Environmental Health Perspectives
Vol. 12, pp. 149–170, 1975

Health Effects of Fossil Fuel Combustion Products: Report of a Workshop*

by C. L. Comar† and Norton Nelson‡

Judgmental positions are presented on research priorities in regard to the health effects from stationary sources of fossil fuel combustion products. Hopefully, they can provide guidance for efforts to ensure that national energy needs are met with minimum environmental and economic burdens on the public. The major areas include epidemiological studies, controlled biological studies, mutagenesis and carcinogenesis, trace elements, monitoring and analysis.

INTRODUCTION AND SUMMARY OF RESEARCH PRIORITIES**

A series of developments has brought the United States to a point where serious decisions have to be made as to energy sources and energy conservation. The elements involved have been diverse: escalating energy usage, intensely heightened apprehensions about the environmental and health costs, and uncertainties as to the extent of and access to fuel reserves. The concerns have been communicated in many studies, including a report to the President of the United States, by Dr. Dixy Lee Ray, Chairman of the Atomic Energy Commission (*1*), a Ford Foundation study (*2*), and National Academy of Sciences-National Research Council studies and reports.

Clearly, some very difficult decisions will need to be made over the next decade in regard to energy research priorities, energy strategies, the planning and design of facilities, and regulatory policies. One of the largest gaps in the understanding required for such decision making is due to lack of knowledge about the direct effects of the fossil fuel combustion products on human health and well-being, since much of our additional electricity and most of our other midterm needs for energy will come from combustion of coal and oil. Indeed, this is of such grave concern that it will be urgent that an appropriate and substantial part of the national budgetary commitment to Project Independence be devoted to the resolution of such health effects. Since many of the studies required to answer these questions have a long lead time, the planning to guide such investigation will, in many cases, need to be started immediately. For this effort a set of directions and priorities is required.

It was toward this end that the present exercise was undertaken. The Workshop on Health Effects of Fossil Fuel Combustion Products was sponsored by the Cornell Energy Project and the Electric Power Research Institute (EPRI) as the first of a series of specialized meetings to provide considered and authoritative guidance for the research needed on a national basis and by the utility industry to assure that energy needs are met with a minimum environmental cost.

Present technology assessment in the United States is recognized as having two important components: the scientific-technological base and public perception. The emphasis of this workshop was entirely on the scientific basis for decision making rel-

*Sponsored by the Cornell Energy Project and Electric Power Research Institute, Indian Wells, California, November 11–13, 1974.

†Scientific Editor and Workshop Coordinator, Environmental Assessment Department, Electric Power Research Institute, P. O. Box 10412, Palo Alto, Calif. 94303.

‡Institute of Environmental Medicine New York University Medical Center, New York, New York 10016.

**Norton Nelson (General Chairman) and C. L. Comar (Scientific Editor and Workshop Coordinator).

Table 1. High priority research studies.

Epidemiological Studies

- Determination and quantification of health effects resulting from exposure to low levels of pollutants and to changes of levels of exposure
- Determination of exposure/effects relationships in special risk groups
- Evaluation and surveillance of new, potentially harmful pollutants
- Development of further international comparisons and cooperation

Controlled Biological Studies

- Human studies
  - Tests of airway narrowing
  - Synergistic effects of gas–aerosol mixtures
  - Form in which sulfur oxides are most damaging
  - Observations and dose response for gas–gas interactions
- Animal and *in vitro* studies
  - Aerosol parameters likely to influence toxicity or irritancy
  - Effects in disease states
  - Chemical changes in the mucus and effects on mucociliary transport mechanisms
  - Effects on alveolar macrophage function
  - Effects on structural elements of the lung
- Pollutant interactions: effects, in humans and animals, of pollutant mixtures similar to those existing in air and quantitatively and qualitatively identified; role of temperature and humidity in modifying such effects

Mutagenesis and Carcinogenesis

- Chromosomal aberrations in populations occupationally exposed to high levels of potential mutagens
- Birth defects and other anomalies among populations exposed to high levels of oxidants (e.g., ozone)
- Mechanisms of interactions of potential mutagens and carcinogens with informational macromolecules
- Study of populations occupationally or otherwise exposed to point sources of known or suspected carcinogens

Trace Elements

- Characterization of trace element emissions from fossil fuel plants
- Determination of concentration, translocation, uptake, and conversions of elements such as lead, arsenic, selenium, and mercury in components of the biosphere
- Study of metabolism and toxicity, in human beings, of selected trace elements such as lead, arsenic, selenium, and nickel
- Evaluation of the role of trace elements in catalysis of atmospheric reactions of gaseous pollutants, especially SO_2 and NO_2

Monitoring and Analysis

- Characterization of trace element emissions (as above)
- Sampling and analytical methods for selenium, mercury, arsenic, and beryllium
- Better methods for NO_2; monitoring of peroxyacetyl nitrate (PAN)
- More definitive methods for particulates, and evaluation of emissions from fly ash dumps and coal piles
- Complete characterization of physical and chemical pathways and factors affecting the sulfur compounds that enter the atmosphere
- Characterization of acid-sulfate aerosols and personal monitoring for the sulfur oxides
- Improved air monitoring for sulfur oxides to permit trend monitoring, compliance, and more reliable retrospective and prospective assessment of health effects

ated to health effects. The intention was not, however, to carry through to ultimate decisions expressed in terms of standards or guidelines, since this is the responsibility of others and, in addition to a scientific and technical data base, requires considerations of a complex economic and sociological nature. Nevertheless, the need for public understanding and the needs of those who must make public policy were kept in mind.

The report is by design concise: it restricts itself primarily to brief judgmental positions on the state of knowledge relating air pollution to health. The key questions are: If our present information is inadequate yet important to the development of national policy, what needs to be done to sharpen the information, and how should the nation go about filling these gaps? There have been many good recent reviews on the relationship of air pollution to health. It was felt that rereviews at this time would be far less useful than an analysis of research needs, with suggestions on how these needs might be filled. It is hoped that the thoughtful advice of the workshop participants, as set forth on the following pages, can provide substantive guidance for national efforts to ensure that national energy needs are met in ways which do not pose unacceptable health or economic burdens on the public.

The report represents an attempt to define research directions aimed at filling energy needs safely. Ionizing radiation and nuclear power were

deliberately not examined, and coverage of automobile exhausts was not meant to be definitive. The report is especially aimed at the problems of the next decade, before major new types of nuclear, solar, or geothermal energy can become available. It is hoped that it will provide a helpful planning basis for those national groups on whom will fall the burden of developing the needed information. These groups include both industry and the research agencies of the federal government. However, there is also an important role to be played by local agencies, the scientific community generally, and research foundations. Moreover, it seems probable that the major inputs to the field discussed here will come from the academic community, where the largest resources in health research are to be found.

The various sections of the report represent the products of the working groups as identified in the respective footnote. Each section was examined in plenary sessions involving all members of the workshop leading to agreement with the general thrust of the report although not necessarily with every detail. A list of proposed studies developed in the workshop is given in Table 1. All are considered to be of very high priority; no attempt was made at priority ranking, either among or within the group areas. This list should be regarded only as an identification of the general area of research. The individual sections of the report should be consulted for further details.

EPIDEMIOLOGICAL STUDIES*

Introduction

Epidemiological studies are useful in identifying the factors involved in the development of disease and disability, and then are essential in quantifying the impact of such factors. Such studies become increasingly critical as the risk attributable to a factor becomes smaller and as the time needed for the factor to act becomes greater. The major episodes of air pollution (Meuse, Donora, London, New York City) clearly showed that pollution, when sufficiently severe, could cause illness and death. During the 1950's and 1960's, research was mainly directed toward answering the question: Does pollution at concentrations which are normally encountered in industrial cities cause adverse effects on people's health? During the later 1960's, perhaps stimulated by the preparation of the Air Quality Criteria Documents, interest became more focused on quantifying pollution in relation to the effects it may produce. Now, in the 1970's, with the recognition that fossil fuel supplies with low sulfur content are limited and that consequently it may be necessary to use cruder grades of fuel, quantification of the effects of varying levels of exposure becomes increasingly urgent. Thus while exposure–effects relationships are still the central interest, emphasis has now shifted to the effects of low levels of pollution and the effects of pollutant interactions.

In this section we first consider the measurement of exposure and its effects on man, then indicate some of the difficulties encountered in allowing for confounding variables, and go on to touch lightly on analytical methods which permit sound conclusions. Finally, we turn to promising areas of research and outline a number of studies that we believe should have high priority.

Exposure

Ideally, in quantifying a person's exposure one would like full information on present and past exposures to the relevant gases and to particulate matter carefully specified as to kind and size. Needless to say, even the most admirably designed and brilliantly executed surveys will not provide such full information, and the analysis of available observations must rest upon data which are far from ideal. The following attributes of exposure should be considered by anyone launching an epidemiological survey.

Particulate Matter and Gases

Particles should be characterized both physically and chemically. Particular attention should be given to their surface absorptive characteristics, hygroscopicity, and size distribution. Although emphasis should be on particles within the respiratory size range, large particles should not be ignored. Within the respiratory size range, a case can be made for differentiating between particles above and below 1 μm. Chemical characteristics of interest include pH, oxidation state, and reactive attributes. Particulates include trace metals and potential carcinogens; however, sulfuric acid and acid sulfates are the particle phase pollutants of greatest interest

*Ian Higgins (Chairman), Robert E. Carroll, C. L. Comar, Charles Florey, John R. Goldsmith, Lester B. Lave, David P. Rall, Frank E. Speizer.

at this time. Sulfur dioxide is, of course, the gas of major interest, but ozone and oxidants, carbon monoxide, and oxides of nitrogen are also of concern.

