Critical Issues in Air Pollution Epidemiology

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The epidemiological studies which have had significant impact on the setting of National Ambient Air Quality Standards (NAAQSs) were performed more than twenty years ago. Most of the more recent studies have been seriously flawed in their design and/or execution because they neglected to account for important variables such as: pollutant exposures other than those from ambient air; the influence of personal activity on pollutant uptake; host responsiveness; and the separate contributions of recent transient peak exposures and long-term chronic exposures on the effects endpoints. For particulate pollutants, the influence of composition and size distribution has also received too little consideration. In order to address these deficiencies, research and methods development are needed on: indices for particulate exposures; identification of exposures relevant to the effects; improved indices of effects; acquisition of response data; identification of exposed populations; and identification of susceptible subgroups. Approaches to these needs are discussed, along with brief reviews of several recent studies that have focused on critical issues of concern, made the necessary efforts to characterize the relevant exposures of the populations being studied, and demonstrated human responses to ambient pollutants at current exposure levels.

Introduction

Studies of population responses to air pollutant exposures are as difficult to design and perform as any in environmental epidemiology. There are few cases where the exposures to the pollutants of interest can be well characterized or where the effects of interest are attributable directly and solely to the pollutant exposures. Furthermore, very few investigators have both the necessary sophistication in exposure assessment and in evaluation of sensitive indicators of response. In all studies, success is dependent upon skill and constant attention to detail among field personnel responsible for the collection of environmental and response data, and such capabilities are very difficult to assemble and even more difficult to maintain over extended follow-up periods.

This critical review focuses on the limitations of the widely used indices of exposure and response and on the opportunities for significant contributions by epidemiological studies that account for important exposure variables. It describes some recent studies that have been particularly productive because they have gone beyond the conventional designs and have focused on critical current issues with some new approaches and concepts. It also discusses some of the needs for additional research on methods and/or populations where new approaches could lead to significant advances in our understanding of population responses to air pollutant exposures.

The discussion emphasizes the so-called criteria pollutants, which have been the focus of a large majority of past studies in air pollution epidemiology.

Historical Perspective

The utility of many past air pollution epidemiology studies has been severely limited by our inability either to identify or to measure the pollutant parameters responsible for the observed effects. Other studies have been limited by the insensitivity of the indices used to measure effects or their weak relation to the biological effects produced by the pollutant exposures. This section reviews the limitations of the commonly used indices of exposure and response.

Exposure Indices

Great advances have been made in our ability to measure the airborne concentrations of many pollutant gases and vapors. Sensitive monitors are now available for
the continuous measurement of specific molecular forms such as sulfur dioxide \((\text{SO}_2)\), nitrogen dioxide \((\text{NO}_2)\), ozone \((\text{O}_3)\) and carbon monoxide \((\text{CO})\). With modern calibration and data acquisition systems, we can accumulate, store, and retrieve accurate concentration data for the specific vapor for any given interval of time in terms of either peaks or averages. We no longer have to depend on nonspecific analyzers of electrical conductivity for \(\text{SO}_2\) or total oxidant as a surrogate for \(\text{O}_3\).

Problems still remain in relating ambient concentrations of the pollutant gases and vapors at fixed monitoring sites to the actual exposures of populations of interest, and some of these problems will be addressed further under the topics of “Neglected Variables” and “Research Needs.”

The differences between concentrations at fixed monitoring sites and the actual exposures of individuals in a study population also complicate studies of airborne particles. These differences affect exposure assessments for both gaseous and particulate pollutants. However, with particles, we have many additional variables and even less capacity to measure or account for them than we do with gaseous pollutants.

Two of our criteria air pollutants are present in ambient air as particulate matter and are described in terms of mass concentrations collected on air sampling filters. These are lead \((\text{Pb})\) and total suspended particulate matter \((\text{TSP})\). For both, the biological effects can be strongly influenced by particle size distribution and particle composition. The former determines the distribution of particle deposition along the respiratory tract and hence the local tissue dose and translocation pathways. The latter determines chemical solubility and reactivity and thereby affects uptake by body fluids and access to remote organ systems.

Of the two particulate criteria pollutants, \text{Pb} is clearly the easier one to deal with in terms of exposure-response studies. The toxicity is clearly related to the absorbed \text{Pb} and its toxicokinetics. The TSP standard makes no distinction about either particle size or chemical composition.

The newly proposed particulate matter standard (Federal Register, March 9, 1984) does narrow the range of sampled particles to those which can penetrate through the oral airways into the trachea and more distal airways, on the basis that the expected health effects of particles are those which occur in the lungs or in remote organs after dissolution in the lungs. However, the newly proposed standard still makes no distinction about composition, even though we have no reason to expect that the various constituents have similar biological effects. Thus, both the TSP and the proposed \(\text{PM}_{10}\) standards make the implicit assumption that acidic droplets, oil drops, carbon particles, fly ash and wind blown soil are all equivalent in potential toxicity.

Based upon these considerations, it comes as no surprise to environmental epidemiologists that the associations between nonspecific indices of particulate pollution such as TSP and health-related endpoints is highly variable in time and with target population.

Another distinction between our capability for monitoring gaseous and particulate pollutants lies in temporal response. Particle monitoring is generally done by the States for regulatory purposes by determining sample masses collected over long sampling periods such as 24 hr and may be done only at arbitrary intervals such as every sixth day. Thus, the available data may be useful for estimating annual average concentrations, but are virtually useless in relation to defining human responses to relatively brief pollution episodes or to a series of periodic episodes.

Some other particulate concentration indices which have been used in epidemiological studies include British Smoke (BS) and Coefficient of Haze (CoH) and involve optical measurements of particles collected on filters. They can provide a continuous record of concentrations averaged over much shorter intervals (several hours) but have their own specific limitations.

