe and 0.04 $\mu g/m^3$ for Mn.

There is generally an increase in particulate concentrations with increasing city size. Table II-3 summarizes these results. For TSP the difference between the ambient levels in large cities (population greater than 1,000,000) and the small cities (population less than 100,000) is almost 30 $\mu g/m^3$. For sulfates, however, due to regional influences of atmospheric transport and chemical conversion processes, this difference is noted to be quite small. Higher B(a)P levels in larger urban areas are consistent with the fact that most large cities are the sources of high B(a)P and organic aerosols and that B(a)P neither persists for a long time in the environment nor travels long distances. It should also be noted that at a given time the actual concentrations of these pollutants can be within $\pm$ a factor of 5 the values shown in Table II-3 (see Appendix 2, pp. 17-21).

Table II-3. Mean Concentrations by Population Group*

City Size (People)	B(a)P	Fe	Mn	$SO_4^=$	TSP
> 1,000,000	2.07	1.2	0.02	13.48	92.33
320,000-1,000,000	1.72	1.0	0.03	9.02	79.40
100,000-320,000	1.71	0.89	0.02	9.70	72.63
< 100,000	1.40	1.06	0.07	9.09	64.24

Key Exposure Issues and Uncertainties

- Under most circumstances, extreme cases of high pollution are of concern. The proper description of these events must take into account characteristic random variables such as maximum concentrations, frequencies of exceedances of critical levels, and expected return periods (cf. Georgopoulos and Seinfeld, 1982). In practice, however, averaging time information is not known and risk assessments are constrained by the manner in which air quality data are routinely reported, i.e., 24-hr averages every 6th day. Therefore, due mainly to data limitations, a satisfactory link between the time variability of exposures and the observed morbidity or mortality effects cannot be obtained. For the most part, epidemiologic studies have sought to define the relationship between health and contemporary

*See Appendix 1 for further details on the basis for these estimates. Except for B(a)P, all units are in $\mu g/m^3$. B(a)P units are ng/m^3.

(not integrated long-term or lifetime) ambient concentrations. If air pollution health outcomes are associated with prior exposures, then the effect of contemporary associations between mortality/morbidity and concentration levels could overestimate effects if concentrations are decreasing with time, or underestimate effects if concentrations are increasing with time.

- Typically, the chemical composition of the fine aerosols that are produced by anthropogenic sources are believed to pose more health risks (per unit mass of material inhaled) than the coarse fraction which is produced by natural sources (Mage, 1982; Natusch and Wallace, 1974). In Section III of this report, we discuss further the variable health effects of different chemical compositions of ambient particles.

- In addition to knowing the chemical composition as a function of particle size, it is also necessary to acquire detailed knowledge of the toxicity of the overall particle mixtures (inhaled by different population groups at different times). Recent research on acid sulfate aerosols and their associated health effects has tried to address some of these concerns. As discussed in Appendix 1 and by Lippmann et al. (1980) and Johnston et al. (1982), there is potential for adverse human health consequences resulting from exposures to ambient acid aerosols (especially during high humidity sulfate episodes).

- Human health effects are most likely to be associated with the respirable fraction of particulates resulting from both indoor and outdoor sources. From current measurements, we know that the sulfates, nitrates, and organic compounds comprise the largest portion of the ambient respirable particles. In addition, volatile metals such as Pb, Se, Ni, V, As, Cd, Hg, Sb, Ti, and Be are concentrated in the respirable fraction.

- In terms of indoor sources, cigarette smoke is the major contributor to respirable particles exposures (more than 50%) in homes that have one or more smokers living there.

- In this report, we emphasize respirable particles, sulfates and B(a)P for estimating health effects. Sulfate particles, in most places, are the largest single class of compounds in the respirable size fraction (30-70% by mass). While the term "sulfates" represents a broad range of particulate sulfur compounds with differing toxicity, it represents the only surrogate measure for ammonium bisulfate, sulfuric acid, and other acid compounds. B(a)P is a member of a class of polycyclic organic compounds, of which B(a)P is not the most hazardous. There are other classes of organic compounds that are known mutagens or carcinogens. There are also discrepancies between historic and recent methods for determining B(a)P in the atmosphere which add uncertainty (2-3 orders of magnitude) to the derivation and application of potency factors. However, until more information is available on the concentrations, variations and toxicity (carcinogenicity) of (polar, non-polar) various extractable fractions of organic compounds, B(a)P will have

to serve as a surrogate for fossil fuel-related carcinogenic health effects.

Sections III and IV and articles in Appendix 2 discuss more fully the toxicity of sulfates, B(a)P, and other ambient particles, as well as their utility as surrogates for estimating health effects from particulate exposures.

III. Toxic Effects of Particulate Matter

Review of Toxicities of Components of Airborne Particulates

As a preliminary assessment of the toxicity of various components of airborne particulates, we have summarized the literature on animal and human studies relevant to health effects. We have evaluated a number of particles species that either make up a large fraction of airborne particulate matter or are frequently measured as important surrogates for health effects. Our review has primarily concentrated on metals adsorbed to particulates, sulfates, nitrates, natural dusts, and diesel emission particles. We have also evaluated the use of the concentration of B(a)P in a sample as a surrogate for the carcinogenicity of that sample. These reviews are included in Appendix 2 (Toxic Effects of Airborne Particulates) and are summarized below. We have not evaluated all types of combustion emission particles; neither have we included asbestos or viable particles since they are not usually emitted by energy conversion processes.

Metals

Many trace metals are associated with airborne particles derived from a variety of sources including metal smelters, iron and steel plants, automobiles, and energy technologies involving coal and oil. Ambient urban concentrations in the United States average 2 ng/M^3 for Cd, 10-50 ng/m^3 for Cr, Ni, and V, 50-100 ng/m^3 for Cu and Mn, and 0.1-1.0 $\mu g/m^3$ for Zn and Pb. It is important to note, however, that maximum ambient urban concentrations range from 1 to 2 orders of magnitude above these mean values (NAS, 1979). Metals produce many types of toxic effects, including cancer. The effects of inhaled metals are not limited to the lung, but may occur in other target organs.

Nature and Extent of Toxic Effects

As a method of screening metals for toxic effects, we have compared their U.S. ambient concentrations on particles to threshold limit values (TLVs) set for occupational exposures (see Appendix 2, pp. 109-113). The TLVs have been set on the basis of animal and epidemiological studies and can be considered to represent conclusions about risk to humans. We are aware that the TLVs may not be based on the best data now available and that the rigor of the analyses may have varied. However, if the average ambient concentration of a substance is three or more orders of magnitude lower than its TLV, as it is in most cases, then we assume that the substance is not present in hazardous concentrations, except perhaps in certain regions, e.g., near emissions sources where short-term peak levels may be higher.

For metals that are at an average concentration within two orders of magnitude of the TLV, it is important to check the concentrations in several regions to assess the variability. In our initial analysis, lead was at a high enough level to warrant further investigation. We used data on concentrations of lead for four cities and found that in three of the cities, the levels were only slightly lower than the National Ambient Air Quality Standard

for lead, which is 1/100 the TLV. These results suggest that more careful analysis is needed. A higher occupational standard than ambient air standard is reasonable, because these exposures are for only 8 hours per day.

There is not thought to be a threshold or a safe level for carcinogenic metals since total exposure to carcinogens determines the risk. However, we would expect concentrations three or more orders of magnitude below the TLV to add little to carcinogenic risk. For example, in the case of cadmium, the EPA Carcinogen Assessment Group calculated a dose-response relationship of 2.9 lung cancers per year per 100,000 people per $\mu g/m^3$ Cd (EPA, 1978). Data on which the dose-response relationship was based include a study by Lemen (1976) in which a standardized mortality ratio of 2.4 for pulmonary cancers was found in a cadmium refinery. Typical air concentrations of Cd are 0.002 $\mu g/m^3$ (see Appendix 2, p.110), more than 4 orders of magnitude below the TLV of 50 $\mu g/m^3$, and the formula above suggests that ambient Cd levels could pose a small risk of about 12 lung cancers per year if everyone in the U.S. were constantly exposed to typical levels. However, this assumption may not always be valid, especially when there are sharp concentration gradients due to local source influences. In the case of Cd, maximum urban air concentrations are reported to be near 0.4 $\mu g/m^3$, roughly 2 orders of magnitude below the TLV. Thus, large population groups exposed to higher Cd levels may be subjected to lung cancer risks of more than 1 lung cancer per year per 100,000 people.

Another point of caution is that some elements, including Pb, Cd, Zn, Cr, V, Ni, Mn, and Cu, are found in the highest concentrations on the smallest particles. These particles deposit predominantly in alveolar regions of the lung where absorption efficiency for most trace elements is 50-80% (Natusch et al., 1974).

In determining dose to lungs and body, another consideration in addition to particle size concerns differences in the distribution and excretion of different elements. In an assessment of the toxicity of several metals in the in vitro macrophage viability assay, we have utilized concentration data from human lungs to estimate the in vivo dose to macrophages. We ranked the toxic effects of several elements by the fraction of the EC_{50} dose (concentration at which there is a 50% decrease in viability) received per macrophage and found this order: Cd > Ni > Cr > Mn (Appendix 2, p. 156). If we assumed instead that the dose of each metal to a macrophage was proportional to ambient levels, then the order of toxic effects would be: Mn > Cd > Ni > Cr. It is clear that accurately estimating the dose to target organs from ambient levels is very important in determining health effects.

Sulfates

In Figure II-1, it can be seen that 80-90% of the U.S. population is exposed to a mean sulfate concentration of 14 $\mu g/m^3$ or less. A table of exposure data in Appendix 2 (p. 17) shows that average urban ambient concentrations of sulfate range from 2-80 $\mu g/m^3$. Urban concentrations are typically 10-18 $\mu g/m^3$ in the East, 2-6 $\mu g/m^3$ in the West, and 10 $\mu g/m^3$ in the North. In the South, sulfate levels are generally lower than the East except in areas with local sources such as oil refineries.

Nature and Extent of Toxic Effects

In Appendix 2, we present tables of data from studies of animals (pp. 50-55) and humans (pp. 73-75) exposed to sulfuric acid. These results will be summarized briefly here. It should be pointed out that sulfuric acid is more toxic than sulfate salts; thus, comparisons of ambient and experimental exposures will tend to over-estimate health effects.

Morphological Effects

In long term (1-2 year) experiments with guinea pigs and beagle dogs, exposures to concentrations of sulfuric acid ranging from 0.08 to 0.9 mg/m^3 for at least 21 hours per day resulted in no observable morphological changes (Alarie et al., 1973, 1975; Lewis et al., 1973). Cavendar (1978) did not find any histopathological effects in rats or Guinea pigs after exposure to 10 mg/m^3 sulfuric acid for 6 months (6 hours/day, 5 days/week). The lowest exposure level in these long-term experiments (0.08 mg/m^3) is equivalent to the highest urban average for sulfate, as described above.