Existing Monitoring Networks

In the United States, selected pollutants have been monitored for a number of years. The National Air Sampling Network (NASN) has information on variations in particulate pollution and specific components of it at several stations in an increasingly large number of metropolitan areas and other places. The Continuous Air Monitoring Program (CAMP) has provided data on gaseous components for eight cities for over a dozen years. These monitoring systems were designed to evaluate air quality in the regions in which they were placed. They have been useful in combination with emission data for determining and predicting departure from acceptable standards.

As originally planned, the systems were not designed for measurement of exposure in epidemiological surveys. Many of the sites chosen for monitoring have little relevance to particular exposure of study populations. With careful selection of certain sites, however, some of the data have been useful for defining exposure in populations under investigation. In other studies, the degree to which these data reflect actual exposure or dose to the inhabitants is uncertain.

In the United Kingdom, the National Air Sampling Network, coordinated at Warren Spring Laboratories, has provided extensive information for many years on smoke and SO_2 concentrations. Relatively little study, however, has been carried out on other pollutants. Sites are classified as having been chosen for their relevance to industrial pollution sources or to general environmental exposure, and data which are relevant to population exposure have sometimes been correlated with health functions.

The pollutants being monitored may be measured and reported with averaging times from 5 min to one year. The choice of averaging time needs to be appropriate to the type of epidemiological study being conducted. Even with a fairly extensive network of stations in a city, the levels of pollution to which a person is exposed can only be imperfectly estimated. Sampling in or near subjects' homes, indoor and outdoor comparisons, and the use of personal monitors to assess current ambient exposures are desirable.

Biological estimation of exposure has certain advantages when feasible. Examples are the use of blood or expired air samples for carboxyhemoglobin as a measure of carbon monoxide exposure (*3*) and hair samples as an indicator of exposure to lead or mercury.

Effects

Several health indices are available: (1) mortality (all causes of death): causes which might be expected to be related to air pollution, such as respiratory diseases, cardiac diseases, and influenza; and, for comparison within the same population, causes of death which might not be expected to be related to pollution, such as strokes, diabetes, and cirrhosis; (2) morbidity (all causes): disease-specific (as for mortality) but including diseases which may be uncommon causes of death, such as arthritis and rheumatism; (3) symptoms: especially of respiratory symptoms, such as cough, sputum, wheezing, breathlessness, and chest illnesses, usually recorded by means of standardized questionnaires; (4) impairment of lung function, especially impairment measured by simple spirometry; (5) impairment of other functions or performance: work capacity, athletic, CNS (central nervous system) functions, or indirect evidence of impairment as implied by accidents or alterations in mental acuity; (6) eye irritation; (7) annoyance and psychological effects of reduced visibility; (8) accumulation of a potentially harmful pollutant within the body.

One evaluation of pollution abatement is provided through cost/benefit analysis, which is difficult but increasingly necessary. The technological possibility of reducing pollution and the cost of doing so are of great relevance to the rationale for epidemiological investigation. It is desirable, wherever possible, to include indices of effects of pollution on health that can be translated into cost/benefit ratios. Examples of such indices are lost working time, premature disability, sickness, absence, days in bed, and days in hospital.

Exposure-Effects Relationships

The health indices of effects of exposure to pollutants of concern, which were summarized above, are influenced by many factors other than pollution. These factors confound the interpretation of any associations which may be demonstrated between exposure and response. Apart from the demographic characteristics of age, sex, race, and socioeconomic status, the most important confounding variables are tobacco smoking and occupational exposures. Wherever possible, consideration should be given to

these variables in the design of any studies. Where such considerations have been inadequate or overlooked, due attention must be given to the likelihood of such factors having influenced the conclusions in the analysis.

Strategies already exist or can be developed for dealing with the multivariate systems required in epidemiological studies. Examples include path, component, and canonical analyses. These analyses require the combined efforts of mathematical statisticians, epidemiologists, and data systems experts. While such strategies may ultimately be based on multiple regression and correlation procedures, uncritical applications of multiple linear regression computer programs are not likely to provide convincing evidence of exposure/effects relationships. It is important to emphasize that relevant variables must be included, that variables must be in an appropriate form, that nonlinear relationships be explored, and that appropriate statistical criteria must be used.

Interactions

Although possible interactions should be considered in any statement of exposure–effects relationships, they perhaps deserve to be categorized separately as an area of great interest about which far too little is known. There are several types of interactions: (1) interaction of one pollutant or category of pollutants (particulates) with others to produce a more harmful exposure, e.g., particulates and SO_2, SO_2 and ozone, and particulates and NO_2; (2) interaction of pollutants with meteorologic or climatic factors such as temperature, humidity, and possibly barometric pressure to produce a more serious effect; (3) interaction of pollutants with other personal or environmental variables, such as cigarette smoking and occupational or socioeconomic factors; (4) interaction of pollutants with infection, particularly with influenza and other recurrent respiratory infections. Interactions at the physiological level are discussed in the section on biological studies.

Methods

Mortality

Daily deaths in relation to pollution levels and other factors have provided useful information on one type of exposure/effects relationships. The contribution of pollution at present levels to mortality is uncertain. In the New York City metropolitan area, Buechley and his colleagues (*4*) estimated pollution-caused mortality to be about 2 or 3% of total daily mortality, comparing pollution at the lowest and highest levels for the period 1962–1966. On the other hand, Schimmel and Greenburg (*5*) and Schimmel et al. (*6*), using the same data, estimated that pollution was immediately responsible for 14% of all deaths. This is a considerable discrepancy that needs to be resolved. Buechley has analyses from Philadelphia and Chicago which have not been published. The studies of Hexter and Goldsmith (*7*) for Los Angeles for 1962–1964 could be extended to include additional confounding variables and other urban areas.

More recent analyses of daily mortality in London, England, and in Tokyo and Osaka, Japan, would be useful. In London two additional points might be made: (1) it would be interesting to explore the trends in daily deaths and pollution between 1958 and 1974, and (2) daily morbidity could be used as well as mortality.

To date, with the exception of London, no analyses have been made of deaths by cause, stratified by age and sex. Such analyses are desirable. It seems clear that studies of daily mortality in relation to pollution levels should have some priority, as they may shed light on both the exposure/effects relationships and on the overall effect of change over time.

An extension of the effects of daily mortality in relation to daily pollution levels might be an analysis of the distribution of deaths throughout the year (annual cycle). If, as the daily mortality studies suggest, pollution causes immediate deaths and if, as in London and New York City, pollution is worse in the winter than in the summer, with the reduction in pollution which has been achieved in London and is being achieved in New York City there should be a reduction in the winter/summer differences in mortality commensurate with the reduction in pollution.

Trends in mortality in different cities (Standard Metropolitan Statistical Areas, SMSA) and other areas during the past 10–15 yr deserve more attention than they have yet received. In some areas pollution has declined, in others it has remained the same, and still in others it has risen. Age- and cause-specific mortality rates have not been compared in relation to these environmental changes.

In no city has reduction in pollution been more dramatic than in London. Yet there has been peculiarly little interest in relating changes in age-specific mortality to this decline. The statistics are for the most part readily available.

Morbidity

In Britain, records of morbidity of the whole working population of the country were introduced in 1948. Changes in morbidity should be related to changes in pollution between 1948 and the present. The main aims of such a study would be to relate incidence of bronchitis incapacity to levels of pollution around 100 $\mu g/m^3$ instead of around 300 $\mu g/m^3$, as was the situation at the time of the survey carried out by the Ministry of Health. In the United States, long-term morbidity trends are not available for any substantial segment of the working population. Data collected in the National Health Survey can, however, be categorized by SMSA and may be useful in making comparisons of morbidity rates at varying levels of exposure.

Surveys to Monitor Pollution and Health Effects

General Community: Surveys of the type recommended by Rall (*8*) should be made. Thus, representative samples of the community living in different areas should be compared. The areas should be chosen on the basis of levels and type of pollution and of expectation of change. Longitudinal observations should be made to measure change in lung function, respiratory symptoms, disease incidence, and mortality and to relate these to levels and changes in pollution.

Children must be included not only because cohorts of children will provide information on secular changes in pollution but also because the use of children eliminates the confounding effects of smoking and occupational exposures.

Vulnerable Groups: Douglas and Waller (*9*) showed that following a cohort of children from birth to age 15 provided valuable information on the effects on infants and children of air pollution in Britain. No such study has been attempted in this country. A nationwide cohort such as was used in Britain is probably neither practicable nor desirable. Instead, cohorts of newborn in different cities should be chosen and followed for comparisons of respiratory indices such as those used by Douglas and Waller. At the same time, appropriate air monitoring should be carried out. Such a study might show not only the effects of pollution on early development but also the impact of changes in pollution.

Lawther and Waller's studies (*10*) of chronic bronchitic patients were prototypes of investigations of patients with chronic lung and/or cardiac disease. More could and should be extracted from such surveillance than was possible in the 1950's and 1960's. Emerson (*11*) has shown the value of incorporating simple lung function studies into studies of this kind. The possibility of using this group of patients for much more precise measurements of exposure/effects relationships needs to be explored. Home measurement of pollution, personal monitoring, and consideration of multiple pollutants would add appreciably to the value of such studies. Cardiac patients or persons with asthma could similarly be monitored.

For many of the pollutants of interest, occupational exposures occur at higher levels than do exposures in the general community. Such occupational exposures are often quite well defined. Among other occupations to be given consideration are those internal to the power generation and distribution industry and those exposed to combustion products (firemen, metal workers, automobile and traffic workers).

The record-keeping system in industry now being required by the Occupational Safety and Health Administration (OSHA) should be explored both as a source of exposure/effects relationships and as an approach to one of the major confounding effects in other community studies. This is particularly true for conditions such as cancer which develop after a prolonged latent period.