The Appendix presents a brief discussion of some of the more relevant features of the particulate pollution indices most widely used in past epidemiological studies. It demonstrates that BS, when expressed in micrograms per cubic meter, is based on site-specific calibrations. What it actually measures is the blackness of sampled particles. Furthermore, because of its design, only particles with aerodynamic diameter of \(<4.5\ \mu\text{m}\) were sampled. TSP, on the other hand, has a wind speed- and direction-dependent upper cut size of ca. 25 to 50 \(\mu\text{m}\) and can be affected by sampling artifacts such as \(\text{SO}_2\) collection, and loss of volatile particulate mass. Thus, particulate matter indices such as BS and TSP are neither directly comparable nor convertible to each other or to other indices that have different sampling characteristics or analytical procedures.

**Response Indices**

There are a limited number of indices of health-related responses that can be measured among populations under study. There are objective data that can be gathered from routine data files, such as daily mortality, hospital admissions, days lost from work or school. There are also data that can be collected directly from all, or suitably selected subsets, of the population of interest. These include responses to specific questions and measures of functional status or capacity. For each response, care must be taken to account for its cause-specific character and temporal lags between exposure and response.

Some of the indices, such as daily mortality, are useful only for evaluating the presence of acute respiratory disease responses to short-term periods of elevated exposure. Increases in daily mortality were associated with pollution episodes occurring more than 20 years ago, but the excesses were largely confined to subpopulations already having advanced chronic lung disease. Others, such as the incidence or prevalence of chronic diseases, are generally useful in relation to cumulative or long-term average exposure levels. Some functional
measures, such as forced vital capacity (FVC) and forced expiratory volume in 1 sec (FEV\textsubscript{1,0}) may be influenced by both chronic lung damage and by transient peak exposures to pollutants. Thus, their proper interpretation may require knowledge of both recent peak exposures and longer term average exposures, and the time-course of transient changes in function. The usual absence of such information on recent exposures and the duration of transient changes may constitute one of the inherent weaknesses of cross-sectional studies of air pollution health effects.

Few of the widely used indices of air pollution health effects provide any direct or sensitive measures of the early events in the pathogenesis of chronic lung disease. Abnormal baseline values of forced expiratory flows are detectable only with relatively advanced degrees of structural damage in the lungs. Transient decrements in function during and following pollution episodes may be associated with nonmeasurable decrements in baseline function that contribute to a measurable baseline shift only after repeated episodes of exposure, but this possibility remains speculative at this time.

**Neglected Variables**

In studying responses to exposures among populations, it is usually difficult, and sometimes impossible, to collect all of the relevant data on the factors that influence each individual’s pollutant dose or responses. Some of these factors are primarily related to the likelihood or severity of responses, such as genetic predisposition in terms of biological responsiveness to a given dose, variations in airway and airspace sizes which affect the deposition of dose from a given exposure, and immunological status. Others, such as cigarette smoking, have a variety of influences. These include: (1) short-term physiological effects on blood flow and airway caliber that affect the dose received from a given air pollutant exposure; (2) the effects of cumulative toxicity on host defenses; and (3) the incremental exposure from the smoke itself on the cumulative dose of pollutants such as CO, \(\text{NO}_2\), and respirable particulates.

Since most epidemiologists are aware of the influence of factors modifying responsiveness to pollutant exposures, this discussion will focus on those environmental factors which primarily influence the pollutant dose, on the premise that their importance is less well known and appreciated. Some of the more important of these addressed here are: the influence of indoor pollutant sources on an individual’s overall pollutant exposure; the influence of the level of physical activity on pollutant uptake and effects; the influences of particle size distribution and chemical composition on pollutant uptake and effects for nonspecific pollutant classes such as particulate matter; and the influence of transient peak exposures on chronic disease endpoints.

**Indoor Exposures**

Pollutant exposures in pre-industrial societies were primarily related to the use of unvented or poorly vented indoor fires for cooking and space heating. With the shift to gas for cooking and to reasonably well vented central heating furnaces, indoor air has generally been cleaner than outdoor air, and air pollutant health effects were usually associated with pollutants released to, or formed in, the outdoor air.

Since about 1950, air pollution control programs and voluntary shifts in fuel use patterns in the U.S. have led to substantial reductions in ambient pollutant burdens, especially for fly ash and \(\text{SO}_2\). However, since 1973, the increases in energy costs have led to substantial changes in fuel use patterns. As a result, there have been increases in pollutant levels in indoor air, especially in places where air exchange rates have been reduced, and when the use of unvented or poorly ventilated combusters, such as wood stoves and kerosene heaters, has increased.

A number of indoor pollutants have been reported to be associated with adverse health effects, and the potential for such effects should be considered in designing protocols for studies of air pollution epidemiology. These include: passive cigarette smoke exposure related increases in the incidence of acute lung disease in children (1–3) and cancer in spouses (4–6) and reductions in the lung size and/or rate of growth in children (7); \(\text{NO}_2\) exposure, as indicated by the use of gas stoves for cooking, and increases in acute respiratory disease rates in children, (3,8,9); radon and progeny-related lung cancer (10); and formaldehyde-related cases of allergic sensitization and irritation (11). In addition, exposures to various volatile hydrocarbons used as solvents or aerosol propellants have increased, and caused concern in terms of their potential toxicity and carcinogenicity.

Since most people spend most of their time indoors, and indoor concentrations of pollutants such as particulate matter and \(\text{NO}_2\) are often higher than those outdoors, indoor exposures can dominate the total exposure (12). In such cases, pollutant concentrations at central monitoring sites can be very poor surrogates for exposures (13,14).