In general, exposures to higher concentrations of sulfuric acid (25-200 mg/m^3) for relatively short periods of time caused morphological changes. For example, Cockrell (1978) found that exposure to 25 mg/m^3 for 6 hours per day for 2 days caused segmented alveolar hemorrhage, type 1 pneumocyte hyperplasia, and proliferation of macrophages in Guinea pigs. Morphological effects were observed in Guinea pigs after a 4-hour exposure to 32.6 mg/m^3 sulfuric acid (Brownstein, 1980) and in mice after exposure to 50, 100, and 200 mg/m^3 sulfuric acid for 3 hours per day for 20, 10, and 5 days (Ketels, 1977).

Comparing the results with long-term exposures to sulfuric acid at concentrations up to 100 mg/m^3 with those of short-term exposures to concentrations of 25 mg/m^3 and above, there appears to be some kind of threshold concentration for damage, which would suggest that peak exposures may be more important than average exposures. However, there are important exceptions to this observation. For example: Alarie et al (1973) observed morphological changes after exposing cynomologus monkeys to concentrations of 0.38-4.7 mg/m^3 sulfuric acid for 78 weeks. With 1.15 μm (mass median diameter, MMD) particles, they observed hyperplasia of the bronchial epithelium and thickening of the walls of the respiratory bronchioles after exposure to 0.38 mg/m^3. At this concentration, which is about 5 times the highest urban average for sulfate, there was also an increase in the respiratory rate. With 0.54 μm (MMD) particles, there were no morphological changes in the lungs after exposure to a slightly higher concentration (0.48 mg/m^3), but there was thickening of the alveolar wall after exposure to particles of this size at concentrations of 2.43 mg/m^3.

Also, recent work by Schlesinger et al. (1982) showed that daily 1 hour exposures of rabbits to 250 $\mu g/m^3$ of sulfuric acid (more than 5-10 times the ambient levels of aerosol acidity) over a four week period produced proliferation of airway secretions in the middle to small airways and epithelium thickening in these same airways.

Pulmonary Function Changes

Pulmonary function changes in guinea pigs have been seen after exposures to 0.1-1.0 mg/m^3 sulfuric acid for only one hour (Amdur, 1978) and in beagle dogs after exposure to 0.89 mg/m^3 for 20 days (Lewis, 1973). Amdur et al. observed decreased compliance at concentrations as low as 0.1 mg/m^3 for particles of 0.3 μm (mass median aerodynamic diameter, MMAD) and above 0.4 mg/m^3 for particles of 1.0 μm (MMAD) in guinea pigs exposed for 1 hour. The importance of this finding is diminished by results of Alarie et al (1973, 1975), who found no pulmonary function effects in Guinea pigs exposed continuously for 52 weeks to 0.84 μm (MMD) particles at 0.08 mg/m^3 or 2.78 μm (MMD) particles at 0.1 mg/m^3. In cynomologus monkeys, Alarie et al. (1973) found an increased respiratory rate after exposure to concentrations of 0.38, 2.43, and 4.79 mg/m^3 for 78 weeks and a change in the distribution of ventilation after exposure to 2.43 and 4.79 mg/m^3.

Clearance Effects

Changes in pulmonary clearance occurred in many experiments of 1-2 hours duration at levels of sulfuric acid of about 1 mg/m^3, although there are many experiments in which no such effects were observed. In a longer-term experiment, Schlesinger et al. (1979) found that exposure to 0.1 mg/m^3 sulfuric acid (1 hour per day, 5 days per week) resulted in erratic clearance (with increased and decreased rates) in donkeys during the first few weeks. When the exposure was repeated, 4 of 6 animals had reduced bronchial mucociliary clearance rates which remained low for several months post-exposure (EPA, 1981). In human studies, Leikauf (1981) reported increased bronchial mucociliary clearance after a 1 hour exposure to 0.1 mg/m^3 sulfuric acid and decreased clearance after a 1 hour exposure to 1.0 mg/m^3 H_2SO_4.

Variations in the Observed Effects and Key Uncertainties

Although a number of studies have been done on sulfates, it is difficult to draw definitive conclusions from the myriad of experiments using different species, different dosage schedules, and different endpoints, having varying degrees of relevance to human health effects. However, there are results suggesting the possibility that human health effects may result from ambient exposures.

Clearance effects have been observed in humans after 1-hour exposures to H_2SO_4 at concentrations of 0.1-1.0 mg/m^3. In donkeys exposed to 0.1 mg/m^3 for 1 hour per day for several weeks, decreased clearance persisted for several months post-exposure. Since repeated short exposures to elevated levels of H_2SO_4 may be damaging, it is important to determine whether peak ambient acid sulfate levels might approach concentrations at which clearance effects have been demonstrated experimentally. Recent data suggest that more than 60% acid sulfate aerosols can be formed during regional episodes at levels exceeding 25 $\mu g/m^3$ (Ferek, 1982). Clearance effects must be regarded as significant since reduced clearance results in an increased dose of deposited material.

Morphological and functional effects have been observed in some species at concentrations of H_2SO_4 less than 10 times the high urban sulfate average we reported. Verification of these effects should be made in species selected for their anatomical and biochemical similarity to humans. Also, an effort must be made to correlate the types of effects measured with the eventual development of disease.

Natural Dusts

Airborne concentrations of natural dusts vary greatly, depending on topography, season, human activity, and atmospheric conditions. In remote, dry regions, dust concentrations can often range to several hundred $\mu g/m^3$. In areas of higher rainfall and greater vegetation cover, these values may fall as low as 5-10 $\mu g/m^3$. Concentrations of natural particles usually represent up to 50-70% of the total suspended particulate mass.

Nature and Extent of Toxic Effects

Because of the relatively coarse nature of these particles, a majority of them would be expected to deposit in the nasopharyngeal region rather than in the lungs. Many of the common components of natural dust are of low toxicity. Others are more toxic but are present at concentrations unlikely to cause problems.

Silicon is the most toxic element in natural dust. Crystalline forms of silicon, most notably quartz (silicon dioxide), are known to cause the chronic pulmonary disease silicosis after industrial exposures (Hamilton and Handy, 1974). Pulmonary health effects associated with industrial exposures to dusts of feldspar, limestone, slate, and granite are believed to be due to the silica content of these substances, which may also serve as the source materials for certain natural dusts. However, the concentrations of the active crystalline forms of silicon in natural dusts are generally very low compared to occupational exposures that have been demonstrated to cause silocosis, and few cases of silocosis-like disease have been reported among the general population.

Aluminum, the next most common element in this group of particles, has been implicated in the development of fibrotic lung disease and other lung damage, after industrial exposures to Al metal dust at concentrations exceeding 10 mg/m^3 (Smith et al., 1980). Under normal environmental conditions, Al levels are in the range of .04 - 2 $\mu g/m^3$ (Sorenson et al., 1974). At these low levels, adverse health effects are not believed to occur (Smith et al., 1980; Sorenson et al., 1974).

Iron, the third most common natural dust element, as iron oxide, has been shown to cause pulmonary siderosis and/or pneumoconiosis at exposure levels in the range of 10-15 mg/m^3 for 6-10 years (Smith et al., 1980). These levels are far in excess of those found in any natural dust.

Nitrates

On the average, nitrates make up about 16% of the fine particulate fraction. Concentrations vary from about 1 $\mu g/m^3$ in remote areas to 4

$\mu g/m^3$ in some urban areas (see Appendix 2, p. 17). As discussed in Appendix 2, the chemistry of atmospheric nitric acid and particulate nitrate (nitrate salt) formation is rather complex and is not fully characterized. Furthermore, measurements of ambient levels of nitrates are confounded by technical problems.

Nature of Effects

Inorganic nitrate and nitrite salts are readily absorbed when ingested (Friedman et al., 1972). Such particles may be inhaled, cleared from the lungs and swallowed, providing a route of entry into the bloodstream. It is also likely that they are absorbed directly through the pulmonary epithelium (EPA, 1974). Within the body, reduction of the inhaled nitrates to nitrites may occur. These nitrites are capable of oxidizing the heme iron of hemoglobin to the ferric state, forming methemoglobin and resulting in a loss of oxygen-carrying ability. Under normal circumstances, the overall airborne contribution of nitrates is likely to be insignificant compared to the total body burden from other sources such as water and food (EPA, 1974), but in certain situations, airborne sources can be a problem. For example, a study of New York City tunnel workers (1973) showed a significant increase in methemoglobin levels among tunnel workers exposed to automotive exhaust compared to non-exposed workers (Ayres et al., 1973).

Nitrates have also been associated with respiratory illness. Shy et al. (1970) detected elevated rates of respiratory symptoms in family groups living in communities with average 24-hour suspended nitrate levels of 3.8-7.2 $\mu g/m^3$. However, this association also held for NO_2, with concentrations ranging from .062-.109 ppm.

Particulate nitrates may exhibit a degree of carcinogenic potential. Nitrosamines and other N-nitroso compounds, which are potent carcinogens, may be formed within the acid environment of the mammalian gut (EPA, 1974) via chemical reactions involving nitrites, potentially derived from the reduction of inhaled nitrates, and amine groups. Due to the small amount of nitrate reaching the gut after inhalation, this is not likely to be a significant problem. However, the production of N-nitroso compounds in the atmosphere itself may also occur (Pitts, 1977) with direct effects upon the lung possible.

Nature of Uncertainties

Although nitrates comprise a significant portion of airborne particulates, their health effects have not been well-studied. There are no definite indications of strong health effects of nitrates at ambient concentrations, but there are not enough animal or human data to conclude that they have no toxic effects.

Another source of uncertainty is the lack of information on actual concentration and composition of nitrates that the general population is

exposed to. It is now believed that considerable error in measurement of nitrate occurred in the past due to artifact nitrate formation. In addition, most of the nitrates present in the ambient environment may well be in the gas phase as nitric acid. Since nitric acid toxicity data are limited, in the interim it would be reasonable to use the toxicity data derived from exposures to other strong acids, such as sulfuric acid, to analyze the range of potential health effects resulting from exposures to ambient nitrates approximated by nitric acid.

Diesel Exhaust

The health effects of the increased use of diesel engines as a fuel economy measure must be evaluated since diesel engines produce 20-100 times more particulate matter than gasoline engines. Regional annual mean air concentrations of diesel emission particles (DEPs) have been estimated at 2-10 $\mu g/m^3$ for the year 2000 (Dziedzic, 1981). A roadside concentration of 12 $\mu g/m^3$ has been projected for 1985. Diesel engines emit particles made of a carbonaceous core with organic compounds or gases adsorbed to the surface. The diesel exhaust particles have a mass median diameter of 0.3 µm, which puts them in the respirable size range.

Morphological and Functional Effects

Morphological and physiological effects of DEP exposures in animals are summarized in Appendix 2. Concentrations used in these experiments were one to three orders of magnitude higher than the ambient levels projected for the year 2000.