European Studies

Studies at present being conducted in Europe are designed to identify the effects on health of exposure to individual pollutants, to establish exposure/effects relationships, and to determine the effect of reduction in air pollution. Two studies are international in scope, one under the auspices of the World Health Organization (WHO) (*12*) and the other under the Commission of the European Communities (CEC). A third study, in the United Kingdom, is investigating the effects of change in pollution (*13*). All the studies are concerned with children as indicator populations because of their freedom from the confounding exposures of cigarette smoking and occupational pollution. Approximately 1500–2000 children aged 6–10 are chosen in areas defined by high (>100 $\mu g/m^3$) or low (<50 $\mu g/m^3$) levels of smoke or SO_2. At present other pollutants are not being considered, as they are so rarely measured routinely. Physical measurements (height, weight, and peak expiratory flow rate) and a symptom questionnaire are completed. Both the WHO and CEC studies are cross-sectional, but their design permits conversion to longitudinal

studies if appropriate. The U.K. survey is longitudinal and is planned to last 4 yr. Countries involved in the WHO study are Poland, Czechoslovakia, Yugoslavia, Denmark, the Netherlands, Spain, and possibly Greece; those in the CEC study are Belgium, France, West German Federal Republic, Ireland, Italy, and the U.K. Uniform protocols prepared by a panel of experts are being used. Although these cooperative studies are in their infancy, European epidemiologists feel strongly that studies using common protocols will advance understanding much more rapidly than those in which, without such standardization, the data are not comparable.

The need for improving comparability in epidemiological studies of chronic respiratory disease in the U.S. has been recognized by the National Heart and Lung Institute and the American Thoracic Society. A committee of the American Thoracic Society on standardization of epidemiological procedures, with subcommittees on questionnaires, lung function procedures, and chest x-rays, has recently been established. Plans are being formulated with the National Heart and Lung Institute (NHLI) to assess the methods and procedures now in use and to develop ways of improving them.

A number of studies of children, with varying levels of monitoring of environmental exposure, some of them similar to the European studies, are being conducted in this country. For example, one group of investigators has embarked on a prospective study of children in several cities with varying levels of exposure, using a common protocol. In addition, other groups are engaged in studies of children, with varying levels of monitoring of environmental exposure. The desirability of comparability not only between these studies but also, wherever possible, with those being conducted in Europe is clear. We strongly urge that high priority be given to increasing cooperation and communication among the various international groups so that common protocols and measurement techniques can be developed to enhance the comparability of the investigations.

Many of the concepts underlying the Environmental Protection Agency's Community Health and Environmental Surveillance Studies (CHESS) (*14*) are similar to those specified above. Some of the earlier CHESS studies indicated all too clearly the problems involved in carrying out adequate epidemiological investigation. In fact, there are few centers with the experience and resources required to conduct such taxing studies in a satisfactory manner. In part, this is due to the lack of adequate financial support.

Support of Epidemiological Research

Epidemiological research, as is clear from the points already mentioned, is becoming ever more urgently needed for the planning and control of technological development. A major problem has been that such research has not been adequately supported either in level or in duration. Federal and industrial support, whether or not in academic centers, has tended to be short-term, volatile, and often inadequately planned—and hence incapable of useful interpretation. This difficulty is also faced by other types of research, but chronic disease epidemiology is particularly sensitive to the need for critical levels and duration of effort to avoid useless or, even worse, misleading results. In view of the critical need for institutional support strategies, the following suggestions are offered.

There should be encouragement, motivation, and support for the National Center of Health Statistics to become more sensitive to and more involved in epidemiological and epidemiologically directed research. This, in combination with other ongoing activities, would provide a much more useful data base than is now available. Examples of such opportunities in the U.S. can be seen in the reports on occupational mortality (*15*) and on occupational and environmental factors in disablement (*16*). An outstanding example of the use of these kinds of data is the British Registrar-General's Decennial Reports on social and occupational factors in mortality (*17*).

There are a few centers in the U.S. that have the competence and facilities for the long-term studies required for successful epidemiological research. Urgent epidemiological studies should be encouraged and initiated in selected centers by commitment of long-term personnel and operating support. This is being done in some of the Medical Research Council units in the U.K. but not significantly in the various U.S. national laboratories.

Long-term studies of a number of communities in the U.S. have of course been conducted for many years, e.g., at Framingham (*18*), Tecumseh (*19*), and Hagerstown (*20*), as have some cohort studies of occupational groups (rubber, steel, and mine workers) (*21*).

In some instances where there is no predefined population of special interest, it is possible to gain important data from cooperative community-sample studies involving cohorts based on a probability sample which has appropriate attributes and is available for periodic follow-up examination, data interpretation, and analysis. Examples include the

Ferris-Speizer project, the American Cancer Society longitudinal study (*22*), the WHO and CEC studies of children, and the Douglas-Waller cohort study (*9*). Adequate support for such studies should be maintained.

It is suggested that a task group be established to maintain support among epidemiologists and their funding sources to assure appropriate financial and institutional commitment. Such a group might include representation from professional bodies, e.g., the American Thoracic Society, the Society for Epidemiological Research, and the International Epidemiological Association.

Research Priorities

The areas of research considered to have the highest priority are presented in four categories.

1. *Determination and quantification of health effects resulting from exposure to low levels of pollutants and to changes of levels of exposure*: Of particular importance are the combined effects of SO_2 and particulates. Also important are effects of interactions and changes of different classes of pollutants in the atmosphere, such as the formation of sulfates or acid droplets.

High priority should be given to detailed study of existing data in areas where change is known to have occurred. In addition, studies of short- and long-term effects of anticipated change in air quality should be made.

2. *Determination of exposure–effects relationships in special risk groups*: Of particular interest are groups that may be unusually sensitive to pollutants, e.g., asthmatics, chronically disabled persons, persons with added burdens of exposure from other sources such as occupational or personal pollution (smoking), and infants and children.

3. *Evaluation and surveillance of new, potentially harmful pollutants*: Better communication among chemists, toxicologists, and epidemiologists to anticipate potentially toxic new substances or new processes can lead to earlier identification and control. This requires research collaboration among several disciplines and must involve governmental, academic, and industrial organizations. In addition, a further search must be made for more subtle effects of existing pollutants, e.g., performance in a physical and psychological sense.

4. *Development of further international comparisons and cooperation*: Pollution and health effects vary from country to country; however, studies in other countries can have great importance to the U.S. Utilization of data would be enhanced by improved comparability, and every effort should be made to standardize methods.

CONTROLLED BIOLOGICAL STUDIES*

Introduction

A full understanding of the role of environmental factors affecting health depends critically on the interplay of epidemiological, animal, and human laboratory studies. Epidemiological studies are important in uncovering possible associations which can then be tested under controlled laboratory conditions; they are also important in the evaluation of human risks suggested by laboratory experiments. As in other fields of biological research, animal studies are extremely important. They can often determine efficiently the sites of effects, mechanisms, and exposure/effects relationships, and they lend themselves more easily to chronic studies than does human research. However, because of species differences, human laboratory studies are still needed to establish the presence and importance of specific responses and to determine the influence of altered human states (e.g., disease) on these effects.

Human Studies

General

In the design of human studies, ethical considerations are imperative. Because it is desirable to limit their total number, human studies should be designed carefully on the basis of information obtained from appropriate animal and epidemiological studies. As an illustration, a large number of experiments can be performed in animals to determine the sulfur-containing compounds that are most potent in narrowing airways,

*Jay Nadel (Chairman, Human Studies), Robert Frank (Chairman, Animal and *in Vitro* Studies), David V. Bates (Chairman, Interaction of Agents), William Coate, John F. Finklea, Charles Florey, Bernard D. Goldstein, Elliot Goldstein, Steven M. Horvath, Sidney Marks, Byron Mechalas, David P. Rall, Frank E. Speizer.

impairing mucociliary clearance, or increasing susceptibility to infection. From the results of these experiments, a few critical studies in humans can be designed. Information on the acute effects of air pollutants on humans is woefully sparse, and more studies are urgently needed. Fortunately, information from animal and epidemiological studies has identified areas where human studies are likely to be profitable.

Features of Experimentation

Human exposures should generally be limited to "realistic" concentrations of pollutants which have occurred in some ambient atmospheres. Characteristics of the individuals studied (e.g., age, environmental exposure, place of residence, cigarette smoking and disease history) must be considered and described in detail. Generally, healthy subjects should be studied first. In order to discover whether responses are changed as a result of environment, acute effects of pollutant exposure should be studied in individuals exposed chronically to the pollutant either in the ambient atmosphere or at work and the responses should be compared with those of matched groups not chronically exposed. Subjects can also be studied early and late in the "smog season" to determine whether adaptation occurs. Present evidence suggests that some patients with lung disease may be most susceptible; studies are badly needed to establish this. Among groups which may provide useful information are young asthmatics, young symptomatic smokers, individuals with a history of frequent respiratory infections, and healthy subjects during and following respiratory viral infections (responses may be increased during viral infections, so the healthy subject serves as his own control). It must be emphasized that animals can provide much valuable information which can be useful in designing studies in potentially susceptible populations of humans. For example, healthy unanesthetized dogs can be utilized for studies at rest and during exercise. In these animals experimental asthma can be produced which is similar immunologically to the human disease. Results from such experiments will be useful in designing critical human studies.

Performance

Performance in humans can be defined as "physical" and "mental," and both kinds have been shown to be influenced to some extent by the presence of atmospheric pollutants. Physical performance requiring 50–100% aerobic capacity has been voluntarily terminated by individuals of all ages when certain levels of air pollutants have occurred in the free atmosphere. The factor or factors responsible have not been identified completely, and studies to eliminate the reasons for and the effects of various pollutant combinations in terms of physiological and biochemical alternations in the organism need to be performed. Examination of the possible interaction of ambient temperatures, vapor pressure, and pollutant levels is essential in such studies.