**Influence of Activity**

The concentrations of pollutants in the air surrounding the head can be measured with personal samplers or modeled from data collected by fixed indoor and/or outdoor samplers. Dose depends on exposure concentration, but also on respiratory rates and volumetric flows. Increasing levels of physical activity can lead to substantial increases in dose to epithelial tissues in lung airways. A shift to oral breathing by-passes the more effective filtration capacity of the nasal passages. Higher flow rates lead to increased inertial deposition on airway bifurcations and turbulent mixing. Larger tidal volumes lead to greater penetration of tidal air into peripheral
Aerosol Composition and Size Distribution

Ambient particulate matter includes primary submicrometer particles such as carbon and lead oxides from motor vehicle exhaust, primary coarse particles such as wind blown soil and fly ash, secondary submicrometer particles such as H\textsubscript{2}SO\textsubscript{4} and its ammonium salts and various oxidized organic compounds, and coarse mode particles with primary particle cores coated with nitrates from surface reactions with HNO\textsubscript{3} vapor. The particle size distribution of the inhaled particles, together with respiratory rates and flows and the airway size of the exposed individuals, determines deposition efficiency in the airways. Chemical composition determines dissolution rates and/or chemical reactivity with airway fluids and cells.

For H\textsubscript{2}SO\textsubscript{4}, Amdur et al. (21) found an increasing effect on flow resistance in guinea pigs with decreasing droplet size. For sulfate salts, the effect on flow resistance for a constant particle size varied with cation, in the order: H\textsubscript{2}SO\textsubscript{4} > Fe\textsubscript{3}(SO\textsubscript{4})\textsubscript{2} > ZnSO\textsubscript{4} > (NH\textsubscript{4})\textsubscript{2}SO\textsubscript{4} > NH\textsubscript{4}HSO\textsubscript{4} > CuSO\textsubscript{4} > FeSO\textsubscript{4} > Na\textsubscript{2}SO\textsubscript{4} > MnSO\textsubscript{4} (22). In humans, Utell et al. (23) found that airway conductance was directly related to aerosol acidity. Similar observations were made for the effects of acidic sulfates on mucociliary clearance in rabbits by Schlesinger et al. (24). If aerosol acidity is an important factor in particulate pollution health effects, then sulfate ion concentration is a poor surrogate index since the ambient H\textsuperscript{+}/SO\textsubscript{4}\textsuperscript{2−} ratio varies widely over the range 0 to 2.

Influence of Transient Peak Exposures on Chronic Disease Endpoints

Chronic exposures to inhaled cigarette smoke can lead to reduced rates of lung growth in children (7) and increased rates of loss of function in adults (25). This model is being used by the Harvard six-cities group to see if ambient particulate matter has the same effect. One potential confounding factor is the transient influence of pollution episodes on the same variables. If an annual re-examination of a population for lung function coincides with a pollution episode, the relative contributions to the overall change in function of the long-term baseline change in function, and the episode-related transient change in function would be unknown.

Some Air Pollution Exposure of Current Concern Being Addressed by Recent Focused Studies

In this section, we describe several recent studies which have broken new ground and generated health effects data of direct relevance to the establishment of NAAQSs. While each is very different in design and execution, they are similar in that they have asked some new and different questions, selected available health effects endpoints directly relevant to the questions asked, and used available air monitoring networks effectively to characterize the relevant exposures of the populations under study.

Two of the studies focused on acute responses to short-term peak exposures, one by direct measurements of functional responses, the other by use of available data on hospital admissions. The third study focused on the association between chronic disease endpoints, as determined from questionnaire responses, and long-term chronic exposures.

Acute Effects of Ozone on Respiratory Function

Our recent studies of the effects of exposures to summer haze episodes provides an example of a protocol focused on a critical issue in a population with a minimum of confounding factors. It is well known that hazy air masses containing elevated ambient concentrations of O\textsubscript{3} and/or acidic secondary aerosol develop and persist over large areas of the eastern U.S. each summer.

The issue was whether periodic exposures to these hazes were having any effect on human health or function. The highest exposures generally occur in the midwestern and northeastern states, with significant episodes of 3–5 days duration generally occurring about four to six times each summer. The O\textsubscript{3} concentrations in such episodes usually exceed the National Ambient Air Quality Standard (NAAQS) of 1-hr maximum above 120 parts per billion (ppb), and may reach 200 ppb. Acid aerosol concentrations, as H\textsubscript{2}SO\textsubscript{4} equivalent for 6-hr averages of 15 to 20 μg/m\textsuperscript{3} have been observed.

Our approach was to select a population having the following characteristics: (1) located in an area expected to be subject to frequent passages of hazy air with high O\textsubscript{3} and H\textsubscript{2}SO\textsubscript{4} concentrations; (2) located in a study area with a minimum of locally generated air pollution which could affect the health endpoints to be measured; (3) nonsmokers, since cigarette smoking affects the functions and symptoms of interest; (4) out-of-doors activities, since O\textsubscript{3} and H\textsubscript{2}SO\textsubscript{4} concentrations can be substantially lower indoors than outdoors, and the indoor exposures

| Group | No. of children | FVC, mL/ppb | FEV\textsubscript{1}, mL/ppb |
|-------|----------------|-------------|-----------------------------|
| Girls | 34             | −1.27 ± 2.07† | −1.94 ± 2.27† |
| Boys  | 24             | −0.76 ± 1.85* | −0.41 ± 2.23 |
| Total | 58             | −1.06 ± 2.00‡ | −0.78 ± 2.28‡ |

* p < 0.05 (t-test, one-tailed).
† p < 0.01.
‡ p < 0.001.
would not be known; (5) high level of physical activity, since measurable responses to exposures to pollutants such as O₃ and SO₂ are more likely to occur in exercising individuals (15–20); (6) accessibility for daily measurements of respiratory function, so that changes in function could be related to changes in pollution exposure.