The most obvious effect of exposure to high levels of DEP was the graying of lung tissue (Barnhart et al., 1981, 1982; Hastings et al., 1980; Kaplan et al., 1982; Vinegar et al., 1980; Vostal et al., 1980; White and Garg, 1981). DEPs were observed in macrophages, and there was an increase in the number of macrophages in the alveoli (Barnhart, 1981, 1982). In cases of extreme overloading, DEPs were seen within membrane-bound vesicles in the interstitium and in epithelial type 1 cells, which do not normally phagocytose material. Once the material enters the epithelial type 1 cells or interstitium, clearance time from the lung is lengthened considerably.

Another morphological observation was an increase in epithelial type 2 cells (Barnhart et al., 1981, 1982; White and Garg, 1981), which are present in small numbers in normal lung tissue. These cells may be able to differentiate into type 1 cells and their proliferation may be a step in the repair of the alveoli.

In general, functional changes have not been observed in studies of less than on year duration, even though high levels of exposure have been utilized (Gross, 1981; Hastings et al., 1980; Pepelko, 1980). With very high concentrations (12 mg/m^3) of DEPs, Pepelko (1982) reported a decrease in the carbon dioxide diffusion capacity in Chinese hamsters after 6 months

of exposure and in cats after more than one year of exposure. Barnhart (1981) observed the analogous morphological anomaly, thickening of the alveolar epithelium, after exposures to concentrations of less than 1.5 $\mu g/m^3$ after 6 months, but decreased CO_2 diffusion capacity was not found.

For the most part, the experiments discussed in this section focused on the clearance problem and used large, acute doses of particulates; thus, they do not really address the problem of assessing the chronic effects of low levels of particulates. Studies in which animals were monitored post-exposure showed that particles were eventually cleared from the lung (Kaplan et al., 1982). Kaplan et al. exposed rats, hamsters, and mice to 1.5 mg/m^3 of DEP 20 hours/day, 7 days/week for three months. Six months post-exposure there was a considerable decrease in pigment and it was largely in focal accumulations with intervening tissue usually pink and normal looking. Lymph nodes were still deeply pigmented, but there were no indications of pathology in the lung or other organs.

Carcinogenic Potency

As of the date of this report, inhalation exposures to diesel engine exhaust have not been shown to cause lung cancer in animals. However, many studies have shown that extracts of diesel emission particles contain substances active in various short-term assays relevant to carcinogenesis, and exposure to diesel engine exhaust would be expected to contribute to the total carcinogenic risk from air pollution. Cuddihy et al. (1981) summarized bioassay data on diesel engine exhaust and various comparative emissions. In these short-term assays, DEP extracts were generally less potent than coke oven emissions, roofing tar vapors, and gasoline engine exhaust, but more potent than cigarette smoke condensate. There was less variation in activity among samples in the mouse skin carcinogenesis assay than in other assays.

The diesel particle extract was the most active sample in the Ames assay and was unusual in having more activity in the absence of metabolic activation than in its presence. This direct-acting mutagenic activity is thought to be due mainly to nitropyrenes and other nitro-compounds which can be activated by bacterial nitroreductases (McCoy et al., 1981; Pederson and Siak, 1981). Their potency in mammalian cells is thought to be less than in bacteria, but two components of diesel exhaust, 1-nitropyrene (1-NP) and 3-nitrofluoranthene, have been shown to cause tumors in rats after subcutaneous injection (Ohgaki et al., 1932) with the tumors at the site of injection.

Cuddihy et al. (1981) concluded that bioassay studies indicated that DEPs could be about 3 times more carcinogenic than cigarette smoke, but only about one third as carcinogenic as coke oven emissions and roofing tar. However, this does not mean that the hazard from DEPs is greater than that from inhaling cigarette smoke which causes a large fraction of the lung cancers in the U.S., because exposures to cigarette smoke by direct inhalation are orders of magnitude higher than other human particulate exposures.

Another important consideration in comparing the hazard of DEPs and cigarette smoke is the fact that the bioassays utilized do not adequately measure the biological activities of cigarette smoke which may be most

relevant to its carcinogenicity, that is its co-carcinogenic and promotional activities (see Appendix 2, pp. 299-309). We do not yet know whether these effects could be relevant to diesel exposures because DEPs have not yet been evaluated adequately for co-carinogenic effects. It is possible that these effects are seen with cigarette smoke because of the high levels of exposure. Promoters probably differ from initiators in having threshold concentrations and requiring continuous exposure. Also, co-carcinogenic effects due to induction of enzymes could also require high levels of exposure.

Ranges of Risk Estimates and Associated Uncertainties for Carcinogenic Effects

In estimating the cancer risk from exposure to diesel engine particulates, Cuddihy et al. (1981) have utilized median values for the relative potencies in short-term bioassays of various surrogate samples. They divided the lung cancer risk factors for various exposed populations by the bioassay potency of the substance relative to DEP in order to obtain risk factors for human exposure to DEP. Using relative bioassay potency values to modify risk factors calculated for human exposures to coke oven emissions, roofing tar vapor, cigarette smoke, and urban soot, they obtained risk factors ranging from 0.007 to 0.3 lung cancers per 10^5 people per ug/m^3 lifetime exposure to diesel particulates. Cuddihy et al. (1981) calculated a modified risk factor of 0.12 lung cancers per 10^5 people per ug/m^3 diesel particulate from the results of DuMouchel and Harris (1981). DuMouchel and Harris determined the risk (upper 95th percentile confidence limit) for ambient exposure to diesel exhaust based on results from a study of London Transport Authority workers. They used data on garage mechanics, who were the most highly exposed workers. This risk factor is questionable because the bus mechanics had a lower lung cancer rate than the control population.

Using an annual lung cancer risk factor of 0.1 cancers per 100,000 people per ug/m^3 exposure, Cuddihy et al. estimated that 5-180 lung cancers per year could be caused by diesel emissions, based on an average emission of 0.12 g/km, or 12-420 lung cancers per year based on an average emission 0.3 g/km. They pointed out that the calculations are based on indirect information and that cancer effects could be negligible. These estimates are subject to great uncertainty (the magnitude of uncertainty is within 2-3 orders) from the epidemiological studies as well as the bioassay inadequacies discussed above. Given the multifactorial nature of cancer, it is difficult to ascribe confidently any number of cancers to a single cause.

B(a)P as a Surrogate for Carcinogenicity

Two approaches can be taken in assessing the carcinogenicity of urban air. One involves evaluating the carcinogenicity of specific types of particles such as the diesel emission particles discussed above and then attempting to sum their carcinogenicities. Another approach involves using a surrogate chemical representative of the carcinogenicity of a variety of emissions from different sources.

The carcinogenic activity of airborne particulates is due mainly to a variety of combustion emissions particles to which a large number of organic carcinogens and pro-carcinogens and also some metallic carcinogens are adsorbed.

Benzo(a)pyrene (B(a)P) is an organic compound emitted by most combustion processes. It is the only carcinogenic organic material which has been measured in a number of places and over a reasonable time span. Therefore, the concentration of B(a)P in a sample has often been used as a crude indicator of the carcinogenicity of organic components of samples.

Lung cancer risk estimates for exposure to B(a)P have been developed based on animal and epidemiological studies (Wilson et al., 1980, Table 5-4). Studies where animals have inhaled B(a)P, other hydrocarbons, or combustion emissions have shown a much smaller sensitivity than expected from epidemiological studies. Assuming proportionality, population studies (Stocks, 1958; Carnow and Meier, 1973) yielded a risk of 1.0 cancers per 10^5 people per ng/m^3 B(a)P (Wilson et al., 1980). Studies of gas workers (Doll et al., 1965) and roofers (Hammond et al., 1976) yielded a risk of 0.2 cancers per 10^5 people per ng/m^3 B(a)P (Wilson et al., 1980). Wilson et al. qualified these risk estimates as follows: "These estimates are all crude and cannot be taken as proof of causality. The risk, in fact, could be zero." We have utilized the B(a)P content of the emissions from a number of light and heavy duty diesel-powered vehicles to express Cuddihy's risk estimate in terms of B(a)P so that we could compare it to the Wilson estimate. The estimates (based on selecting a median value of different diesel emissions) is typically above 0.8 cancers per 100,000 people per ng/m^3 B(a)P. Recognizing that the actual risks may in fact be zero, it seems reasonable to conclude that the risk of cancer due to B(a)P exposures is bounded by 0 and 4 cancers per 100,000 people per ng/m^3 B(a)P. The upper bound is estimated by taking the total death rate for malignant neoplasms of the respiratory system and subtracting 80% of the total as attributable to cancers caused by cigarette smoking.

If the relative percentages of organic compounds in ambient particulate matter were invariant, then the application of B(a)P as an indicator of carcinogenic potency would be reasonable. As reviewed by Daisey in Appendix 1, organic composition of urban particles varies considerably among locations and across seasons. In most locations away from industrial point sources automobile emissions and residential and commercial space-heating are the largest contributors to anthropogenic carbonated particulate matter. A microscopic analysis of TSP filters from 14 cities collected during the early 1970s indicated that oil and coal soot comprises 1-22% of the mass by weight (EPA, 1976). In several studies using elemental-chemical balance techniques, automobile exhaust was found to contribute 8-25% of the mass of fine fraction aerosols (Pace and Meyers, 1979; Dzubay et al., 1979: Cooper et al., 1979).

Variation in Biological Activity and Evaluation of Uncertainties

As one means of evaluating the B(a)P surrogate, we have looked at the variation in biological activity relevant to carcinogenesis in relation to the B(a)P content for a variety of samples. Since most data available are from short-term assays, we have utilized these in our analysis.

Zweidinger (1981) presented data, including mutagenicity of emissions from a variety of light duty and heavy duty vehicles in the Ames assay in the presence and absence of metabolic activation (rat liver S-9). to determine which of the measurements might be the best indicators of biological activity. We calculated the mutagenic activity per quantity of material from his data for total particulate, organic material, B(a)P,

and 1-NP (Appendix 2, p. 197). The percentage spread among emissions from various vehicles for each of these indicators is shown in Table III-1. In the absence of S-9, mutagenicity per µg B(a)P has a greater spread than mutagenicity per mile or per quantity of particulate, organics, or 1-NP. In the presence of S-9, the spread in mutagenic activity per µg B(a)P is greater than the spread in mutagenicity per mile or per mg organics, but less than the spread in mutagenicity per amount of 1-NP or particulate. Since B(a)P is mutagenic in the Ames assay only in the presence of S-9, it is reasonable that it is a better indicator when S-9 is present than when it is not. Nitropyrenes and other nitroaromatic compounds are responsible for much of the mutagenic activity in diesel engine emissions, but are not significant components of gasoline engine emissions and would not be expected to be good indicators.