Another investigative tool is sustained physical effort at levels such as 35% of maximum aerobic capacity, which has been shown to represent the level of activity at which man can continue to perform for 8-hr days over several years. The effect of pollutants on such performance may be partly related to the changes in mass delivery of pollutants, but it may also involve other physiological systems besides the lung (e.g., heart rates increase faster during 4 hr of 35% work in polluted environments than in filtered air). In subjects exposed to pollutants, more striking physiological changes in lung function have been shown to occur during modest bouts of exercise than under conditions of rest. It is conceivable that effects on or within other physiological systems will be induced when activity of this level is utilized as part of the experimental system.

Mental, or more precisely "behavioral," alterations representing subtle changes in CNS (central nervous system) function have been shown to occur consequent to exposure to some pollutants. The most precisely evaluated system—changes in vigilance—has shown decrements of as much as 50%. Similar studies on this and other dynamic CNS functions are indicated, not solely because they have already been implicated but also because they may represent the "other" effects of contaminants. Sociological behavior patterns may also be a reflection of the peculiar ambient conditions which favor high pollutant levels. More subtle "behavioral malfunctions" have been suggested to occur as a consequence.

Exercise is a unique physiological tool in that almost every function of the organism is enhanced or altered to meet the various levels of activity. It is also a function which all organisms undergo and without which survival may be difficult. The interplay of multiple systems provides for stress-strain relationships which may be induced to breakdown points if a further stress, such as a pollutant, is superimposed. To many investigators the best experimental tool is the utilization of

multiple stresses to an organism as a means of providing more effective insight into the functioning capabilities and adaptive potential of the organism. The combination of exercise and pollutant exposure fits into this concept.

Research Priorities

In evaluating responses, tests of airway narrowing still appear to be the simplest and most useful, and they are presently given the highest priority. However, evidence suggests that, especially in susceptible individuals, morbidity and mortality may be related to effects on mucociliary transport and/or susceptibility to infection. It is suggested that these systems be given careful scrutiny in animal experiments and, if important clues are developed, that they then be tested in humans. Patients with cardiovascular disease also appear to be more susceptible to the effects of air pollutants. It is possible that inhaled pollutants have effects on the cardiovascular and other systems (e.g., blood and central nervous system) either reflexly or by circulating in the blood. While these areas may prove very important, present information does not suggest specific studies in humans that are likely to be fruitful at this time.

Results from previous epidemiological, animal, human, and meterologic studies suggest that four groups of experiments need to be performed in human subjects. These should be performed first with the subjects at rest. However, since exercise increases ventilation (and therefore increases exposure to atmospheric pollutants), critical observations need to be repeated following exposure during exercise. The four groups are as follows:

Synergistic Effects of Gas—Aerosol Mixtures: Studies originally performed in guinea pigs demonstrated increased effects of irritant gases on airflow resistance in the presence of aerosols, but these results could not be confirmed subsequently in cats or humans. A recent study suggests that elevated relative humidity enhances the interaction between SO_2 and certain aerosols and thus increases gas—aerosol synergism. These studies must be repeated in healthy and then in susceptible humans, using lower ranges of SO_2 gas concentrations and small aerosol particles (0.1—1.0 μm), with careful control of particle size, relative humidity, and temperature, The effect of changing the concentration of aerosol, temperature, and relative humidity should be evaluated.

Form in Which SO_2 Is Most Damaging: Recent evidence for the presence of sulfur-containing submicronic particles in the ambient atmosphere requires further evaluation of their effects. The effects of various sulfur-containing aerosols of known particle size (in the submicronic range) and concentration should be studied to identify the most irritant compounds.

It is emphasized that the planning of such human studies depends critically on concomitant animal and "bench" experimentation. For example, animal studies can narrow the range of sulfur-containing aerosols that need to be tested in humans. Rates of growth of soluble aerosols can be tested in humans as well as in controlled atmospheres, in lung models, and in animals. Animal studies can also be utilized to determine whether these pollutants have effects on other systems (besides bronchomotor).

Gas–Gas Interactions: The recent observation that low concentrations of ozone in combination with SO_2 have greater bronchoconstrictor effects than either pollutant alone requires further evaluation. Studies need to be performed to confirm and extend this observation and to determine the mechanism of the response. Dose–response curves are necessary to determine whether potentiation is occurring.

Central Nervous System Function and Behavioral Patterns: A number of subtle but important changes may be induced in other than the respiratory system, e.g., changes in red cell morphology, shifts in activity levels in enzyme systems, and alterations in CNS function and behavioral patterns. Behavioral modification and CNS dysfunction may well be the most important of all effects. The marked decrement in "vigilance" reported for at least one pollutant has significance beyond its simple effect in that performance is considerably influenced by this loss of vigilance. Other complex CNS functions and behavioral modifications have not been studied to any great extent. Animal work suggests that some striking shifts and investigations on humans may now be warranted. Cross-pollutant effects have not been studied. Nor have any "age"-related studies been undertaken—an area of extreme concern, with the known changes in CNS function already present consequent to aging. More exploration of all CNS functions seems highly desirable (animal and human studies).

There remain a number of unexplainable and unverified secondary effects in other systems related to pollutant exposure. These effects need to be clarified, as does their potential impact on the functioning of the total system.

More information is needed on the question of "adaptation to pollutants." We have little information on this possibility. Even the simple question of adaptation to CO has never been resolved. Are there physiological changes in humans or animals consequent to prolonged or even intermittent exposures over years?

Animal and *in Vitro* Studies

General

Among the advantages of animal experiments which have proven valuable for study of the biological effects of air pollution, the following may be cited: (1) they are ideal for determining mechanisms of effects; (2) they permit assessment of structural and biochemical responses which, because of ethical and legal constraints, often cannot be done in man; (3) they can be used to sort out and test hypotheses as a preamble to clinical investigation and as an aid in the design of epidemiological studies; (4) they are appropriate for chronic exposures in which the endpoint may involve irreversible or serious damage to the target organ or changes in the rate of development or aging of the entire organism, or of a specific organ; there is no other acceptable means of obtaining such information.

Species differ in their susceptibility to pollutants, a factor that must be weighed in the design of experiments and evaluation of results. Thus, dogs are tenfold more resistant to injury from nitrogen dioxide than are rodents. Among rodents, mice and rats appear to be more susceptible to injury from oxidants than do rabbits or guinea pigs. The use of subhuman primates in acute and chronic studies is to be encouraged. Finally, *in vitro* studies in which cellular or subcellular components are exposed to a pollutant are of value in suggesting mechanisms of toxicity and in indicating parameters suitable for use in dose–response experiments with the whole animal.

Physicochemical Systems

There is considerable interest in the effects that individual pollutant gases, gas–gas interactions, gas–aerosol interactions, and specific ambient aerosols may have on the respiratory and circulatory systems. It is important to emphasize that the chemistry and aerosol physics involved in such research are exceedingly complex and that collaboration is essential between physical and biological scientists.

Atmospheric aerosols appear to be essentially bimodal in size distribution (*23*). The smaller mode ranges from about 0.02 to 2μm in diameter, the larger mode extends up to about 100 μm in diameter. Chemical transformations in the atmosphere involving SO_2 and photochemical oxidants contribute to the formation of the submicronic particles (*24–26*). These particles are largely soluble (by contrast, the supramicronic particles tend to be insoluble) and contain most of the sulfates, nitrates, and trace metals present in polluted air (*27*). Since the submicronic mode is probably more hazardous to health, it should receive major emphasis in laboratory research.

Experiments utilizing soluble and, in particular, hygroscopic aerosols should control and monitor relative humidity. Sulfuric acid serves to illustrate the importance of relative humidity and at the same time the complexity of such systems. There is an intimate relation between the pH of the H_2SO_4 aerosol and the ambient relative humidity. This relation determines the size of the particle at equilibrium. In turn, the size of the particle prior to inhalation will determine the rate at which it grows to a new state of equilibrium within the airways. This rate of growth (hydration) may be expected to influence not only where the particle is deposited and how much is deposited, but also its pH at the instant of deposition. All of these factors are likely to influence the nature and magnitude of the biological response. To illustrate even further the complexity of the system, it should be noted that ammonia, a common contaminant of laboratory environments, may in concentrations as low as several parts per billion by volume alter the pH of H_2SO_4 and other aerosols. Ordinarily, the problem of understanding and controlling these critical factors is beyond the competence of biologists.

Biological Measurements

There are a number of conventional physiological, biochemical, and structural (light and electron microscopy) measurements that have proven useful in toxicological research. Familiarity with these techniques and the fact that some of them, especially the physiological measurements, are used routinely in human studies add to their value. Most of these functional measurements can be

made repeatedly and safely in animals, although anesthesia and tracheal intubation may be required in some instances. These measurements may include flow resistance, compliance, and flow–volume curves. They are appropriate for studying the evolution of changes during chronic exposure to pollutants. The development and use of models which mimic abnormal human states such as asthma, acute and chronic infections, and degenerative diseases are of value for assessing changes in susceptibility to pollutants.

Epidemiological studies suggest that infants and children may be especially vulnerable to air pollution. It is possible that pollution experienced early in life and even in the prenatal period may have effects that are either unusually persistent or slow to manifest themselves. These questions warrant study with animal models.

Air pollution may increase human susceptibility to infection. Animal models can be useful in determining the mechanisms by which resistance to infection is impaired. Injuries to the mucociliary and macrophage systems are considered to be important factors. The effect of pollutants on the ability of pulmonary macrophages to inactivate inhaled bacteria has been tested in rodents. Dose–response relations for individual pollutants (e.g., ozone and nitrogen dioxide) and for the same pollutants in combination have been established, but little work has been done thus far with realistic concentrations of irritant aerosols. Exposures to the latter should be combined with other forms of stress that appear to have significance epidemiologically, i.e., cold, malnutrition, and underlying injury or disease of the respiratory system. Exercise or hyperventilation (produced, for example, by adding carbon dioxide to inspired air) may be expected to increase the magnitude of the animal's exposure to the pollutant and thereby alter the effect. It should be noted, however, that the effects associated with exercise and hyperventilation might be quite different, despite similar increases in ventilation for the two circumstances.