For our first study of this kind, in the summer of 1980, we were fortunate to locate, and secure the cooperation of, a population having all of the desired attributes (26). It consisted of a group of children attending a YMCA-sponsored summer day camp program in Indiana, PA. The study was made possible by the cooperation and participation of Dr. Frank Speizer and some of his associates, who were carrying out an investigation in the Chestnut Ridge area (27), for which Indiana was one of the “clean” control communities.

The period studied (June 30–July 12, 1980) turned out to be highly atypical and the only “normal” summer haze episode occurred late in August, long after the camp program had ended. The summer was relatively cool, total suspended particulate and acidic aerosol concentrations were very low, and the highest peak 1-hr O₃ concentration occurring in a study day was 110 ppb. Thus, we were somewhat surprised to find O₃-related decrements in daily average FVC and FEV₁₀ (26). These results are summarized in Table 1 and Figure 1.

A re-analysis of the Indiana peak flow data by Lebowitz (28) showed that averages for nonrainy days with O₃ < 100 ppb were significantly greater than for days with O₃ ≥ 100 ppb. Further analysis by Hazucha (29) indicated one outlier, the day with the lowest O₃ concentration; when it was removed, the regression of peak flow on O₃ was significant.

The observation of O₃-related decrements in function stimulated us and others to do additional studies of the effects of O₃ on the respiratory mechanical function of children in the summers of 1982 and 1983.

In the summer of 1982, we studied a group of children at a summer day camp program in Mendham, NJ. The children were not as physically active in this camp as were the children in Indiana, PA, and we did not observe an O₃-dependent change in FVC. Also, as shown in Table 2, the change in FEV₁₀ with O₃ in girls was smaller. However, there was a very marked O₃-dependent change in peak expiratory flow rate (PEFR). In both studies, the O₃-related decrements were greater in girls than boys.

In the Mendham, NJ, study, the highest peak 1-hr O₃ concentration on a study day was 143 ppb. This was the first of four successive days with peak 1-hr O₃ concentrations above the NAAQS (i.e., 143, 185, 165, 134 ppb). We therefore also examined whether this sustained period of high O₃ exposure had any persistent effect on the measured functions. For PEFR, there apparently was a baseline shift lasting for about one week. Figure 2 shows the average residual deviation for each child's PEFR-0₁₀ regression versus calendar day. The high values of deviation during the week following the period of high O₃ exposure indicate a persistently re-

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**Table 2. Summary of mean slopes for function changes vs. peak ozone concentration for children in Mendham, NJ.**

| Group  | No. of children | FVC, mL/ppb | FEV₁₀, mL/ppb | PEFR, m/sec/ppb | MMEF, m/sec/ppb |
|--------|-----------------|-------------|---------------|----------------|-----------------|
| Girls  | 22              | -0.29 ± 1.15| -0.42 ± 1.34*| -3.95 ± 4.33† | -0.68 ± 2.55    |
| Boys   | 17              | +0.06 ± 1.69| -0.11 ± 1.36  | -1.74 ± 5.86   | -0.38 ± 3.54    |
| Total  | 39              | -0.12 ± 1.40| -0.28 ± 1.34  | -2.99 ± 5.10†  | -0.55 ± 2.98    |

* p < 0.10 (t-test, one-tailed).
† p < 0.0005 (t-test, one-tailed).
duced level of PEFR. In comparison, the deviations during the following three weeks of the study appear to be randomly distributed around an average level indicating higher PEFRs. As in the Indiana, PA, study, high concentrations of acidic aerosol were not observed, suggesting that the response was primarily attributable to O₃.

In a 1982 study in Tucson, AZ, Lebowitz et al. (30) found O₃-related decrements in peak flow rates in children for O₃ levels at and below the NAAQS (Table 3). In 1983, Avol et al. (31) at Rancho Los Amigos Hospital studied exercising children in a mobile laboratory in

![Graph showing peak 1-hr ozone concentration vs. day of study in Mendham, NJ; average of the percent deviation of each child's peak expiratory flow rate (PEFR) from PEFR-O₃ regression for that child vs. day of study.]

which they were exposed to ambient air. They found O₃-related effects on respiratory mechanics, with greater responses in girls than boys. In a chamber exposure at the EPA Clinical Studies Lab in 1983, McDonnell (32) found that 2-hr exposures with exercise at 120 ppb produces small but statistically significant decrements in FEV₁₀ in children.

Our studies and those of Lebowitz et al. (30) show that children exposed to ambient O₃ during normal activities do respond with reductions in respiratory mechanical function. The studies of McDonnell (32) produced comparable responses with exposure to pure O₃, reinforcing our hypothesis that the response in the natural settings is primarily associated with O₃. However, some important issues raised by the NYU studies remain unresolved. One is whether other pollutants, if present at higher concentrations, would modify the O₃ response. Another is the magnitude and duration of baseline shifts in function resulting from prolonged high levels of exposure during intense pollution episodes.

Acute Effects of Ozone and Sulfur Dioxide on Hospital Admissions

Bates and Sizto (33) have recently shown that very useful insights into air pollution health effects can be obtained from available large scale data sets collected for other purposes. They correlated four years of routinely collected hourly pollutant indices from 15 sampling stations in southern Ontario with hospital admissions in all of the 79 acute care hospitals serving the same region. They found highly significant (p < 0.001) associations between summer hospital admissions for respiratory disease and SO₂, O₃, and temperature, with 24- and 48-hr lags for the environmental variables (Table 4). In the winter, only temperature affected admissions. Nonrespiratory hospital admissions were not associated with the environmental variables. Also, there were no significant associations between respiratory admission and levels of NO₂ and CoH.