It is not good to rely on one bioassay to evaluate B(a)P as a surrogate for carcinogenicity since different bioassays are more sensitive to different carcinogens. Nesnow and Huisingh (1980) have compared the activity of a variety of different samples in several bioassays. Dichloromethane (DCM) extracts from diesel engine, gasoline engine, coke oven, and roofing tar samples and an acetone extract of cigarette smoke condensate were tested in several bioassays of mutagenicity/carcinogenicity. Tables in Appendix 2 (pp. 198 and 200) show normalized results per quantity of extract and per quantity of B(a)P for assays done in the presence of rat liver S-9. The percentage spreads for activity relative to total organics and relative to B(a)P were calculated for the various assays and are shown in Table III-2. The percentage spread was greater for B(a)P (a factor of 3 to 40 of the median value) than for organics (a factor of 2 to 20 of the median value) in 3 assays: the Ames assay, Balb cell transformation, and skin tumor initiation. In 4 assays, sister chromatid exchange, mutagenesis in Balb and L-5178Y cells, and viral enhancement of transformation, the spread was greater for organics (a factor of 3 to 40 of the median value) than for B(a)P (a factor of 3 to 5 of the median value). These results suggest that B(a)P is probably not a better indicator of the biological activity of a variety of combustion emission samples than the total organic content is; that is, B(a)P does not appear to be particularly representative of active compounds.

The B(a)P content of the variety of samples described above does have a positive correlation with results in all the bioassays, as shown in Table III-3, with the highest correlation coefficient (0.922) for the SCE assay in Chinese hamster ovary cells and the lowest correlation coefficient (0.43) for mutation at the ouabain locus in mouse embryo Balb/c 3T3 cells.

Besides looking at emissions from specific sources, it is also useful to evaluate how representative B(a)P is of carcinogenic activity in urban air. Pitts et al. (1977) showed that urban air samples from California were mutagenic in the Ames test without metabolic activation and that the mutagenic activity was not enhanced by the addition of a mammalian metabolic activation system. Since B(a)P requires metabolic activation to be mutagenic in the Ames assay, this activity could not be due to the presence of B(a)P.

Besides the direct-acting nitro-compounds found in diesel exhaust, another source of direct-acting mutagens may be oxygenated and nitro-derivatives of such compounds as B(a)P formed by reaction with O_3 or NO_2 in polluted air.

Since the compounds responsible for the carcinogenic activity do not necessarily include B(a)P or other measured compounds, or vary in amount with them, the activity in a variety of bioassays that measure activities relevant to different steps in carcinogenesis should be measured whenever possible (see Appendix 2). The association between the B(a)P concentration and carcinogenic potency of the particulate emissions from new technologies must be determined if this surrogate is to be at all useful.

Table III-1. Percentage Spread* in Mutagenic Activity Calculated for Different Indicators from Data in Table III-1.

	-S9		+S9	
	Spread	Rank	Spread	Rank
per mile	318	3	128	1
per mg particulate	163	2	426	5
per mg organics	150	1	235	2
per µg B(a)P	770	5	306	3
per µg 1-NP	635	4	381	4

* Spreads are calculated as the interquartile ranges divided by the median and can be considered as a robust percentage standard deviation.

Table III-2. Percentage Spread in Biological Activity in Different Assays Relative to B(a)P Content and to Extracted Organics (Calculated from data given in Appendix 2, pp. 198 and 200)

Assay	Spread per µg B(a)P	Spread Per mg Extract
*Ames	1103	252
*Sister Chromatid Exchange	384	518
*L-5178Y Mutation	259	320
*Balb Mutation	343	3733
Viral Enhancement	538	895
*Balb Transformation	10350	1892
Skin Tumor Initiation	378	182

*Assays performed in the presence of rat liver S-9.

Table III-3. Rank Correlation Coefficients for B(a)P Content and Bioassay Activity for a Variety of Combustion Emission Samples (Calculated from data on p. 198, Appendix 2)

Assay	Correlation Coefficient	Fraction of Variance Explained
*Sister Chromatid Exchange	0.92	0.85
Skin Tumor Initiation	0.87	0.76
*Balb Transformation	0.76	0,58
*L-5178Y Mutation	0.72	0.52
Viral Enhancement	0.66	0.43
*Ames (Mutation)	0.61	0.38
*Balb Mutation	0.43	0.18

*Assays performed in the presence of rat liver S-9.

IV. Epidemiological Evaluations of Health Effects of Exposures to Ambient Particulate Matter

In this section, we summarize the evidence from retrospective health effects studies of human populations. Following a brief discussion of the general problems associated with such epidemiological studies, we re-examine the evidence from large scale statistical (mostly cross-sectional) studies relating total mortality with air pollution and socioeconomic variables. A preliminary analysis of studies on the air pollution effects on morbidity is also provided. The reader is referred to various papers in Appendix 3 for further details.

Problems with Epidemiological Studies on Health Effects of Particulate Air Pollution

The two most important problems in interpreting air pollution epidemiology are exposure misclassification and confounding. For example, in a geographical cross-sectional analysis, patterns of migration may invalidate the assumption that current measurements adequately represent exposure histories. In a prospective morbidity study, indoor sources and activity patterns may weaken the ability of central-city monitors to characterize individual exposures. If errors in exposure classification are random and unrelated to health effects, the most serious implication will be a loss in precision. However, if misclassifications are related to health status, there may be concern for confounding.

In a confounded study, an observed effect may be attributed incorrectly to a non-causal agent (e.g., air pollution). Among the most frequently suggested confounding factors are: smoking, occupation, diet, and medical care. Due to the similarity of the exposure mechanism, the large impact of smoking on community mortality rates and the potentially synergistic impacts of smoking and air pollution, smoking is perhaps the most intuitively plausible of these potential confounding factors. Although it is clear that attempts should always be made to control for potential confounding factors, it is not clear that the mere suggestion of confounding compels the risk analyst to abandon the results of any one study. Often a corrected analysis will provide usable results. However, unless these confounding factors are dealt with, the risk analyst must caution any reader that the conclusions are only tentative and subject to extreme uncertainty.

In addition to the general problems discussed above, A.B. Hill (1965) lists several specific points to be considered in evaluating the internal validity of results from epidemiological studies. These include:

- strength of association
- consistency of results
- specificity of results
- temporal gradient (cause precedes effect)

- biological gradient (variation in response with dose)
- biological plausibility (consistency of theory, experimentation, and epidemiology)

We encourage the serious consideration of all of these issues during the process of risk assessment, and we have attempted to consider these precepts of A.B. Hill in this analysis.

IV.1 Estimates Derived from Cross-Sectional Mortality Studies

Since a great deal of effort has been devoted over the past three decades to studying the relationships between geographic differences in air pollution levels and community mortality rates, we have decided to re-examine the evidence from cross-sectional mortality studies. In this section, the results of our investigation of these cross-sectional mortality studies are presented. It should be mentioned here that our results do not dictate significant changes in the interpretation of these studies. We confirm the previously reported positive correlation, and demonstrate that this association cannot be made to vanish by reasonable adjustments. However, we have not yet shed any further light on the plausibility of the associations.

The investigation had as its goal the development of a mathematical model, relating exposure to airborne particles with community mortality rates, representative of the relationships which have emerged from cross-sectional studies. The work was conducted in three phases: (1) literature search, and review of each of the major studies and/or critiques; (2) a quantitative summary and analysis of the coefficients from these studies; and (3) a statistical analysis of one of the central cross-sectional data bases.

Literature Review

The literature review indicated that at least thirteen research groups have conducted cross-sectional mortality studies and that at least as many have contributed critical reviews of this work (see Table 1, in Appendix 3, p. 4). The conclusion of the literature summary was that although the relationships developed by the various investigators are quite different, most of them are indicative of a plausible positive relationship between exposure to air pollution and reduced life expectancy. Nevertheless, it is quite difficult to: (a) draw valid comparisons between studies from the plethera of published results, (b) objectively derive representative results from the literature, or (c) conclude that the observed associations are causal.

We expected the critiques of cross-sectional studies to provide insight into the interpretation of results. Unfortunately, our review of the critiques left us with the sense that most had been written from advocacy positions. Therefore, as often as not, the critiques tended to obfuscate, rather than illuminate, the meaning of these studies.

Meta-Analysis

The second phase of our research was intended to summarize quantitatively the results of the cross-sectional studies and to present these results in such a way that a risk assessment expert could efficiently use them. In order to avoid a selection bias, virtually all the cross-sectional studies were considered for inclusion. The minimum screening requirements were that linear exposure-response coefficients be provided and that enough information exist to construct standard errors for the coefficients. The key conclusions from the meta-analysis that was conducted were (see Appendix 3, p. 49 for details):

- Arithmetic mean coefficients of TSP and $SO_4^=$ from the regressions on crude mortality are similar to those from the first published equation of Lave and Seskin (1970).
- The order of magnitude of the mean coefficients for TSP and $SO_4^=$ seem to be related approximately inversely to the respective mean ambient concentration of these pollutants.
- For TSP, $SO_4^=$, and B(a)P, the mean coefficients were higher for the older age group.
- The primary effect of including diet and smoking as variables is to increase the standard error of the sulfate and TSP coefficients.
- Inclusion of additional TSP statistics is shown to significantly reduce TSP coefficients. The same is true of the sulfate coefficients. This is believed to be due to the strong positive correlations among minimum, mean, and maximum values for these pollutants.

In summary, this phase of our work emphasized the variability of coefficient estimates in the literature and gave us insight into the factors with strong influences on the estimates. However, we were unable to estimate the covariances between coefficients for different pollutants, important statistics for assessing "uncertainty".

These considerations, as well as our basic criticisms of all the cross-sectional studies, lead us to the third phase of the project, an analysis of a representative data base.

Re-Analysis of the 1960 SMSA Data and Coefficient Estimation

The basic 1960 117 SMSA data set analyzed included total mortality rate, (TMR), the sixty explanatory variables of Lave and Seskin (1977), and median age. To this data set, six variables taken from Lipfert's dissertation (1978) were added. Three of these were additional pollution measures and three were socio-economic controls.

After completing a comprehensive preliminary analysis (see Appendix 3, pp. 56 - 78 for further information), we estimated the parameters of our basic eight independent variable model. The dependent variable was total mortality rate. The explanatory variables included:

- percent of the population over 65 years old (GE65)
- median age of the population (MEDAGE)
- percent of the population which was non-white (NW)
- decimal logarithm of the population density (LOGDEN)
- percent of the population with 4 or more years of college (COLLEGE)
- smoking index: packs/person-yr (SMOKING)
- annual mean sulfate concentration (MEAN_S)
- percent poor (POOR)

The variables were chosen on the basis both of physical plausibility and explanatory power in previous analyses. The basic model was linear in these variables. Values of all eight were available for only 98 of the full 117 SMSAs. The sulfate coefficient from this regression was 2.63 deaths/100,000 per year per $\mu g/m^3$. The estimated standard error of the regressions coefficient was 1.40 deaths/100,000 per year per $\mu g/m^3$. The plot and a map of residuals versus predicted values (see Figures IV-3a and IV-3b in Appendix 3) did not indicate a strong systematic behavior of residuals. Thus, several variations on this basic model were then estimated, in the spirit of sensitivity analysis. The results (i.e., estimates and uncertainties) are summarized in Table IV-1 and fully discussed in Appendix 3, pp. 67 - 70. In these twenty-five regressions the coefficient varied from 1.22 to 4.80 and the standard error varied from 1.02 to 2.41.