A large body of biochemical data indicates that pollutants, especially oxidants, are capable of altering specific enzymatic systems. Some of these changes have implications for aging, for susceptibility to infection, and for the development of pulmonary fibrosis and degenerative disease. The potential importance of these findings warrants continuing research. Caution is necessary in designing and evaluation such experiments, owing to the complexity of the biochemical systems. The techniques for isolating and studying individual types of cells, especially of the respiratory system, are still in need of refinement.

Research Priorities

Physicochemical Systems: High priority should be given to the study of aerosol parameters which are likely to influence toxicity or irritancy. For soluble aerosols, these parameters include: ambient relative humidity and temperature, pH, particle growth, relative toxicity, and site of reactions.

Ambient relative humidity and temperature are especially important if the aerosol is mixed with soluble gases such as SO_2, NO_2, and O_3.

Chemical transformations in the atmosphere involving these same gaseous pollutants produce acids such as H_2SO_4 and acid salts such as $(NH_4)_2SO_4$. It would be useful to know how important the hydrogen ion concentration of the aerosol is in determining toxicity.

The influence that particle growth within the airways, during hydration, may have on the rate and site of deposition of the particles, and consequently on the biological response, may be significant. To date, the bulk of our information on particle behavior within the respiratory system has been obtained using hydrophobic particles. As noted earlier, the soluble, hydrated aerosols are probably of greater significance for health.

The relative toxicity of specific sulfate and nitrate aerosols that are indigenous to polluted atmospheres needs investigation. It is common to refer to the toxicity of "sulfate aerosols" as a group, as if sulfate itself were responsible. There is no evidence that this is so. Certainly, differences in toxicity have been found in aerosols among such species as $ZnNH_4SO_4$, $ZnSO_4$, and $(NH_4)_2SO_4$. Further, it is not known whether bisulfate (HSO_3^-) and sulfite ($SO_3^=$), two ions that are formed when SO_4 dissolves in water, may contribute to toxicity; it is known, however, that sulfite ion does enter the bloodstream where it is reversibly bound.

In experiments combining gases and aerosols, or two or more gases, the site of interaction should be determined. The reaction may occur in the ambient air (reaction chamber), in the air stream within the respiratory system, or at the tissue level, especially in the mucus layer. In the past, inferences unsupported by physicochemical measurements or by theory have been drawn with regard to where reactions occurred.

The results of such research should contribute to the design and interpretation of epidemiological investigations, and possibly both to the setting of more explicit ambient air quality standards and to decisions on the control of emissions. It would seem appropriate to carry out such studies on animals, at least initially. The results could then be used to

design more selective clinical studies. Most of these studies could be accomplished within 3–5 yr.

Biological Systems: High priority should be given to experiments involving chronic exposures of animals, preferably those which utilize (realistic) irritant aerosols, alone or in combination with reactive gases, and which take into account environmental and biological factors that are thought to interact with pollutants, i.e., temperature, humidity, age, and nutritional state. There is strong epidemiological evidence for the effects of air pollution on children which should be examined experimentally in newborn and young animals. In assessing the effects of pollutants, the use of animal models that are analogues of asthma, bronchitis, and perhaps alveolar injury is of potential value.

More data are required on the chemical, physical, and rheological changes in mucus that may occur following the uptake of gases and particles. Little is known about the buffering capacity of mucus. Such factors have implications for mucociliary clearance and resistance to infection. Indeed, the progressive thinning of the mucus layer which occurs in small peripheral airways may be responsible in part for the apparent vulnerability of these airways to pollutants. Changes in mucus chemistry may indicate changes in the bronchomotor tone either by stimulating sensory (reflex) receptors or by direction action on the smooth muscle.

Since pollutants are known to alter airway clearance, studies are needed to define effects on clearance efficiency of pollutants and the importance of such changes for increased susceptibility to other agents.

Studies of the relations between pollutant exposures and the function of alveolar macrophage are needed. It is suggested that they focus on the adverse effects of pollutants on the biochemical and histochemical system for killing infectious organisms within the cell. Such efforts should be directed at determining dose–response relationships at low levels of the pollutants.

Studies which delineate the effects of pollutants on the structural elements of the lung should be undertaken. Damage to these elements has implications for elastic behavior (and morphometry), rate of aging, and predisposition of the lung to degenerative disease.

Pollutant Interactions

It has long been recognized that the effects of air pollutants on humans may be additive to or synergistic with other environmental factors, most particularly cigarette smoking, occupational exposures, and the stress of unusually high or low temperatures. In this section, attention will be drawn to interactions of pollutants with each other and to the possible influence of other environmental factors on the effects of pollutants on the respiratory system.

It is possible to define at least four possible ways in which one pollutant may modify the effect of another: (1) by one pollutant affecting the site of deposition of another—as, for example, the deposition of a soluble gas within the airway being affected by its adsorption onto a submicronic particle; (2) by one pollutant interacting within the lung in combination with another to produce an aerosol—the lung may accelerate aerosol formation by functioning as a mixing and reaction chamber in which gas is heated, humidified, and exposed to a large surface; (3) by one pollutant affecting a lung mechanism so that the clearance of another is adversely affected, as might occur if one pollutant affected mucociliary clearance or the alveolar macrophage; and (4) by one pollutant producing an effect on the lung which makes it more vulnerable to another—as, for example, an effect on lung elasticity compromising airway clearance mechanism.

The principal ambient factors which influence droplet size, aerosol formation, and the acidity of an aerosol are relative humidity and temperature. The study and understanding of these interactions are in a very preliminary stage. A high priority should be accorded human and animal exposures in which the aerometric conditions of mixtures of pollutants are precisely measured and in which techniques are used in animals to identify sites of deposition and mechanisms of action. This work is made urgent by the changing nature and increasing complexity of the pollutant mixtures to which people are being exposed, and it is essential if answers to questions of comparative hazards of compounds formed from sulfur, oxides of nitrogen, and oxidants are to rest on a solid foundation.

A second concern is to characterize more precisely the influence of temperature and relative humidity in modifying the effects of similar concentrations of pollutants. Such measurements should be made not only in animal experiments but also in humans during different kinds of physical activity.

It may be true to say that the complexity of the environments to which children and adults are now being exposed has far outdistanced the laboratory

potential to study, on a short-term basis, the possible consequences of such exposures. Much of the complexity consists in problems of pollutant interaction.

MUTAGENESIS AND CARCINOGENESIS*

Introduction

The quantitative relationship of fossil fuel combustion products to mutagenesis and carcinogenesis in man requires a closer definition than present data permit. Verification of a mutagenic or carcinogenic hazard for man from an environmental source must include: (1) identification of the chemical or physical agent (a single agent need not be identified for preventive purposes) and the production of mutation or cancer in an appropriate biological system, and (2) demonstration of an increased risk of mutation or cancer in an exposed population. While the first criterion has been met by several fossil fuel combustion products for mutagenesis and carcinogensis, for the second criterion, despite suggestive data for a relationship of pollution to cancer, there is no general agreement on the increased risk of mutation or cancer in man from exposure to air pollution. This is not to say that such risks do not occur but that the methods hitherto used to study those relationships have yielded inconsistent results.

Mutagenesis

The potential mutagenic agents produced by fossil fuel combustion include, as shown by laboratory experiments, sulfate and nitrite in the chemical transformation of SO_2 and NO_2, benzo-[a] pyrene (BAP), and trace metals (e.g., arsenic, chromium usually present in particulate, radionuclides, and oxidants (e.g., ozone). These mutagens are present in low concentrations and except for ozone, which has produced chromatic-type aberrations in human lymphocytes (*28*), there have been no demonstrated mutational effects on man.

Carcinogenesis

The classes of carcinogenic agents identified as present in small amounts in fossil fuel combustion products are: polycyclic and other aromatic hydrocarbons; trace metals; and radionuclides. Particulates may contain potential carcinogens such as trace metals and hydrocarbons. In addition, there is evidence that in experimental animals SO_x potentiates the carcinogenic activity of BAP. Because of the known mutagenic activity of oxidants, one should keep in mind their possible carcinogenic activity, although there has been no substantial evidence of their carcinogenicity to date.

These carcinogenic agents or their reaction products are present in only small amounts in fossil fuel combustion products compared with levels that might be expected to produce detectable effects. There thus exists considerable uncertainty as to their actual impact on man.

Uncertainties in Epidemiology of Pollution-Induced Cancer

Lung cancer has been more studied by epidemiologists than any other cancers that might be associated with air pollution. The principal arguments that air pollution is a causal factor in lung cancer in urban areas are: polluted atmospheres contain known potent carcinogens; lung cancer in urban areas and in some international migrant groups can be associated statistically with urban residence and by inference with urban pollution; workmen occupationally exposed to benzo [a] pyrene, asbestos, and other materials present as pollutants have excess cancer; and cigarette smoking causes bronchitis, emphysema, and lung cancer (*29*). Urban pollution contains ingredients similar to those in cigarette smoke.

The arguments against air pollution being a causal factor in urban area excess of lung cancer are as follows. The differential excess due to the urban factor should be detected as a relative or absolute excess in those states and countries where there is the greatest urban pollution. It is not. If exposure to urban pollution increases lung cancer, then rates should be higher in lifetime urban residents than in migrants to urban areas. They are not. Correlations of lung cancer rates with measured pollution should be found in the U.K. studies where lung cancer rates are high and pollution has been great. The positive correlation is with population density, not with pollution. If the urban factor were community air pollution, it should affect women as much as men. It does not appear to

*Leonard Hamilton (Chairman), Robert E. Carroll, C. L. Comar, John R. Goldsmith, Ian Higgins, Lester B. Lave, Sidney Marks.

do so. If urban pollution by benzo[a]pyrene makes an important contribution to the urban excess, lung cancer in locations most polluted by this agent should be highest; when the agent decreases, lung cancer should do so as well. This has not yet been found.