It was not possible, from these data, to separate out the influences of SO₂ and O₃. With data from additional

Table 3. Average PEFR in children in relation to daily outdoor O₃ and TSP in Tucson, AZ.*

| PEFR, mL/sec/ppb | TSP | TSP | TSP |
|-----------------|-----|-----|-----|
|                 |     | < 56 μg/m³ | 56–76 μg/m³ | > 77 μg/m³ | All |
| O₃ (ppb)        |     |     |     |     |
| < 38            | +0.108 | +0.239 | +0.156 | 0.069 |
| 38–51           | +0.042 | -0.162 | -0.061 | 0.024 |
| 52–79           | +0.242 | -0.021 | -0.474 | -0.115 |
| 80–120          | -0.088 | -0.196 | -0.804 | -0.310* |
| All             | 0.155 | -0.027 | -0.227 |       |

* From Lebowitz et al. (30).

* Adjusted for other outdoor variables.

* Reduced sample size due to lack of TSP data for all days.

*ANOVA, p < 0.0001, Δ = -12%.

*ANOVA, p < 0.0001, Δ = -18%.

*ANOVA, p < 0.0001, Δ = -28%.
years, or comparable data from other regions having different mixtures and concentration levels of \( \text{O}_3 \) and \( \text{SO}_2 \), it may be possible to extend the utility of such analyses. Prospectively, it should be possible to utilize hospital admissions data to address additional pollutant associations. The pollutant monitoring network could be expanded to give more spatial discrimination and to include continuous measurements of pertinent aerosol characteristics, such as the concentrations of acid aerosol, sulfate, nitrate and organic and elemental carbon in coarse and fine mode particles. Also, closer attention could be given to appropriate adjustments for some of the inherent limitations of hospital admissions data, such as day-of-week and basis for notation of clinical condition justifying the admission.

Unfortunately, the densely populated regions where hospital admission data are routinely collected according to well-defined and uniform criteria are largely in other countries (Canada, U.K., Scandinavia). In regions where hospital admission data comparable to those of southern Ontario are being collected, they should be similarly analyzed. In the U.S., where such data are not now being collected, efforts should be made to establish appropriate data collection systems. Such data may provide a basis for testing hypotheses concerning acute respiratory responses to pollutant exposures and meteorological variables. With a sufficiently large data set, it may be possible to identify the influences of each pollutant separately, their joint actions, and the temporal aspects of pollutant response.

### Chronic Effects of Sulfur Dioxide on Respiratory Symptoms

Schenker et al. (27) studied the influence of coal combustion effluents on a downwind rural population in the Chestnut Ridge area of western Pennsylvania. Questionnaires were administered to 5557 adult women, and they were assigned exposures on the basis of their proximity to the nearest three of the seventeen air monitoring sites in the region. Over the 4-yr study, the 1420 women in the high exposure area had 24 hr and annual average \( \text{SO}_2 \) exposures that were either at or above the current NAAQS values. For 3222 women in the medium exposure group, the \( \text{SO}_2 \) exposures were below the NAAQS. The 24-hr particulate concentrations were all below the NAAQS and were influenced by nonpower plant sources. The highest annual average TSP was 90 \( \mu \text{g/m}^3 \). The concentrations of \( \text{NO}_2 \) were highly correlated with those of \( \text{SO}_2 \).

As a risk factor, \( \text{SO}_2 \) was associated with "wheeze most days or nights" in nonsmokers, with the relative risks of residents of low, median and high \( \text{SO}_2 \) areas being 1:1.26:1.58, respectively (\( p = 0.02 \)). As shown in Table 5, the relative risks for those living in the same areas for at least five years were 1:1.40:1.95, respectively (\( p < 0.01 \)). For grade 3 dyspnea among long-term resident nonsmokers, the relative risk for elevated \( \text{SO}_2 \) was 1.23, with a confidence limit of 0.98 to 1.54 (\( p = 0.11 \)).

Thus, \( \text{SO}_2 \) concentrations at and below the NAAQS levels...
Table 5. Absolute and relative risk of wheeze most days and nights in nonsmoking residents > 5 years in relation to mean (range) of SO$_2$ concentrations in Chestnut Ridge study areas.*

| Area | SO$_2$, µg/m$^3$$^b$ | Risk |
|------|----------------------|------|
| Low  | 219 (208–230)        | 0.051 1.00 |
| Medium | 274 (234–325)    | 0.071 1.40 |
| High | 423 (347–496)       | 0.100 1.95 |

* From Schenker et al. (27).
$^b$ Concentration means are for running averages, 1975–1978.
$^c$ Absolute risk expressed as a probability. Risks based on age 36–54 yr, and medium SES.

appear to be associated with increased wheeze in nonsmokers, with greater risks associated with long-term (> 5 yr) exposure. This represents the first association of a chronic health effect with SO$_2$ at levels near the current NAAQS where the influence of particulates did not appear to be a major confounding factor.

Further prospective studies in subgroups of this population, emphasizing sensitive subjects with asthma and wheezing are planned, and should be able to clarify and extend our understanding of the health effects of chronic SO$_2$ exposure.

Research Needs

Improved Indices of PM and Specific PM Components

The incorporation of upper limit particle size specifications in the newly proposed ambient particulate matter standard represents a small first step toward providing an exposure parameter for particles with some direct tie to potential health effects. As well characterized and calibrated PM$_{10}$ samplers become available, they should be incorporated into all future epidemiological studies of particulates. However, epidemiologists should not limit themselves to PM$_{10}$. They should consider the need to determine the specific chemical compounds or classes within the PM$_{10}$ and other size fractions in relation to the health endpoints under study. For example, the concentrations of H$^+$, NO$_3^-$, SO$_4^{2-}$ and selected organic compounds may be important in specific studies.