The largest sulfate coefficient, 4.80, came from a regression in which mean sulfates were the only pollution measure. This coefficient is not only large in an absolute sense, but is also statistically significant ($t = 2.2$). Under approximately normal distributional assumptions, a result so large would occur by chance less than three percent of the time.

The risk coefficients taken from regression equations 6 and 7 in Table IV-1 represent estimates in which both coefficients were simultaneously determined. These results are particularly important if risk assessments are to be based upon exposure estimates for more than one particulate coefficient, e.g., sulfate and TSP. In this circumstance, the estimated standard error in incremental mortality rates should reflect not only the standard error of each coefficient estimate but also the covariance of the estimates. For this purpose we have summarized the detailed results of a joint regression in Table IV-2. Table 21 in Appendix 3, p. 74 - 76, summarizes results from several single and joint pollutant regressions.

Comparison of the 5 pollutant estimates with their corresponding variance/covariance values reveals the influence of multicollinearity and surrogate behavior of the pollutant variables. Application of these risk estimates to actual population weighted ambient particulate concentrations in the U.S. (see Appendix 3, p.156) has also supported this observation, namely:

Table IV-1. Sensitivity Analysis - Estimates of Mean Sulfate Coefficient and Standard Errors

Regression		Sulfate Coeff.	Std. Err. of Coeff.	R^2	n	p
1 - basic model		2.63	1.40	0.863	98	9
2 - basic/5 outliers removed		1.41	1.04	0.909	93	9
3 - basic/5 influential points removed		3.59	1.54	0.880	93	9
4 - basic/5 influential points and 3 outliers removed		2.60	1.29	0.910	90	9
5 - basic/only SMSAs with all five pollution measures	a)	3.72	1.90	0.851	66	9
	b)	4.80	1.77	0.918	58	9
6 - basic/add mean TSP, same subset	a)	2.77	2.27	0.853	66	10
	b)	4.07	2.10	0.919	58	10
7 - basic/all 5 pollutants, (TSP, $SO_4^=$, Mn, B(a)P, Fe)	a)	3.00	2.41	0.854	66	13
	b)	4.26	2.24	0.920	58	13
8 - basic/occupational variables, F=3.82, p=0.0005		1.22	1.28	0.904	98	18
9 - basic/unemployment and white collar variable		2.37	1.35	0.875	98	11
10 - basic/home heating variables, F=3.21, p=0.0002		1.64	1.29	0.927	98	28
11 - basic/climate variables, F=1.77, p=0.06		1.72	1.55	0.897	98	23
12 - basic/5 highest and 5 lowest in-migration SMSAs deleted		1.35	1.02	0.897	88	9
13 - naive model-only 3 variables:GE65,MEDAGE,MEAN-S		2.68	1.50	0.788	98	4
14 - basic model/age-sex-race adjusted mortality substituted for TMR and GE65, MEDAGE and NW deleted		3.54	1.58	0.327	98	6
15 - basic model/with MEDAGE variable deleted		3.31	1.58	0.820	98	8
16 - basic model/with HOUSING variable added		1.46	1.38	0.877	98	10
17 - basic model/subset with values for all 5 pollutants both mean-s and nettsp in equation (nettsp = mean_p - 1.375mean_s)	a)	3.02	2.12	0.853	66	10
	b)	4.22	1.98	0.919	58	10
18 - basic model/various thresholds for mean-S						
(a) 2 $\mu g/m^3$		2.63	1.40	0.863	98	9
(b) 4 $\mu g/m^3$		2.59	1.41	0.863	98	9
(c) 6 $\mu g/m^3$		2.58	1.47	0.862	98	9
(d) 8 $\mu g/m^3$		2.39	1.59	0.861	98	9

Note: In run series 5, 6, 7 and 17, the a estimates include 66 observations. The b estimates are based upon a fit to 58 SMSAs after deletion of five influential points and three outliers. n = number of observations. p = number of variables (including the intercept).

Table IV-2. Estimated Pollution Coefficients, Variances, and Covariances of these Coefficients from Regression Involving Multiple Pollutants*

N.B. - All coefficients are in units of deaths/yr/100,000 persons per $\mu g/m^3$. Variances and covariances are in consistent units. Estimates are from 66 Observation Data Set.

$$\hat{\beta}_S = 3.00 \quad \hat{\beta}_P = 0.118 \quad \hat{\beta}_I = 1.91 \quad \hat{\beta}_M = -8.90 \quad \hat{\beta}_B = -421.$$

$$\mathrm{Var}_{\hat{\beta}} = \begin{array}{c} \\ S \\ P \\ I \\ M \\ B \end{array} \begin{array}{c} \begin{array}{ccccc} S & P & I & M & B \end{array} \\ \begin{bmatrix} 5.80 & - & - & - & - \\ -0.382 & 0.121 & - & - & - \\ 1.81 & -1.33 & 28.6 & - & - \\ -17.3 & 1.38 & -40.6 & 905.0 & - \\ 78.3 & -50.4 & 471.0 & -3240.0 & 654000. \end{bmatrix} \end{array}$$

*Variances (square of standard errors) are the diagonal elements and covariances are the off-diagonal elements of the matrix displayed. [S = $SO_4^=$, P = TSP, I = Fe, M = Mn, B = B(a)P]

- More than 80% of the net excess mortality risk seems to be attributable to sulfates, even though the biological plausibility of this relationship has not been established.

- However, coefficients of variation for the excess mortality estimates are typically around 50%, which suggests that the mathematical evidence to support any of the pollutants considered to be good surrogates for air pollution health effects is quite weak.

- Covariance between estimated pollutant risk coefficients account for about one third of the standard errors contributed by the variance terms.

- The range of variation resulting from the application of different sets of risk coefficients is not considerable (variations are about 25% of the projected excess mortality risks) which is again an indication of collinear/surrogate behavior.

Principal Findings: Estimates and Uncertainties

In summary, using several plausible models on a single data set, we have produced coefficient estimates which vary by a factor of almost five, and estimates of the standard errors of these coefficients which vary by a factor of nearly two and a half. As we have emphasized in the analysis above, the uncertainty surrounding the mortality risk coefficients is large -- so large that the true mortality risk might in fact be somewhere between zero and a large number such as 10 deaths/yr/10^5 persons per $\mu g/m^3$ of sulfate (see also Figure 8, Appendix 3, p. 73). Although quite variable, the coefficients, however, are not as sensitive to reasonable differences in model choice as the papers of Thibodeau et al. (1980) and Gibbons and McDonald (1981) might suggest. In addition, although many of the estimates are small in comparison with their standard errors, all of the sulfate coefficients are positive. Even so, without a clear a priori understanding of the determinants of community mortality rates, it is difficult to objectively choose the best of these models. For the purposes of obtaining rough bounding estimates, we provide the following excess mortality risk coefficients (β) along with their respective coefficients of variation (CV) to characterize typical uncertainties*:

- Estimate for the mean sulfate coefficient, based on 66 SMSAs with value for all five pollutant measures:

  > $\beta_{SO_4^=}$ = 3.72 $CV_{SO_4^=}$ = 51%

- Estimate for the mean TSP coefficient from the same 66 observation data set.

  > β_{TSP} = 0.4 CV_{TSP} = 60%

- For the combined two pollutant set, i.e. joint estimations consisting of $SO_4^=$ and TSP:

  > $\beta_{SO_4^=}$ = 2.77 $CV_{SO_4^=}$ = 82%

  > β_{TSP} = 0.18 CV_{TSP} = 130%

*All coefficients are in units of excess deaths/year/100,000 persons per $\mu g/m^3$.

- For the combined five pollutant set, i.e. joint estimations consisting of $SO_4^=$, TSP, B(a)P, Fe and Mn:

  > $\beta_{SO_4^=} = 3.00$ $CV_{SO_4^=} = 80\%$

  > $\beta_{TSP} = 0.12$ $CV_{TSP} = 300\%$

  > $\beta_{B(a)P} = -421$ $CV_{B(a)P} = 190\%$

  > $\beta_{Fe} = 1.91$ $CV_{Fe} = 280\%$

  > $\beta_{Mn} = -8.90$ $CV_{Mn} = 340\%$

It should be emphasized again that these estimates contain significant errors represented by large coefficients of variation (typically greater than 100%). As mentioned earlier, it is difficult to interpret individually the species specific risk estimates, since there are strong covariances among the concentrations of pollutants considered and the estimated risk coefficients for these pollutants. In the ultimate analysis these and other results derived from cross-sectional studies may have to be viewed as primarily qualitative in nature.

IV.2 Preliminary Analysis of Results from Time-Series Mortality Studies

An alternative to the cross-sectional mortality study is the time-series mortality study. Early time-series studies concentrated on the role of "episodes" of high pollution days on community mortality rates. More recently, the work has been extended to include the study of the importance of small day-to-day perturbations in ambient pollution levels.

The most comprehensive studies have been those in London and New York City, which are discussed in some detail in Appendix 3, p. 85. These analyses provide strong evidence of a relationship between daily pollution levels and mortality rates. The mortality effect appears to be strongest on the same day as the increased air pollution; however, there is evidence in some of the studies for smaller effects persisting for one to seven days afterwards.

The increased deaths, following days of high pollution, seem to occur primarily as deaths due to cardiorespiratory disease. This result corresponds to that found by Lave and Seskin in their disease-specific cross-sectional analysis.* Although the traditional point of view has been that daily time-series studies measure the acute impacts of air pollution and that cross-sectional studies measure the chronic impacts, this may not be so. After our preliminary analysis, we have concluded that it is possible that the coefficients from cross-sectional studies may in fact reflect a mixture of acute and chronic impacts.

The primary purpose of our initial research with the time-series mortality studies was to investigate whether the results from time-series studies were consistent with those from the cross-sectional studies. The preliminary findings from the analysis of the New York and London time-series mortality studies have indicated that:

*In Lave and Seskin's results, cardiovascular disease dominated the air pollution induced deaths.

Thus, the projected mortality impacts might occur in the same year as the projected increase in emissions, or the mortality impacts might be spread over the twenty or thirty years following the increase in emissions.

- The studies have been unable to differentiate among several alternative plausible forms of exposure-response function. Therefore, while the coefficients may be used with some confidence to predict the impact of small changes in particulate concentrations in areas with exposures near those typical of the SMSAs involved in these studies,* they must be used with caution to predict the impacts of (a) large increments in exposure, (b) incremental exposures on low (or high) baseline exposures, (c) intermittant emissions patterns which would influence differentially the parameters of the distribution of daily exposures.

Beyond these three caveats related to "extrapolation" of the results, there are more serious issues. Paramount among them are the related issues of confounding and causality. From our point of view, it is as likely that the parameters have been underestimated (due to inclusion of non-causal variables in the models which are positively correlated with air pollution) as that they are overestimated due to confounding.