There may be explanations other than air pollution for the urban factor (greater smoking, domestic exposures, occupational exposure, population density, infectious agents). The evidence presently available does not support the conclusion that air pollution *per se* is the factor; nor can this possibility be rejected.

Even though air pollution has not yet decisively been shown to be the causal agent of lung cancer in urban areas, there are important practical considerations. Control of soot, suspended particular matter, and products of incomplete combustion is appropriately among the highest and most urgent goals of air pollution control. This is because of the evidence on the the induction of chronic bronchitis and because of other undesirable features of such pollution. Reducing this type of pollution will *pari passu* decrease pollution by benzo[a]pyrene and other possible carcinogens.

Research Priorities

Mutagenesis

Because of the need to establish whether any of these previously mentioned potential mutagens are indeed mutagenic in man, the following studies should be undertaken in humans: a search for elevated prevalence of chromosomal aberrations in populations occupationally exposed to high levels of oxidants (e.g., ozone); correlations between birth defects, spontaneous abortion and miscarriage rates, etc., and air pollution; and the mechanism of the action of these agents on the informational macromolecules, including their transport to sensitive sites. The problem of environmental mutagenic hazards, with emphasis on screening, has recently been reviewed (*30*). One can assume that the products of fossil fuel combustion would be appropriately included.

Carcinogenesis

Occupational exposures to carcinogenic agents are likely to be higher than exposures of the general population, and with better characterization of dose and possibly, therefore, of response. Populations exposed near point sources of known and suspected carcinogens can and should also be studied. We propose that priority be given to the study of persons occupationally exposed to known or suspected carcinogens and to the study of other population groups who are exposed to point sources and whose health may be followed in a cohort study, with morbidity data and mortality data being analyzed and periodically reported. It is important to compare cancer rates in areas where pollution differs and also in areas where pollution has changed over time. As for mutagens, the interaction of carcinogens and informational macromolecules needs further study.

TRACE ELEMENTS*

Introduction

Trace elements of particular importance from fossil fuel combustion are considered to be lead, mercury, arsenic, vanadium, selenium, nickel, some heavy radionuclides, and possibly cadmium and fluoride. This selection is based on probable emission rates, likelihood of uptake from air, accumulation in food and water, and the known toxicity of some of the chemical forms of the trace elements. The anthropogenic contribution to the environment from fossil fuel combustion has been estimated as up to 50% or more for selenium, vanadium, and chromium and as not more than 20% for mercury. Even so, the health significance of these emissions remains uncertain. The emission of trace elements from the combustion of fossil fuels at stationary plants has not as yet been shown to have health significance for population. Nevertheless, areas around such power plants would be of importance for future studies. As new fuels and new technologies are developed, the kinds, forms, and levels of trace elements in the environment around power plants may change and research strategy should be adjusted accordingly. As a result of activity in different disciplines, it should be possible to maintain an ongoing review of trace elements in regard to sources, combustion chemistry, atmospheric interactions, and possible

*Edward P. Radford (Chairman), A. H. Colton, Morton Corn, James R. Fancher, Bernard D. Goldstein, Elliot Goldstein, Steven M. Horvath, Harry A. Kornberg, Byron Mechalas.

health effects. Some general references are cited to provide guidance in this area (*31–37*).

Emission Characteristics

The emission of trace elements from stationary sources of fossil fuel combustion products has not been characterized to the extent necessary to determine the health significance of these materials. Although there is considerable knowledge about fuel constituents, the extent to which the trace element component escapes into the environment is poorly understood and the chemical nature of the trace effluents is not known.

In general, a wide range of trace elements is found in coal, some of the more important being lead, chromium, manganese, arsenic, fluoride, nickel, cadmium, zinc, and copper. Mercury and antimony are generally in low concentration but may be important nevertheless. In oil the trace constituents are less well defined, but cadmium and vanadium are of particular importance. Nickel, manganese, selenium, and mercury may be significant in oil from some sources.

Further characterization of the emissions of trace elements from fossil fuel plants needs to be done. This is obviously closely related to monitoring of fossil fuel plants, which is discussed separately later. Here we emphasize that determining the chemical form of trace elements in the effluent and in the environment has a high priority. Detailed emission inventories need to be done only in a few prototype plants.

The characterization of trace element content in fuel ash is relatively simple and may serve several purposes. First, it aids in establishing a mass balance for a plant (if the fuel is also analyzed for the elements of interest). Second, the ash itself represents a pathway for possible concentration of elements and for possible reintroduction into the biosphere. Although we do not recommend such studies as being of high priority, they may be of value for analysis of exposure related to particular classes of plants and fuels.

The effects of various kinds of control equipment upon emission of individual trace elements, by particle size and species, are not well known and should be studied for the elements of primary interest. As control technology becomes more widely applied, its impact on the trace constituents of plumes is an important consideration; for example, enrichment of some volatile elements in small particles escaping an electrostatic precipitator may lead to greater dispersal of these elements than would be expected.

Environmental Assessment

In order to relate possible health effects with the emission data on the trace elements of interest, it is necessary to know what is actually found in the environment. This involves identifying the elements in air and in the plant surroundings, with emphasis on those which may accumulate in soil or sediments and ultimately reach man. We consider it of great importance that research be done to determine the concentration, translocation, and uptake into components of the biosphere of elements such as lead, arsenic, selenium, and mercury.

Trace elements deposited on the land may follow several pathways. Depending on soil and elemental characteristics, the materials may pass on through the soil column, may be trapped within the soil column, or may accumulate on the soil surface. Important factors are soil alkalinity, amount of rainfall, and acidity of rainfall. It is expected, for example, that highly alkaline western desert soils in areas of sparse rainfall would show a different accumulation pattern than would eastern acid soils receiving heavy rainfall. Thus the accumulation of trace elements in soils is a function of the source of fuel, the soil type, the amount of rainfall, and the pH of the rain.

Trace elements may pass through the soil column to the groundwater or be washed off the surface of soil by rain runoff, eventually ending up in the various surface waters—lakes, streams, oceans. These products may also enter bodies of water directly as fallout from the atmosphere. In the receiving waters many of the same chemical interactions that take place on land may occur. Solubility changes and chemical transformation may occur, controlled by such factors as salinity, presence of other reactive elements, and pH. Eventually many of these materials enter the bottom sediments, where they may undergo further changes or remain buried.

A controlling force that can modify the form and mode of transport of trace elements through the physical environment is the interaction with the biota. Some of the trace element fallout may coat out on the surface of vegetation where it may be directly ingested by animals, especially in areas of low rainfall. In many other cases plants may actively take up certain elements, accumulating them in their tissues. Again these materials may enter animals that ingest the plants. An important point here is that not only may a material be passed from one living form to another but that at each step there may be an accumulation which could magnify the exposure of the ultimate consumer in the food chain.

In the aquatic environment, processes similar to those on land may occur. In addition, the sediments are a biologically rich zone in which many chemical transformations take place, mediated in part by a rich microbial flora. Here elements may undergo changes to more soluble forms or even to more biologically active compounds, an example being the conversion of inorganic mercury to the highly toxic forms of alkyl mercury.

A special issue related to airborne trace elements is their use as markers of power plant sources of suspended particulates in urban atmospheres. If one or more elements can be shown to be characteristic of effluents from a power plant in a particular region, then determination of these elements in urban air may provide a useful estimate of the contribution of the plant to the urban air mass. This aspect of trace element research could be of considerable interest.

Health Aspects

Uptake, excretion, and accumulation of trace elements in human subjects exposed to these elements from power plant emissions constitute an important area for future research. Current data on emissions have not included detailed evaluation of the chemical form that is inhaled by human subjects or is taken up by components of the biosphere. It is known that the absorption, excretion, and indeed the toxic effect of many elements of toxicological importance depend on the chemical form, including the valence of the element. For this reason, one cannot state with confidence the extent to which fixed sources of fossil fuel effluents are contributing to the body burden of these elements, in comparison with other sources such as food.

Lead and arsenic are likely to be important quantitatively as effluents from power plants burning coal; these could be of toxicological significance because of relatively slow excretion, with a potential for accumulation. Cadmium may also be significant for this reason, but it is a relatively minor constituent of fuels and in many would only be of significance via food sources contaminated with airborne particulates. It appears unlikely that this route of exposure is important as a source of cadmium in food.

It is most important to have knowledge of the metabolism of many elements arising from fossil fuel combustion. Much is already known about many of the elements of concern; however, more research is needed for others such as arsenic and selenium.

In addition to emission, distribution in the environment, and metabolism, it is most important to study the toxicity of the trace elements of concern, taking into account the route of exposure. In particular, toxicity studies of selenium and nickel may be needed and the problem of arsenic as a potential carcinogen will have to be investigated. In addition, other elements that we believe may be important as possible health problems from fossil fuel plants are mercury and perhaps also vanadium and some of the heavy radioelements, especially lead-210. Obviously the study of toxicity at low levels has inherent difficulties and requires large-scale, long-term commitments.

Atmospheric oxidation products of SO_2, and perhaps also of oxides of nitrogen, may be important factors in community health effects associated with stationary source combustion of fossil fuel. Trace elements emitted with SO_2 and NO_x from such sources may act as catalysts of these reactions. In the case of SO_2, the reactions are highly complex and are governed by a number of independent and interdependent variables, including temperature, relative humidity, and particle size, as well as trace element composition. As a simplification, atmospheric SO_2 oxidation may be envisioned as two sequential steps: the formation of SO_3 (H_2SO_4), followed by its conversion to metallic or ammonium sulfates. Based on the sketchy evidence available at present, it would appear that the reaction rates for both these processes are governed by the exact chemical composition of the trace element constituents, including the valence and the associated anionic component. However, much more information is greatly needed, particularly in view of the potential importance of this conversion process to human health.