Identification of Relevant Exposures

Too little attention has been paid in the past to the selection of appropriate sample averaging times. For mechanical function responses to irritants, the peak concentrations appear to be much more important than the long-term average concentrations. When peak exposures are of interest, the practical monitoring problems are often most pronounced, since peak exposures vary widely over both time and location. In order to improve our capability to measure relevant peak exposures in natural settings, we need to have lightweight, continuous recording personal monitors with sufficient sensitivity and specificity for the pollutants of interest. A technical basis exists for some of the gaseous air pollutants, but their costs have, up to this time, generally been prohibitive in terms of widespread use. However, with the rapid progress currently being made in microsensor technology and microprocessors, it should be possible to develop inexpensive personal monitors within the next decade (34). Research and development work in this area should have high priority.

Relevant exposures in epidemiological studies include exposures to air pollutants other than those which are the primary focus of the study. For example, a study of responses to O$_3$ exposure must consider the possible influences of exposure to NO$_2$, SO$_2$, H$_2$SO$_4$, and sidestream cigarette smoke, since these other pollutants can readily affect the available health endpoints. The problem is especially severe for populations which spend most of their time indoors, since there are very large variations in the penetration and persistence of outdoor O$_3$, and highly variable sources of NO$_2$ and cigarette smoke.

In most cases, it is much better to select the population to be studied on the basis of their having a minimum of confounding pollutant exposures rather than in trying to measure and correct for such exposures.

Improved Indices of Effects

For most studies, investigations of responses in specific individuals are limited to noninvasive physiological measurements and questionnaire responses. The sensitivity of the physiological endpoints can be improved, sometimes markedly, by the administration of additional agents or stresses. These include exercise challenge (15–20), cold air challenge (35), and administration of a bronchodilator (3) or bronchoconstrictor (23) drug. Such interventions require informed consent and, for the drugs, the presence of a licensed health professional at the time of the test. Also, it may be much more difficult to recruit participants for the study. Furthermore, the significance of the enhanced responses, if any, may be difficult to determine in relation to effects produced by natural exposures. On the other hand, the added information may be extremely valuable in defining mechanisms for response, and the selection of endpoints for further studies of larger populations in natural settings.

In some cases, improved indices of effects can be obtained without interventions. Standard spirometric measurements can yield additional parameters beyond the conventional indices of FVC and FEV$_{1.0}$. For example, our second study of children’s responses to ambient ozone examined PEFR as well as FVC and FEV$_{1.0}$ and found that it provided a more sensitive indication
that O₃ affected airway mechanics. Other kinds of measurements can also be performed, such as ear vein oximetry, used by Linn et al. (36) for detecting responses to O₃ inhalation by COPD patients.

**Improved Acquisition of Response Data**

For each of the kinds of health effects endpoints available to the air pollution epidemiologist, there are some improvements and refinements in data collection which can improve the precision of measurement and therefore the power of the analysis to detect subtle effects.

The standardized respiratory health questionnaire of The American Thoracic Society (ATS) represents a significant advance over earlier versions, and helps produce relatively unambiguous data in a uniform format (37). However, it may not be sufficient for specialized studies. Additional questions may be needed for studies involving children and other potentially sensitive sub-populations. Also, where the effects of specialized exposure environments are being studied, such as indoor residential, commercial and transportation microenvironmments, many more questions about the characteristics of the microenvironment and the individual's activity patterns and lifestyles need to be asked.

The deficiencies in the recording of cause of death are well known to all epidemiologists with experience in mortality studies. However, practical remedies for this poor state of affairs are not obvious. It is also well known that the reporting of morbidity data is nonuniform. There are exceptions, such as the hospital admission data used by Bates and Sizto (33) in southern Ontario, which were available because of reporting requirements set up for the benefit to financial analyses in a system of socialized medicine. The attempts in the U.S. toward hospital care cost containment may provide an opportunity to establish a more uniform basis of reporting of hospital admissions in this country.

Respiratory function data can also be made more precise, primarily in terms of obtaining optimal efforts from the subjects undergoing forced expiratory maneuvers. In the past, the performance of effort-dependent maneuvers were difficult to evaluate from visual examination of spiromgrams or simple flow indicators. The recent development of microprocessor systems for spirometry provides an opportunity for direct, real-time comparisons of pulmonary performance with previously collected data from the same individual, or with population-based norms. Disparities can be resolved or confirmed by collecting additional data on the same occasion.

**Identification of Exposed Populations**

The ability of studies in natural populations to detect health effects depends, in large measure, on identifying an accessible population with a reasonably high exposure to the pollutant(s) of interest and minimal exposure to other pollutants or cofactors which affect the available response endpoints. In this sense, the success of the Clean Air act in reducing ambient air pollution has made it more difficult to design studies capable of detecting effects.

One approach to characterizing health effects from air pollutant exposure is to conduct studies outside the U.S., where exposures are much greater. For example, exposures to "old-fashioned" coal smoke are particularly high in Beijing, China, in the winter months (38), and there is a minimum of pollution from other major source categories, such as motor vehicles. Exposures to photochemical smog are particularly high in Mexico City, where fuel use for space heating is minimal and there are 2.5 million automobile without emissions controls (39).

Populations within the U.S. with special exposures of interest include rural communities in Oregon (40) and other rural U.S. regions (41) where extensive use is made of wood for space heating, users of unvented kerosene space heaters which produce high indoor concentrations of NO₂ and SO₂, and residents of forested areas of the northeastern U.S. who have maximal periodic exposures to acidic aerosols in the summer.