Another important issue is the biological plausibility of measured TSP or sulfate as a cause of the observed excess mortality. In the case of sulfate, we expect that damage would most likely be done by acid sulfates. Since only a minor and variable fraction of atmospheric sulfate is acid, it is not clear that total sulfate levels serve as an adequate surrogate for sulfate health effects. Due, however, to statistical correlations between TSP, fine particles, total sulfates, and acid sulfates, it is likely that the measurement of any of these will reflect the effect of the harmful components of airborne particles without shedding any additional light on the biological plausibility of the individual components.

Since the coefficients from cross-sectional mortality studies are often used to estimate the risk of mortality associated with exposure to particulate air pollution, we must stress repeatedly that there are large uncertainties surrounding these damage coefficients, and specify a large number of precautions for their use. In particular, our review of DOE technology HEEDs indicates that damage coefficients derived from cross-sectional studies have been used, often without adequate attention to the uncertainties involved, to predict mortality risks. Due to the nature and extent of these uncertainties, we recommend that, whenever possible, policy decisions be based upon analysis of exposures, rather than health risks. For instance, most of the information concerning the relative merits of alternative facility siting strategies might be contained in the exposure estimates. Here the application of health risk coefficients might add greatly to uncertainty, without commensurately improving the power of the analysis.

In many cases, risk analyses are really comparing exposure estimates and the value of the hazard coefficient is only used to indicate that the

---

*See Table 18 in Appendix 3, p. 58 for the range of typical pollutant concentrations in the SMSAs mentioned.

- The damage coefficient estimates derived from cross-sectional mortality studies were not inconsistent with the time-series mortality coefficients which ranged from 0.033 to 0.331 deaths/year per 10^5 persons per $\mu g/m^3$ of TSP (the associated coefficients of variation ranged from 20 to 80%).

- Typically, time-series mortality studies have shown lags between exposure and death of no more than 3 to 5 days.

As with the cross-sectional studies, the numerical results reported here must also be viewed in perspective. The time-series studies have many limitations, and have been the subject of strong criticisms. Some of the difficulties with the interpretation of the results from time-series studies include:

- One set of pollutant measures (e.g., COH, BS) is commonly available in time series studies and another set (such as sulfates, TSP, B(a)P) is used in cross-sectional studies on health effects.

- Sensitivity of the estimates to the methods used to filter data and remove the influence of temperature on mortality.

- Biological plausibility of the results:

  --Are the deaths the result of an additional stress on subgroup of highly susceptible persons?

- Are risks uniform for "healthy" and "diseased" groups?

As discussed in Appendix 3, further analytical efforts are needed to reduce existing uncertainties associated with the interpretation of findings from time-series mortality studies.

IV.3 Conclusions and Caveats Regarding the Use of Mortality Risk Coefficients

Of at least equal importance as the procedures for deriving quantitative risk estimates from epidemiologic studies on mortality effects of air pollution, is an appreciation of the limitations of the estimates so derived. Based upon our literature review, meta-analysis, and coefficient estimation studies we have come to the tentative conclusions that:

- To some extent all of the particulate pollution variables must be viewed as surrogates for whatever are the truly pernicious components of airborne particulate matter. Therefore, risk assessments based upon these numbers will be most valid for emissions similar to those represented by the "typical" ambient aerosol of the 1960s. Certainly they are of limited value for distinguishing among technologies which are only subtly different in their air pollution impacts.

- It is still uncertain as to what extent the cross-sectional studies measure the sum of acute impacts on mortality from chronic disease or the impact of chronic exposure on development of chronic disease.

exposure differences are important. In these cases, we recommend that the risk analysis be done, the results compared and the hazard coefficient only be brought in in the last paragraph of the analysis. In the cases where exposure alone cannot resolve the issues, we recommend that the coefficients and confidence levels based on standard errors from cross-sectional studies be used in assessing the health effects of the respirable fraction of ambient particulate matter.*

For assessing benefits and risks associated with mitigative measures to reduce pollutant emissions (mostly SO_2) and economic incentives for pollution reduction, we currently have no alternative but to suggest continued use of sulfates as a surrogate, although we advise caution. More importantly, we discourage the use of sulfate as a surrogate in cases where sulfur emissions are reduced in greater proportions than particulates or the trace metals. In circumstances such as these, we believe that the use of respirable particles as surrogates may be more advisable.

Even when all these conditions are met and proper confidence intervals specified, the risk analyst should still mention all the caveats that question the causality and the utility of these estimates. Basically, the risk coefficients from cross-sectional mortality studies are crude, appropriate only for development of rough bounding estimates. Nonetheless, they are the only tools readily available to the air pollution risk analyst today.

IV.4 Implications of Evidence from Observational Studies of the Association Between Particulate Matter and Morbidity Outcomes

Introduction

We have initiated an assessment of the morbidity effects of particulate matter air pollution. If the mortality rates cited in Section IV. are a biologically plausible result of air pollution exposure we would expect to find relationships between airborne particles and measures of morbidity. Unfortunately, very few studies exist that can be used to derive quantitative relationships between particle air pollution and nonfatal health outcomes. There are several important reasons for this gap. First, morbidity outcomes (e.g., lung function, respiratory symptoms, and hospital admissions) are measured or counted much less precisely than is death as an outcome. Second, most of the morbidity measures must be collected directly by the investigator, therefore limiting the size of the study population and reducing the possibility of observing relatively small effects. For this reason, most morbidity studies do not have the large aggregate populations that are available for those who use vital statistics for studies of mortality in large populations.

Interpretation of the morbidity studies must also be qualified similarly to the mortality studies and, in fact, to all nonexperimental epidemiologic studies. As we have stated above and repeat here, the individual epidemiologic studies of morbidity can demonstrate an association between

*See Appendix 1, Section V, p.185 for comments on estimating confidence intervals based on the standard errors.

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 advantage is that the individual-level analysis in these studies permits more careful control of person-factors (e.g., smoking and occupation) that might otherwise act as confounding items in an aggregate-level study.

Many individual characteristics other than air pollution exposure (e.g., passive and direct cigarette smoking, occupation, and socioeconomic status) may influence the morbidity outcomes of interest (e.g., lung function, respiratory symptoms, and respiratory infection). The inability to control for all of these individual characteristics produces nonsampling errors that increase the uncertainty in the results of morbidity studies. Since we might reasonably assume that other factors may exert a stronger influence on the health outcomes of interest than will air pollution at current levels, we expect even greater difficulty in using observational studies to resolve the questions that remain for low concentration particle exposure.

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 TSP equivalents) concentration in excess of approximately 180 $\mu g/m^3$ (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 $\mu g/m^3$ (24-hour average). These few studies suggest increased hospital admissions for cardiac or respiratory illness (TSP at 600 $\mu g/m^3$ in association with SO_2 at 400 $\mu g/m^3$) and worsening of health status among bronchitics (TSP at 350 $\mu g/m^3$ in combination with SO_2 at 500 $\mu g/m^3$) (Ware et al, 1981). 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. Unfortunately, very little evidence exists to indicate that the relationships observed at higher particle concentrations do or do not hold at lower concentrations. With these qualifications, coefficients were derived and are presented in Table IV.3.

The range for coefficients must logically include 0 because of the extrapolation below concentrations observed in the studies. More effort would be required to derive quantitative error estimates but these would be of limited usefulness because of the probability of large nonsampling

Table IV.3 Initial 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 Male Smokers	170	BS (90-170)	Smoke (OECD calibration)	14-27% reporting symptoms
Bronchitis in Female Smokers	0			10% reporting symptoms (no variation across areas)
Bronchitis in Male Non-Smokers	100	BS (90-170)	Smoke (OECD calibration)	4-7% reporting symptoms
Bronchitis in Female Non-Smokers	10			2-3% reporting symptoms
Excess Emergency Room Visits for Respiratory Disease*	13	TSP (14-696) SO_2 (4-369)	TSP	24.5 ± 9.3 daily++ visits
Excess Total Emergency Room Visits*	20			94.3 ± 14.2 daily visits (standard errors represented after ± symbol)

* These coefficients are based upon regression results for which TSP explained only approximately 1% of the variance in hospital emergency room visits (Samet et al., 1981).

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

++ Assuming population base for hospital to be 20,000.

errors. These coefficients are left in the original air pollutant form (i.e., Smoke, BS, or TSP) but nonetheless present a biologically consistent impression with the coefficients derived for mortality. The right hand column of Table IV-3 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 effect range will produce an uncertain error. Of course, all of the caveats for use of mortality coefficients must be imposed on the morbidity estimates. Furthermore, our efforts on this question are preliminary and these values should be considered as tentative.

V. Principal Conclusions and Future Research Needs

During our analysis of the health effects resulting from exposures to ambient particles, we identified several areas for future research which will help reduce some of the uncertainties reported in this HEED. In the paragraphs following, we present the key conclusions, uncertainties, and suggested research needs associated with the main components of our study.

Particle Toxicity and Exposure Analysis

We have concluded from our review of the toxic effects of ambient particulate matter that a number of the pollutants (e.g., acid sulfates, diesel emission particles, organic aerosols) may produce adverse health effects. However, we were unable to resolve with certainty the components and amounts of particulate air pollution that are responsible for the most deleterious health effects. The gaps in knowledge that presently exist in this assessment are primarily associated with the limitations of the available data on exposures and animal, controlled human, and short-term bioassay results, as well as with the techniques used to analyze these data.

The important areas of uncertainty influencing the evaluation of particle toxicities include:

- Inadequate characterization of ambient particles by:
  - Source or emission type,
  - Elemental and chemical composition, and
  - Size fraction,
- Shortage of analyses of samples of airborne particles from cities and rural areas,
- Lack of comprehensive and comparative risk analysis of different pollutants, and
- Not enough use of occupational data in connection with the analysis of particle toxicity.

The research that is recommended to reduce some of these uncertainties includes:

- Evaluation of the relative toxicity of particles by jointly utilizing:
  - The *in vitro* and *in vivo* bioassays,
  - Toxicity of samples of ambient particles from as many cities and rural areas as possible, and
  - Incorporation of occupational data.

The approach recommended above is similar to one being utilized by EPA in their evaluation of the carcinogenicity of diesel emission particles. What is now needed is an expanded analysis including a much greater variety of types of emissions and an evaluation of toxicity for chronic

lung diseases as well as cancer.

- Defining the origin and composition of particles with the aid of various analytical techniques of source apportionment for the purpose of characterizing historic exposures to fine, respirable, and total suspended particles. This information is needed to reduce uncertainties associated with the estimation of population exposures to various toxicants. It is also fundamental to the reconstitution of particle toxicity information by region and year.

- Collection of more data on nitrates and acid aerosols (in particular, on the sulfuric acid fraction of sulfates) in order to understand the extent of exposures and observed effects due to nitrates and sulfates in ambient air.

- Collection and analysis of more data to determine the extent and nature of personal exposures to respirable particles. For this purpose, the relationship between indoor and outdoor exposures to various aerosols needs to be analyzed.