Smog chamber studies of the reaction rates and kinetics of SO_2 oxidation should focus on mimicking ambient conditions, using realistic pollutant and trace element compositions as well as appropriate temperature and humidity. Reaction rates with the different trace elements should be determined with the hope that such information might be useful in eventual control measures. Studies of the process should also be performed in power plant plumes and in the general atmosphere, partly with a view toward ascertaining to what extent trace elements emitted from point sources are responsible for atmospheric oxidation.

Less information is available concerning possible interactions of trace elements with gaseous pollutants other than SO_2. However, there is some indication that potentially toxic agents might also be derived from nitrogen dioxide through the

catalytic action of trace elements. Further study of this area would also appear indicated, although the priority is not as great as with sulfur oxides.

Research Priorities

Research needs have been discussed in the body of this chapter. Subject areas considered to be of highest priority are: characterization of trace element emissions from fossil fuel plants; determination of concentration, translocation, uptake, and conversions of elements such as lead, arsenic, selenium, and mercury in components of the biosphere; study of metabolism and toxicity, in human beings, of selected trace elements such as lead, arsenic, selenium, and nickel; evaluation of the role of trace elements in catalysis of atmospheric reactions of gaseous pollutants, especially SO_2 and NO_2.

MONITORING AND ANALYSIS*

Introduction

The capability for adequate monitoring and analysis of air pollutants is essential for assessment of exposure/effects relationships in epidemiological studies, for establishment of air quality criteria, for maintenance of compliance, and for design and execution of controlled experiments. In this discussion, emphasis is given to the trace elements, oxides of nitrogen, particulates, and sulfur oxides. Attention is directed to the following sorts of questions: What is the relationship between the personal exposure to pollutants experienced by individuals in their day-to-day activities and the exposure predicted by samplers operating at fixed locations in a network? How dense must the sampling grid be in different topographical settings in order to provide a valid estimate of personal exposure? To what extent can biological monitoring be used to evaluate dosages received by subjects exposed to pollutants?

Trace Elements

Sufficient data are available to conclude that trace elements in outdoor air are primarily associated with particulate matter (*38*). The emissions inventory of trace elements from power plant emissions—indeed, from all source emissions—is inadequate, as mentioned above. One needs to know not only elemental composition of emissions but also the chemical species and properties. The capacity of inhaled particulate matter to evoke responses in man depends on particle size, which determines the site of particle deposition in the human respiratory tract. Therefore, source emissions from fossil fuel combustion products should be assessed for trace element composition as a function of particle size. This should minimally include analysis of respirable and nonrespirable portions of suspended particulate matter in effluents. More complete size-composition analysis, such as that derived from cascade impactor analysis, would be desirable. Methods to obtain these data are available, but improvements are required (*39, 40*). The solubility of respirable and nonrespirable particulates will also influence their potential to evoke responses and must therefore be evaluated (*41*). Because chemical reaction occurs in plumes, data on particle size, composition, and solubility should be obtained for material in plumes as well as in stack emissions (*42*). To evaluate exposure to individuals at ground level, the same data must be collected at sites where human subjects may be exposed. The relationship between volatile trace elements in the vapor stage in stack emissions should be studied because those elements may subsequently condense on nuclei or particulates during or following emission.

The above factors should be studied for typical power plants using fuels which can be considered representative of current or future industry practice, including new fuels (i.e., reused oil, solid waste).

Depending upon local topographical and meteorological factors, monitoring at ground level must be considered for distances up to, and possibly exceeding, 25 km from point sources.

It is recommended that more satisfactory sampling and analytical capability be developed for the elements Se, Hg, As, and Be. Again, knowledge of the combined forms of these elements is essential for evaluating their hazard potential; elemental analysis is helpful but not sufficient.

Because selected trace elements have been shown to participate, as catalysts or reactants in conversion of gas phase components of power plant plumes (e.g., iron, manganese, and vanadium),

*Morton Corn (Chairman), A. H. Colton, James R. Fancher, John F. Finklea, Leonard Hamilton, Harry A. Kornberg, Edward P. Radford.

laboratory studies should be performed to identify those trace elements and the chemical forms which are associated with acceleration or deceleration of gas phase reactions in power plant plumes. Investigations with this scope are beginning (*43*).

Oxides of Nitrogen

Oxides of nitrogen emissions from power plants are almost entirely in the form of NO. The inventory for annual emissions of nitrogen oxides is well established, but establishing inventories over shorter time periods presents some difficulties. Methodology for monitoring NO_2 in air now appears adequate for measuring the ambient concentrations usually encountered, but developmental effort is desirable, particularly for short-term sampling.

The occurrence and transformation of NO_2 in air are widespread and must be evaluated on an area basis, rather than stressing plume studies. However, there is need for further delineating the reactions and reaction rates, including the influence of type of combustion process, fuel, and meteorology. These investigations could profitably be included in other plume studies.

There is a substantial base for retrospective data from the National Air Sampling Network for NH_4^+ and NO_3^- in air (*44*). These data should be examined for their possible utilization in evaluation of past exposures of inhabitants of areas monitored. Selective limited studies of NO_2 in air indoors (from gas combustion) suggest potentially high intermittent peak exposures to nitrogen pollutants (*45*). The extent and effects of indoor exposure should be carefully investigated.

The capability for monitoring more complex nitrogen compounds in air is severely limited in the laboratory and in the field because the methods are difficult and complicated. Despite this limitation, it is recommended that investigations be performed of peroxyacetylnitrate (PAN) in air in both the western and eastern United States.

Monitoring of nitric acid will require development of satisfactory analytical methods for this compound.

Research on NO_x and its mechanisms of transformation in air can be advantageously pursued in laboratory chamber-type research. We recommend that such studies be performed in conjunction with field studies.

Particulates

This section is concerned only with problems being experienced in monitoring for particulates. Fugitive emissions from power plant fly ash dumps and coal piles appear to have been largely neglected, and a further problem arises from wetting these dumps. These conditions require evaluation. Improvements for measurement and analysis of total suspended particulate matter in ambient air are possible along several fronts: particle size cuts, analysis for metals, and anions. When studies related to health effects of pollutants are undertaken, values from routine monitoring at network stations should be augmented with measurements of particle size and chemical composition. However, it should be recognized that network capabilities may be modified with time and that ongoing investigations may require rebuilding and improving the capacity of existing stations.

Sulfur Oxides

Sulfur oxides include anthropogenic sulfur dioxide, sulfonates, sulfuric acid, ammonium sulfate, ammonium acid sulfate, and other sulfate salts. Acid-sulfate aerosols (sulfuric acid, ammonium sulfate, and ammonium acid sulfate) can be formed in the atmosphere by conversion of sulfur compounds emitted from combustion processes (*46*). Being hygroscopic, sulfur trioxide combines with water to form sulfuric acid. Any research which would further clarify the pathways of primary and intermediate sulfur compounds entering into, remaining in, or leaving the atmosphere is of highest priority. Studies of plume chemistry and mesoscale studies of transport and transformation are required. The influence of humidity, hydrocarbons, trace elements, oxides of nitrogen, and other atmospheric constituents must be sorted out and quantified. The effect of cooling towers on plume chemistry should be ascertained. Both chamber and field studies will be required to elucidate transformation mechanisms. Dispersion models applicable to complex terrain are generally lacking but obviously needed.

Present measurement methods allow routine monitoring of sulfur dioxide in emissions and ambient air. Acid-sulfate aerosols can be differentiated by size and chemical species, using special research techniques that are not yet applicable to routine monitoring. However, water-soluble suspended sulfate extracted from high-volume filters

is a useful method to estimate total acid-sulfate exposures which can be used in community studies. For exposure studies involving laboratory animals or human volunteers it is most desirable to characterize exposures, using measurements that apply precise particle sizing to aerosols of known chemical composition.

Personal monitors for sulfur dioxide and for acid-sulfate aerosols or their proxies are in a rudimentary, generally unsatisfactory stage of development. It is recommended that improved measurement methods be developed to characterize the size distribution and chemical composition of acid-sulfate aerosols and that personal monitoring techniques be developed for sulfur oxides.

Annual emissions inventories for sulfur oxides were tabulated for each air quality control region as a part of the state implementation plans required by the Clean Air Act. Except for a few cities, it is difficult to ascertain how emissions have changed during past decades or to obtain the degree of temporal resolution needed to improve models of the source-receptor relationship. Therefore, to support health effects studies and studies of atmospheric transport and transformation it may be necessary to reconstruct emissions inventories as a means of achieving the necessary degree of temporal resolution.

Human exposure to sulfur oxides may be estimated from sulfur dioxide and water-soluble sulfate measurements available from sampling stations in commercial, residential, or industrial areas.

Both 24-hr and annual average exposures are of interest. Selection of populations for health studies is best restricted to those who live within a 2- to 3-km radius of an appropriately sited monitoring station. Indoor monitoring of sulfur oxides is urgently required. Until personal exposure meters are available, it would seem appropriate to study individual activity patterns and to estimate time-weighted exposures. Therefore, it is recommended that air monitoring stations be appropriately sited and that indoor and outdoor monitoring be utilized to estimate time-weighted exposures.

Air monitoring stations established for trend monitoring or assessment of compliance with air pollution controls may provide useful information once quality assurance problems are surmounted. For example, measurement of sulfur dioxide and total suspended particulate matter in suspected impact areas around power plants may be used in health studies, together with meteorologic data to improve or validate existing models of short-term exposures. Modest augmentation of these monitoring efforts by analyzing high-volume filters for sulfate, nitrate, ammonium, and selected trace elements would greatly enhance the utility of these otherwise routine measurements. Instrumentation of existing stations can be further augmented by installing suitable particle sizing devices for special studies (*47*). Studies of exposures lasting less than 24 hr require more expensive instrumentation and sophisticated data acquisition systems. It is recommended that health studies employ existing monitoring networks whenever possible, provided these networks augment their particulate analyses, use federal reference methods of their equivalent, and participate in a recognized quality assurance program.