**Identification of Susceptible Subgroups**

Individuals may be at special risk when exposed to air pollutions for several reasons. These include: (1) constitutional factors, such as variations in airway and air-space sizes, which can significantly affect the dose received from a given exposure (42); (2) genetic defects, such as severe homozygous α₁-antitrypsin deficiency, which leads to degeneration of peripheral lung structures (43); (3) reduced ventilatory capacity because of in utero exposures arising from maternal smoking and/or passive cigarette smoke exposure as a child (7); (4) occupational and/or hobby related exposures to airborne toxic chemicals; and (5) lifestyle related activities, such as jogging, which substantially increases lung uptake of ambient pollutants.

Some potential risk factors can be identified by screening tests. For example, average airway and air-space sizes and evidence for minimal airway obstruction can be measured in vivo inhalation tests using inert monodisperse aerosols as probes (44). Responsiveness to inhaled bronchoconstrictive drugs can be used to indicate susceptibility to the development of airway obstruction from cigarette smoking (45), and presumably from air pollutants having similar effects on the lungs. Utell et al. (23) have shown that transient responses in respiratory mechanics of asthmatics following inhalation exposures to H₂SO₄ are correlated with the subjects' responses to bronchoconstrictor challenge. Other host characteristics, e.g., atopy, immunological responsiveness, etc., should also be considered.

Further development and refinement of screening tests are needed to demonstrate their utility for screening populations of interest for prospective epidemiological studies.
Conclusions

Epidemiological research in the last two decades has had remarkably little impact on the health effects knowledge base for air pollutants available in the recently prepared series of EPA Criteria Documents and Staff Papers for CO, NO₂, SO₂, and particulate matter. The only study directly cited in the recommendations on the numerical values of the primary standards was that of Mazumdar et al. (46) for particulate matter and SO₂. It should be noted that this paper represented a re-analysis of data from London in the period 1958–1972 and not a study of the effect of more recent exposures.

A primary reason for the failure of many of the more recent epidemiological studies to have any impact on the standards setting process was their inadequate attention to the exposure side of the exposure-response relationship.

The studies briefly reviewed in this paper should have significant impact in the next round of NAAQS reviews because they were well designed to consider the quantitative aspects of both exposure and response. Other studies currently in progress, such as the six-cities study, have made serious efforts to characterize the relevant exposures, and appear to be on the threshold of providing a substantial body of critically needed data on the chronic health effects of long-term exposures to SO₂ and particulates.

This brief review of neglected variables and research needs was designed to stimulate more well focussed population studies of the health effects of air pollutants. We now have the understanding to frame testable hypotheses and access to the technology to adequately make reliable quantitative measurements of both relevant exposures and responses. Air pollution epidemiology may now be ready to make its appropriate contributions to our understanding of the human health consequences of exposures to ambient pollutants.

Appendix

Characteristics of Indices of Nonspecific Particulate Matter Concentration

British Smoke

The British Smoke Sampler, which is shown schematically in Figure 3, is of great historic interest with regard to documented adverse health effects of ambient airborne particles. A major fraction of the quantitative human epidemiology demonstrating adverse effects used BS as the index of particulate pollution exposure. Thus, it is important to understand what it was that was actually measured in these studies, and the relation between British Smoke and other indices of particulate mass concentrations used in other places and times.

The most important distinctions to be noted are: (1) the particles collected on the filters of BS samplers were of relatively small aerodynamic size (Fig. 4); (2) the amount of particulate matter collected on the filter was assessed in terms of light reflectance from the surface of the filter and not directly in the reported units of (μg/m³); (3) the reflectance of particles on a filter depends upon factors other than mass density per unit of surface area and varies with particle size, shape and color, and therefore with location, season, and changing fuel usage and combustion conditions. Such differences are illustrated in Figure 5.

![Figure 3. British smoke shade sampler.](image)

![Figure 4. Penetration of aerosol through the inlet of the British Smoke Shade Sampler and through the complete system.](image)
While there is no intentional selection of particle size range measured, the physical configuration of the sampler and the ambient air velocity combine to impose an effective upper size limit on the particles that are sampled. Unfortunately, the upper size-cut is dependent on wind speed and direction, which vary with time and sampling location. It also depends on the inlet size, which can vary sufficiently from instrument to instrument within the dimensional specification to affect the cut-size. The effect of wind speed on the upper size cut of a Hi-Vol is illustrated in Figure 7. These data were obtained in wind tunnel tests in which the sampler was rotated at one revolution per minute to eliminate the additional variable of wind direction. Variations in the size cut can have an important effect on TSP when wind speeds are high and there are large particles suspended in the ambient air, since the largest particles sampled tend to dominate the sampled mass under those conditions.

Another problem with Hi-Vol-determined TSPs can result from the collection of sampled vapors which increase the incremental mass. The major problem of this type is the collection of sulfur dioxide (SO2) on conventional glass fiber filters. The bulk of routine samples were compromised by this "sulfate artifact" collection for many years before the problem was recognized (47-51). Nitric acid vapor can also be collected on sampling filters (52) while nitrates and organics collected on filters can be lost before analysis because of volatilization (53-55).

Size-Selective Sampling for Health Hazard Evaluations

If sampling is conducted for evaluating the extent of actual or potential inhalation hazards, then the sampling should be restricted to those particles which can contribute to the hazard. The first explicit application of

![Diagram of the standard sampler for ambient particulate matter in the U.S.](image)

**FIGURE 5.** Calibration curves made at various times for British Smoke Shade Sampler using Eel reflectometer and Whatman No. 1 1-in. diameter filters.