Risk Assessment Based on Epidemiological Evaluations

In Section IV, we have discussed the surrogates and potency factors (damage coefficients) that are now being used and have cited the uncertainties and limitations of using them. From this phase of our study, we have concluded that:

- For evaluating the extent of effects of airborne particles, total respirable particulates would be an intuitively plausible surrogate, however, in the absence of good concentration data on inhalable or respirable particles, we find no reasonable alternative to the continued use of sulfates as a surrogate. The role of sulfate as a surrogate will remain uncertain until further research indicates the causality of sulfate or of some other factor.

- B(a)P is a poor surrogate for assessing air pollution-related cancer risks and should be replaced by a more complex scheme of assessment of exposures to organic compounds including bioassay activity and results of relevant occupational studies (see Section III, p. 29).

- For rough estimation of mortality risks associated with emissions of sulfates and other particles, mortality coefficients provided in Table IV.2, together with the standard errors for these coefficients, may be used, but only with extreme precaution.

- Results from observational morbidity studies are difficult to interpret in the context of risk assessment. The morbidity risk coefficients provided in Table IV.3 represent an initial attempt to report risk coefficients in the same form used to present mortality risk coefficients.

- The risk estimates derived from mortality and morbidity analysis must reflect the likelihood that zero mortality or morbidity risk is a possible outcome under current ambient exposure.

- The use of any risk coefficients must always be accompanied by statements of the qualifications and uncertainties (see Section IV.3).

The key uncertainties surrounding risk estimates derived from epidemiological evaluations are mainly due to the following factors:

- No clearly established biological mechanisms for cross-sectional and time-series mortality/exposure relations.
- An insufficient set of reliable exposure/response data relating respirable particles to morbidity effects.
- Little or no evidence indicating that the morbidity relationships observed at higher levels can be extrapolated to lower concentrations.
- Limitations of the data bases used for control purposes in statistical evaluations (e.g., smoking and socioeconomic).
- Inherent problems with the statistical models used to analyze historical exposures and mortality/morbidity rates.

Directions for future research that would help to reduce some uncertainties of risk estimates include:

- Better quantification (through experimental and epidemiological studies) of the possible role of particle exposures in:
  - Altering short and long-term measures of lung function,
  - Affecting pre-disposition to diseases in later years, and
  - Aggravating an existing disease state.
- Health effects modeling activities, especially in the areas of lung deposition, lung function decline, the nature of lagged effects, and relating morbidity with mortality risk.
- New cross-sectional investigations with:
  - Recent data.
  - More biologically appropriate age categories and disease groups.
  - New sets of exposure variables that are more pertinent to effects investigated.
  - New approaches.
- Expanding time-series studies to include:
  - Pulmonary function effects of air pollution in children.
  - More biologically plausible air pollution indices.
- Conducting additional observational morbidity studies designed to provide quantitative risk (or dose-response) estimates.

References

Adamsen, L.F., and R. Bruce (1979). Suspended particulate matter. A report to Congress. U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Research Triangle Park, N.C. EPA-600/9-79-006.

Alarie, Y., W.M. Busey, A.A. Krumm, and C.E. Ulrich (1973). Long-term continuous exposure to sulfuric acid mist in cynomolgus monkeys and guinea pigs. Arch. Environ. Health 27: 16-24.

Alarie, Y.C., A.A. Krumm, W.M. Busey, C.E. Ulrich, and R.J. Kantz (1975). Long-term exposure to sulfur dioxide, sulfuric acid mist, fly ash, and their mixtures. Results of studies in monkeys and guinea pigs. Arch. Environ. Health 30: 254-262.

Amdur, M.O., J. Bayles, V. Urgo, and D.W. Underhill (1978). Comparative irritant potency of sulfate salts. Environ. Res. 16: 1-8.

Amdur, M.O., M. Dubriel, and D. Creasia (1978). Respiratory response of guinea pigs to low levels of sulfuric acid. Environ. Res. 15: 418-423.

American Conference of Governmental Industrial Hygiene Association (1970). Guide for respirable dust sampling. AIHA J: 31-133.

Atmospheric and Environmental Research, Inc. (1981). Study of the role of transport in fine and total suspended particulate air quality. AER report prepared for NCAQ, Washington, D.C. NTIS pub. PB81-168031.

Ayres, S.M. et al. (1973). Health effects of exposure to high concentrations of automotive emissions. Arch. Environ. Health 27: 168.

Barnhart, M.I., S. Chen, S.O. Salley, and H. Puro (1981). Ultrastructure and morphometry of the alveolar lung of guinea pigs chronically exposed to diesel engine exhaust: six month's experience. J. Appl. Toxicol. 1: 88-103.

Barnhart, M.I., S.O. Salley, S. Chen, and H. Puro (1982). Morphometric ultrastructural analysis of alveolar lungs of guinea pigs chronically exposed by inhalation of diesel exhaust (DE). In: Toxicological Effects of Emissions from Diesel Engines, Proceedings of the Environmental Protection Agency 1981 Diesel Emissions Symposium, Oct. 5-7, 1981 (Joellen Lewtas, ed.), Elsevier Science Publishing Co., Inc., New York. pp. 183-200.

Beliten, R.P. (1975). Metals. In: Toxicology, the Basic Science of Poisons (Casarett, L. and J. Doull, eds.). Macmillan Publishing Co., Inc., New York, Chapter 18.

Brownstein, D.G. (1980). Reflex-mediated desquamation of bronchiolar epithelium in guinea pigs exposed acutely to sulfuric acid aerosol. Am. J. Path. 98: 577-590.

Carnow, B.W., and P. Meier (1973). Air pollution and pulmonary cancer. Arch. Environ. Health 27: 207-218.

Casarett, L.J. (1975). Toxicology of the respiratory system. In: Toxicology, the Basic Science of Poisons (Casarett, L.J. and J. Doull, eds.). Macmillan Publishing Co., Inc., New York, Chapter 9.

Cavender, F.L. (1978). Effects in rats and guinea pigs of six-month exposure to sulfuric acid mist, ozone, and their combination. J. Toxicology Environ. Health 4: 845-852.

Cockrell, B.Y., and W.M. Busey (1978). Respiratory tract lesions in guinea pigs exposed to sulfuric acid mist. J. Toxicol. Environ. Health 4: 835-844.

Cooper, J.A., J.G. Watson, J.V. Huntzicker (1979). Summary of the Portland aerosol characterization study (PACS). University of Oregon Graduate Research Center Report.

Cuddihy, R.G., W.C. Griffith, C.R. Clark, and R.O. McClellan (1981). Potential health and environmental effects of light duty diesel vehicles II. Prepared for HERAP, U.S. Department of Energy.

Daisey, J.M. (1982). Airborne particulate carbon and carbon compounds: a review. Prepared in support of Harvard study in health effects of exposures to ambient particles.

Department of Energy (1981). Health and environmental effects document for oil shale - 1981. Prepared by IWG Corp and Center for Environmental Science, University of Colorado at Denver for HERAP, DOE, November 1981.

Doll, R. (1978). Atmospheric pollution and lung cancer. Environ. Health Perspect. 22: 23-31.

Doll, R., R.E.W. Fisher, E.J. Gammen, W. Gunn, G.O. Hughes, F.H. Tyree, and W. Wilson (1965). Mortality of gas workers with special reference to cancers of the lung and bladder, chronic bronchitis, and pneumoconiosis. Brit. J. Ind. Med. 22: 1.

DuMouchel, W.H., and J.E. Harris (1981). Bayes and empirical Bayes methods for combining cancer experiments in man and other species. M.I.T. Technical Report No. 24, Department of Mathematics.

Dziedzic, D. (1981). Differential counts of B and T lymphocytes in the lymph nodes, circulating blood and spleen after inhalation of high concentrations of diesel exhaust. J. Appl. Toxicol. 1: 111-115.

Dzubay, T.G., R.K. Steven, W.J. Courtney, and E.A. Drane (1979). Chemical elemental balance analysis of Denver aerosol.

Environmental Protection Agency (1974). Summary report on atmospheric nitrates. External draft. National Environmental Research Center, Research Triangle Park, N.C.

Environmental Protection Agency (1976). National assessment of the urban particulate problem. Vol. I. U.S.E.P.A. 450/3-76-024, Research Triangle Park, N.C.

Environmental Protection Agency (1978). Assessment of carcinogenic risk from population exposure to cadmium in ambient air. Carcinogen Assessment Group, EPA, Washington, D.C. (see DOE, 1981, p. 5-10).

Environmental Protection Agency (1978). Review of the national ambient air quality standards for particulate matter: Assessment of scientific and technical information. OAQPS staff paper. EPA-450/5-82-001.

Environmental Protection Agency (1981). Air quality criteria document for particulate matter and sulfur oxides. Environmental Criteria and Assessment Office, Research Triangle Park, N.C.

Ericsson, G., and P. Camner (1982). Health effects of sulfur oxides and particulate matter in ambient air -- a draft document on health criteria. National Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden.

Ferek, R.J. (1982). A study of aerosol acidity over the northeastern United States. Cooperative thesis No. 68. Florida State University and National Center for Atmospheric Research.

Finlayson, B.J., and J.N. Pitts (1976). Photochemistry of the polluted troposphere. Science 192: 111-119.

French, et al. (1971-1972). Aggravation of asthma by air pollution in two CHESS communities, 1971-1972. (Unpublished, cited in EPA, 1974).

Friedman, M.A., E.J. Greene, and S.S. Epstein (1972). Rapid gastric absorption of sodium nitrite in mice. J. Phar. Sciences 61: 1492-1494.

Georgopoulos, P.G., and J.H. Seinfeld (1982). Statistical distribution of air pollutant concentrations. Envir. Sci. and Tech. 16: 401A-416A.

Gibbons, D.I., and G.C. McDonald (1981). Influential data diagnostics and model building techniques applied to an air pollution mortality analysis, presented at 6th Annual SAS Users Group International Conference, Orlando, FL.

Cross, K. (1981). Pulmonary function testing of animals chronically exposed to diluted diesel exhaust. J. Appl. Toxicol. 1: 116-123.

Hamilton, A., and H.L. Handy (1974). Industrial Toxicology, Publishing Sciences Group, Inc., Acton, MA., pp. 417-419.

Hammond, E.C., J.J. Selikoff, P.L. Lawther, and H. Seidman (1976). Inhalation of benzo(a)pyrene and cancer in man. Ann. N.Y. Acad. Sci. 271: 116-124.

Hastings, L., A. Vinegar, V.N. Finelli, J. Leng, G.P. Cooper, R.D. Laurie, W. Pepelko, and J. Orthoefer (1980). Effects of six-month exposure of rats to particulate carbon and nitrogen dioxide. In: Health Effects of Diesel Engine Emissions (see Barnhart et al., 1980), pp. 728-743.

Hill, A.B. (1965). The environment and diseases: association and causation. Proc. Roy. Soc. Med. Sec. Occup. Med. 58: 272.