Research Priorities

The main features of the research needs are as follows:

(1) There should be more complete studies of trace element emissions to include elemental composition and size-composition analysis, with data being obtained for the plume, for stack emissions, and at ground level.

(2) Better sampling and analytical capabilities are needed for Se, Hg, As, and Be.

(3) Better methods are needed for sampling of NO_2 with special attention to occurrence and transformations on an area basis. Levels of peroxyacetylnitrate (PAN) in air should be monitored.

(4) Emissions of particulate from fly ash dumps and coal piles should be evaluated. Particulate measurements should be improved to provide data on particle size, metal contents, and possibly anions.

(5) For sulfur compounds that enter the atmosphere, the complete physical and chemical pathways which are active and serve to transform the emissions during transport should be clarified, together with the factors that govern them.

(6) Improved measurements are needed for size characterization and analyses of acid-sulfate aerosols and for personal monitoring of exposures to the sulfur oxides.

(7) Air monitoring for sulfur oxides should be studied and improved so that data are as useful as possible for retrospective and prospective assessment of health effects, trend monitoring, and compliance.

REFERENCES

1. Ray, D. L. The Nation's energy future. Report to Richard M. Nixon, President of the United States, submitted by the Chairman of the U.S. Atomic Energy Commission, December 1, 1973,
2. Freeman, S. D. A time to choose: America's energy future. Ballinger, Cambridge, Mass., 1974.
3. Goldsmith, J. R. Contribution of motor vehicle exhaust, industry and cigarette smoking to community carbon monoxide exposures. Ann N.Y. Acad. Sci. 174: 122 (1970).
4. Buechley, R. W., et al. SO_2 levels and perturbation in mortality. Arch. Environ. Health 27: 134 (1973).
5. Schimmel, H., and Greenburg, L. A study of the relation of pollution to mortality: New York City, 1963-1968. J. Air Pollut. Control Assoc. 22: 607 (1972).
6. Schimmel, H., Murawski, T. S., and Gutfield, N. Relation of pollution to mortality, New York City (1963–72). Paper presented at Annual Meeting of the Air Pollution Control Association, Denver, June 1974.
7. Hexter, A. C., and Goldsmith, J. R. Carbon monoxide: association of community air pollution with mortality. Science 172: 265 (1971).
8. Rall, D. P. A review of the health effects of sulfur oxides. Submitted to the Office of Management and Budget on behalf of a panel of consultants, 1973.
9. Douglas, J. W. B., and Waller, R. E. Air pollution and respiratory infection in children. Brit. J. Prev. Soc. Med. 20: 1 (1966).
10. Lawther, P. J., Waller, R. E., and Henderson, M. Air pollution and exacerbations of bronchitis. Thorax 25: 525 (1970).
11. Emerson, P. A. Air pollution atmospheric conditions and chronic airways obstruction. J. Occup. Med. 15: 635 (1973).
12. World Health Organization. Long-Term Program in Environmental Pollution Control in Europe: The Long-Term Effects on Health of Air Pollution. Copenhagen, 1973.
13. Irwig, L., et al. Air Pollution: Methods to Study Its Relationship to Respiratory Disease in British Schoolchildren. Proceedings of the International Symposium on Recent Advances in the Assessment of the Health Effects of Environmental Pollution. Paris, 1974.
14. Health Consequences of Sulphur Oxides: A report from CHESS, 1970-71. Environmental Protection Agency, Office of Research and Development, National Environmental Research Center, Research Triangle Park, N.C., 1974.
15. Guralnick, L. Mortality by occupation and cause of death among men 20–64 years of age. Vital Statistics Special Reports, U.S. Department of Health, Education, and Welfare, Vol. 53 1963, p. 53.
16. U.S. Department of Health, Education, and Welfare, Public Health Service, Occupational Health Program and Social Security Administration Bureau of Disability Insurance. Occupational Characteristics of Disabled Workers by Disabling Condition. PHS Publication No. 1531. Washington, D.C., 1967.
17. Her Majesty's Stationery Office. The Registrar-General's Decennial Supplement. Occupational mortality tables, 1971. HMSO, London, 1971.
18. Gordon, T., and Kannel, W. B. The Framingham Study: An Epidemiological Investigation of Cardiovascular Disease. U.S. Government Printing Office, Washington, D.C., 1974.
19. Higgins, M. W., and Keller, J. B. Seven measures of ventilatory lung function: long-term population values and a comparison of their ability to discriminate between persons with and without chronic respiratory disease in Tecumseh, Michigan. Am. Rev. Respir. Dis. 108: 258 (1973).
20. Stebbings, J. H., Jr. Chronic respiratory disease among non-smokers in Hagerstown, Maryland: IV. Effects of urban residence on pulmonary function values. Environ. Res. 4: 283 (1971).
21. McMichael, A. J., Spirtas, R., and Kupper, L. L. An epidemiologic study of mortality within a cohort of rubber workers. J. Occup. Med. 16: 458 (1974).
22. Hammond, E. C. Smoking habits and air pollution in relation to lung cancer. Environmental Factors in Respiratory Disease. Academic Press, New York, 1972.
23. Whitby, K. T., et al. The size of suspended particle matter in air. Science 183: 1098 (1974).
24. Heisler, S. L., Friedlander, S. K., and Husar, R. B. The relationship of smog aerosol size distributions to source characteristics. Atmos. Environ. 7: 633 (1973).
25. Schuetzle, D., Cronn, D. R., and Crittenden, A. L. Molecular composition of secondary aerosol and its origin. Paper presented at 172nd National ACS Meeting; Symposium on Surface and Colloid Chemistry in Air Pollution Control, August 27, 1973.
26. Hidy, G. M. Theory and formation and properties of photochemical aerosols. Paper presented at Summer Institute, Battelle Seattle Research Center, June 18–29, 1973.
27. Natusch, D. F. S., and Wallace, J. R. Urban aerosol toxicity: the influence of particle size. Science 186: 695 (1974).
28. Neuberger, J. S., and Radford, E. P. Review of human health criteria for ambient air quality standards in Maryland. A report to the Bureau of Air Quality Control, Department of Health and Mental Hygiene, State of Maryland, August 1974.
29. Goldsmith, J. R., and Friberg, L. Impact of air pollution on human health. *In*: Air Pollution: A Comprehensive Treatise, A. C. Stern, Ed., Academic Press, New York, in press.
30. Drake, J. W. (Chairman), Committee 17. Environmental mutagenic hazards: mutagenicity screening is now both feasible and necessary for chemicals and entering the environment. Science 187: 503 (1975).
31. Engel, R. E., et al. Environmental Lead and Public Health. Environmental Protection Agency, Air Pollution Control Office, Research Triangle Park, N.C., March 1971.
32. Geochemistry and the Environment. The Reaction of Selected Trace Elements to Health and Disease. Vol. I. National Academy of Sciences, Washington, D.C., 1974.
33. Ruch, R. R., Gluskoter, H. J., and Shimp, N. F. Occurrence and Distribution of Potentially Volatile Trace Elements in Coal. National Environmental Research Center, Research Triangle Park, N.C., July 1974.
34. Smith, W. S., and Raft, R. A. Atmospheric Emissions from Fuel Oil Combustion: An Inventory Guide. U.S. Department of Health, Education, and Welfare, Washington, D.C., November 1962.
35. Smith, W. S., Taft, R. W., and Bruber, C. W. Atmospheric Emissions from Fuel Oil Combustion: An Inventory Guide. U.S. Department of Health, Education, and Welfare, Washington, D.C., April 1966.
36. Stahl, W. R. Preliminary Air Pollution Survey of Mercury and Its Compounds: A Literature Review. National Air Pollution Control Administration, Raleigh, N.C., October 1969.
37. Study of the Emission from Major Air Pollution Sources and Their Atmospheric Interactions: Two-Year Progress Report, 1 Nov. 72-31 Oct. 74. University of Maryland, Department of Chemistry and Institute for Fluid Dynamics and Applied Mathematics, College Park, Md., October 1974.

38. Friedlander, S. K. Chemical element balances and identification of air pollution sources. Environ. Sci. Technol. 7: 235 (1973).
39. Horvath, H., and Rossano, A. T. Technique for measuring dust collector efficiency as a function of particle size. J. Air. Pollut. Control Assoc. 20: 244 (1970).
40. McCain, J. C., Cushing, K. M., and Smith, W. B. Measurement of the fractional efficiency of pollution control devices. APCA Paper 74-117, presented at Annual Meeting of the Air Pollution Control Association, Denver, June 1974.
41. Corn, M. Urban aerosols: problems associated with evaluation of inhalation risk. In Assessment of Airborne Particles, T. T. Mercer, P. E. Morrow, and W. Stober, Eds. Charles C Thomas Co., Springfield, Mass., 1972, Chap. 24.
42. Davis, D. D., Smith, G., and Klauber, G. Trace gas analyses of power plant plumes via aircraft measurements, O_3, NO_x and SO_2 chemistry. Science 186: 733 (1974).
43. Huang, D., et al. Investigation of Atmospheric Chemical Interactions in Coal-Fired Power Plant Plumes. Report No. E-AQ-74-1. Division of Environmental Planning, TVA, May 1974.
44. Monitoring and Air-Quality Trends Report, 1972. EPA-450/1-73-004. Environmental Protection Agency, Research Triangle Park, N.C.
45. Wade, W. A. (A. D. Little Co., Cambridge, Mass.), Indoor pollution-NO_2. Personal communication.
46. Roberts, P., and Friedlander, S. K. Conversion of SO_2 to ambient particulate sulfates in the Los Angeles atmosphere. Paper presented at Conference on Health Consequences of Environmental Controls: Impact of Mobile Emissions Controls. Durham, N.C., April 17-19, 1974.
47. Lee, R. E., Jr., Caldwell, J. S., and Morgan, G. G. The evaluation of methods for measuring suspended particulates in air. Atmos. Environ. 6: 593 (1972).