**FIGURE 6.** Schematic representation of TSP Hi-Vol.

**High Volume Sampler**

The standard sampler for ambient particulate matter in the U.S. has been the high volume sampler (Hi-Vol). As shown in Figure 6, it consists of a high speed, two-stage turbine blower coupled to a 8 × 10-in. filter holder and is mounted within a free-standing rectangular shelter. The filter used generally been a glass fiber mat whose collection efficiency for all particle sizes is close to 100%. The filters are weighed before and after the sampling interval, and the incremental mass divided by the sampled air volume is called the total suspended particulate (TSP) matter concentration.
this approach was the definition of "respirable" dust in relation to the evaluation of the risks of pneumoconiosis resulting from the inhalation of crystalline silica and coal mine dust. Both the British Medical Research Council (BMRC) and the American Conference of Governmental Industrial Hygienists (ACGIH) defined "respirable" dust as that fraction penetrating through the conductive airways of the head and tracheobronchial tree and available for deposition in the nonciliated alveolar zone airspaces where the dusts can cause lung fibrosis (56).

While the size range specified for "respirable" dust may be suitable for particles which cause pneumoconioses or emphysema, they are clearly inappropriate for particles which produce diseases following their deposition on the surfaces of the conductive airways. Thus, for wood and leather dust which can cause nasal cancers in exposed workers, the particles which deposit in the nasal airways should be sampled. Similarly, for particles which contribute to the pathogenesis of chronic bronchitis and bronchial cancer, the particles which deposit in the tracheobronchial airways should be sampled.

Criteria for particle size limits suitable for deposition in the head and tracheobronchial regions have recently been established by the International Standards Organization (ISO) Committee TC 146, and these are summarized in Figure 8 (57). Head deposition is the difference between the inspirable and thoracic fractions, while tracheobronchial deposition is the difference between the thoracic and alveolar fractions.

The U.S. EPA has recently proposed a new primary ambient air quality standard using a concentration index known as $\text{PM}_{10}$. $\text{PM}_{10}$ is essentially the same as the ISO thoracic fraction, i.e., the particles which penetrate through the larynx and are available for deposition on the tracheobronchial and/or the alveolar epithelia. The pending U.S. EPA standard excludes the particles which deposit in the airways of the head on the basis that the diseases which have been associated with ambient air pollution (bronchitis, emphysema, asthma, and lung cancer) are all diseases of the chest. $\text{PM}_{10}$, with a 50% aerodynamic diameter at 10 $\mu$m, will therefore include larger particles than those collected by BS samplers,

Figure 7. Sampling effectiveness of Hi-Vol as a function of windspeed for sampler rotated in a wind tunnel at 1 rpm.
and exclude the larger particles collected by the Hi-Vol samplers.

Because of the difference in upper cut-sizes, the numerical mass concentration limits of the earlier primary ambient air quality standards cannot be translated directly into concentration units of PM$_{10}$ particles. Under stable atmospheric (inversion) conditions at locations where coarse particles are not being generated, the mass concentrations of BS, TSP, and PM$_{10}$ could be very similar. On the other hand, in locations where wind speeds are high and the particles are low in optical opacity, the mass concentrations could differ radically. On the basis of experience with colocated TSP and PM$_{10}$ samplers under a variety of representative current U.S. conditions, the U.S. EPA estimates that the PM$_{10}$/TSP ratio will average about 0.6:1. Under other conditions, especially those associated with wintertime urban and summertime photochemical smog episodes, the ratio could be different.

**Design and Performance of Size-Selective Sampler Inlets**

In preparing for possible revision of its ambient air particulate standard, the U.S. EPA initially considered an upper size cut centered on 15 μm aerodynamic diameter, which it called "inhalable" dust (58). It was considered a conservative cut size, based on a penetration fraction to the thorax of 10%. While the "inhalable" dust was subsequently discarded in favor of PM$_{10}$, a number of axisymmetric sampler inlets were designed and calibrated for the 50% cut at 15 μm. These included the size-selective inlet (SSI) for the Hi-Vol, inlets of intermediate flow rate samplers (4 ft$^3$/min), and inlets

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**Figure 8.** Recommendations of ISO for size-selective sampling according to aerosol fractions inspired and deposited within regions of the human respiratory tract.

**Figure 9.** McFarland-Ortiz PM$_{10}$ inlet for 4-cfm sampler (59).
for the EPA virtual impactor (dichotomous) sampler at 16.7 L/min. Similar size selective inlets are now commercially available for PM<sub>10</sub>. Some are designed as impactors, while others use turning vanes and function more like cyclone collectors. Figures 9 and 10 illustrate the design and performance of an impactor type inlet (59), while Figures 11 and 12 describe the corresponding features of a cyclone type of inlet (60).

The specifications which U.S. EPA promulgates for such inlets are likely to be performance specifications rather than design specifications. As noted earlier, the design specifications for the Hi-Vol sampler permitted significant variations in performance. With a performance specification, the instrument manufacturers have more design freedom, but must submit test data to demonstrate that their sampler inlets do perform the desired cut within the designated tolerance under the specified range of wind speeds.

The designs illustrated in Figures 9 and 11 appear to provide the independence of wind speed and cut characteristics desired by both the U.S. EPA and ISO.

Research described in this paper was supported by the U.S. Environmental Protection Agency under Grant No. R807723 and Contract No. 68-02-3764, and is part of a Center program supported by the National Institute of Environmental Health Sciences under Grant ES-00260. We thank Dr. Frank E. Speizer and Dr. Michael D. Lebowitz for their reviews and comments on the manuscript.
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FIGURE 12. Performance curves for Wedding's 4-cfm PM$_{10}$ inlet (60).
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