Jacobsen, A.R., and S. Morris (1976). The primary air pollutants -- viable particulates. In: Air Pollution: Air Pollutants, Their Transformation and Transport (Stern, A.L., ed.) Academic Press, New York, Chapter 4.

Johnston, M. (1981). Alterations of pulmonary function in a human subject from exposure to low concentrations of sulfur dioxide and respirable aerosols containing iron. Master's thesis submitted to Florida State University, Dept. of Oceanography.

Kaplan, H.L., W.F. MacKenzie, K.J. Springer, R.M. Schreck, and J.J. Vostal (1982). A subchronic study of the effects of exposure of three species of rodents to diesel exhaust. In: Toxicological Effects of Emissions from Diesel Engines, Proceedings of the Environmental Protection Agency 1981 Diesel Emissions Symposium, Oct. 5-7, 1981 (Joellen Lewtas, ed.), Elsevier Science Publishing Co., Inc., New York, pp. 161-182.

Ketels, K.V., J.N. Brador, J.D. Fenters, and R. Ehrlich (1977). SEM studies of the respiratory tract of mice exposed to sulfuric acid mist-carbon particle mixtures. In: Scanning Electron Microscopy. Vol. II, pp. 519-526. ITT Research Institute, Chicago, IL.

Lave, L.B., and E.P. Seskin (1970). Air pollution and human health. Science 169(3947): 723-733.

Lave, L.B., and E.P. Seskin (1977). Air Pollution and Human Health, Johns Hopkins University Press, Baltimore, MD.

Lawther, P.J., and E. Waller (1978). Trends in urban air pollution in the United Kingdom in relation to lung cancer mortality. J. Envir. Health Persp. (Feb): 71-73.

Leikauf, G., D.B. Yeates, K.A. Wales, D. Spedtor, R.E. Albert, and M. Lippmann (1981). Effects of sulfuric acid aerosol on respiratory mechanics and mucociliary particle clearance in healthy nonsmoking adults. Am. Ind. Hyg. Assoc. J. 42: 273-282.

Lemen, R.A., J.S. Lee, J.K. Wagoner, and H.P. Blejer (1976). Cancer mortality among cadmium production workers. Ann. N.Y. Acad. Sci. 271: 273- .

Lewis, T.R., W.J. Moorman, W.F. Ludmann, and K.I. Campbell (1973). Toxicity of long-term exposure to oxides of sulfur. Arch. Environ. Health 26: 16-21.

Lipfert, F.W. (1978). The association of human mortality with air pollution: statistical analyses by region, by age, and by cause of death. Ph.D. Dissertation. Union Graduate School, Cincinnati, Ohio.

Lippmann, M. (1980). Effects of sulfur oxide pollutants on respiratory function, particle deposition, and bronchial clearance. U.S. Environmental Protection Agency. Health Effects Research Laboratory, Office of Research and Development, Research Triangle Park, N.C. EPA-600/1-80-035.

Mage, D.T. (1982). Public health aspects of air quality surveillance. Public Health Reviews (in press).

McCoy, E., H.S. Rosenkranz, and R. Mermelstein (1981). Evidence for the existance of a family of bacterial nitroreductases capable of activating nitrated polycyclics to mutagens. Env. Mutagenesis 3: 421-427.

Miller, F.J., P.E. Gardner, J.A. Graham, R.E. Lee, Jr., W.E. Wilson, and J.D. Bachmann. Size considerations for establishing a standard for inhalable particles. J. Air Pollut. Control Assoc. 29: 612-615.

National Academy of Science (1981). Indoor Pollutants, National Academy Press, Washington, D.C.

National Academy of Science (1972). Particulate polycyclic organic matter. National Academy of Sciences, Washington, D.C.

National Research Council (1979). Airborne particles. Assembly on Life Sciences, Division of Medical Sciences, Committee on Medical and Biological Effects of Environmental Pollutants, Baltimore, MD.

Natusch, D.F.S., J.R. Wallace, and C.A. Evans, Jr. (1974). Toxic trace elements: preferential concentration in respirable particles. Science 183: 202-204.

Natusch, D.F.S., and J.R. Wallace (1974). Urban aerosol toxicity: the influence of particle size. Science 186: 695-699.

Nesnow, S., and J.L. Huisingh (1980). Mutagenic and carcinogenic potency of extracts of diesel and related environmental emissions: summary and discussion of the results. In: Health Effects of Diesel Engine Emissions: Proceedings of an International Symposium, Vol 2 (Pepelko, W.E., R.M. Danner, and N.A. Clarke, eds.), pp. 898-912.

Ohgaki, H., N. Matsukura, K. Morino, T. Kawachi, T. Sugimura, K. Morita, H. Tokiwa, and T. Hirota (1982). Carcinogenicity in rats of the mutagenic compounds 1-nitropyrene and 3-nitrofluorene. Cancer Letters 15: 1-7.

Pace, T.G., and E.L. Meyers, Jr. (1979). Preliminary characterizationof inhalable particulates in urban areas. Proceedings of the 72nd Annual Meeting Air Pollution Control Assoc., Cincinnati, OH.

Pace, T.G., J.G. Watson, and C.E. Rodes (1981). Preliminary interpretation of inhalable particulate network data. Presented at the 1981 Annual Meeting of the Air Pollution Control Association (paper #81-5.2)

Pederson, T.C., and J.S. Siak (1981). The role of nitroaromatic compounds in the direct-acting mutagenicity of diesel particle extracts. J. App. Toxicol. 1: 54-60.

Pepelko, W.E., J. Mattox, W.J. Moorman, and J.C. Clark (1980). Pulmonary function evaluation of cats after one year of exposure to diesel exhaust. In: Health Effects of Diesel Engine Emissions (see Barnhart et al., 1980), pp. 757-765.

Pepelko, W.E. (1982). EPA studies on the toxicological effects of inhaled diesel engine emissions. In: Toxicological Effects of Emissions from Diesel Engines (see Kaplan et al., 1982), pp. 121-142.

Perera, F.P., and A.K. Ahmed (1979). Respirable Particles: Impact of Airborne Fine Particulates on Health and the Environment. Ballinger Publishing Co., Cambridge, MA.

Pitts, J.N. (1977). Keys to photochemical smog control. Environ. Sci. Techn. 11(5): 456-461.

Pitts, J.N., Jr., D. Grosjean, T.M. Mischke, V.F. Simmon, and D. Poole (1977). Mutagenic activity of airborne particulate organic pollutants. Tosicol. Letters 1: 65-70.

Samet, J.M., Y. Bishop, F.E. Speizer, J.D. Spengler, and B.G. Ferris, Jr. (1981) The relationship between air pollution and emergency room visits in an industrial community. J. Air Pollut. Control Assoc. 31, No. 3: 236-240.

Schlesinger, R.B., M. Halpern, R.E. Albert, and M. Lippmann (1979). Effect of chronic inhalation of sulfuric acid mist upon mucociliary clearance from the lungs of donkeys. J. Environ. Path. Toxicol. 2: 1351-1367.

Schlesinger, R.B., M. Lippmann, and R.E. Albert (1978). Effects of short-term exposures to sulfuric acid and ammonium sulfate aerosols upon bronchial airways function in donkeys. J. Am. Ind. Hyg. Assoc. 39: 275-286.

Schlesinger, R.B., and B. Naumann (1982). Effects of repeated inhalations of H_2SO_4 mist upon mucociliary clearance from the lungs of rabbits: Naso versus oral breathing. Presented at the American Industrial Hygiene Conference, Cincinnati, OH, June 1982.

Shy, C.M., et al. (1970). The Chattanooga school children study, effects of community exposure to nitrogen dioxide: II. Incidence of acute respiratory illness. J. Air Pollut. Control Assoc. 20: 582-588.

Smith, S.U., D. Fingleton, and T. Ozaki (1980). A review of concentration, chemical composition, size distribution and health effects related to inorganic inhalable particulates in Illinois. Final draft report, Institute of Natural Resources, Chicago, IL.

Sorenson, J.R.O., I.R. Campbell, L.B. Tepper, and R.D. Lingy (1974). Aluminum in the environment and human health. Environm. Health Persp. 8: 3-95.

Spengler, J.D., D.W. Dockery, W.A. Turner, and B.G. Ferris, Jr. (1981). Long-term measurements of respirable sulfates and particles inside and outside homes. Atm. Env. 15: 23-30.

Spengler, J.D., W.A. Turner, and S. McCarthy (1980). Suspended particle and sulfate measurements. A comparison of high-volume dichotomous and cyclone samples. Presented at the 73rd APCA Annual Meeting and Exhibition, Montreal (paper #80-43.4).

Spengler, J.D., G.D. Thurston, W.A. Turner, and L.E. Letz (1982). Mass and elemental composition of fine and coarse particles in six U.S. cities. Presented at the 75th Annual Meeting of the Air Pollution Control Association, New Orleans, LA, June 1982 (paper #82-79.7).

Stocks, P. (1958). Report on cancer in North Wales and Liverpool region in British empire campaign. Supplement to 1957 annual report.

Thibodeau, L.A., R.B. Reed, Y.M.M. Bishop, and L.A. Kammerman (1980). Air Pollution and human health: a review and reanalysis. Env. Health Persp. 34: 165-183.

Trijonis, J., Y. Horie, and D. Ricker (1979). Statistical analysis of TSP and meteorological data in EPA region 6. U.S. Environmental Protection Agency. EPA 906/9-79-005.

United Nations Economic Commission for Europe (1977). Fine particulate pollution. Pergamon Press, New York, NY.

Vinegar, A., A. Carson, and W.E. Pepelko (1980). Pulmonary function changes in Chinese hamsters exposed six months to diesel exhaust. In: Health Effects of Diesel Engine Emissions (see Barnhart et al., 1980), pp. 749-756.

Vostal, J.J., T.L. Chan, B.D. Garg, P.S. Lee, and K.A. Strom (1980). Lymphatic transport of inhaled diesel particles in lungs of rats and guinea pigs exposed to diluted diesel exhaust. In: Health Effects of Diesel Engine Emissions (see Barnhart et al., 1980), pp. 625-648.

Watson, J.G., J.C. Chow, and J.J. Shah (1981). Analysis of inhalable and fine particulate matter measurements. Prepared for U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards, Research Triangle Park, N.C., December 1981, EPA-450/4-81-035.

White, H.J., and B.D. Garg (1981). Early pulmonary response of the rat lung to inhalation of high concentrations of diesel particles. J. Appl. Toxic. 1: 104-110.

Wilson, R., S.D. Colome, J.D. Spengler, and D.G. Wilson (1980). Health Effects of Fossil Fuel Burning, Assessment and Mitigation. Ballinger Publishing Co., Cambridge, MA.

World Health Organization (1982). Estimating human exposure to air pollutants. EFP/81.31.

Zweidinger (1981). Emission factors from diesel and gasoline powered vehicles; correlation with the Ames test. In: U.S. EPA Diesel Symposium Abstracts.