Health Effects of the Gas-Aerosol Complex

Report to Special Committee on Health and Ecological Effects of Increased Coal Utilization

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Combustion products derived from the burning of coal are definitely capable of producing adverse human health effects. No single component of the combustion product mixture is solely responsible. Rather, effects are due to a group of compounds, both gases and aerosols, in the effluents of stationary source combustion processes. Although incompletely defined, the individual components of the gas-aerosol complex appear to be capable of interacting both in terms of atmospheric chemistry and health effects. The three primary air quality standards pertinent to regulating coal combustion all represent to some extent indirect, although reasonable, measures of this gas-aerosol complex. As a group, these standards appear to be adequate to protect human health. Conventional toxicological considerations suggest that the adverse health effects of any necessary increase in coal combustion effluents would be greatest per unit of coal in those areas which are most heavily populated and have the highest preexisting levels of the gas-aerosol complex. In order to decrease the degree of uncertainty for future decisions of this type, it is important that prospective epidemiological and air monitoring studies be initiated in conjunction with any large scale introduction of coal use.

Introduction

Combustion products derived from the burning of coal are clearly deleterious to human health. The causal relationship between coal emissions from combustion and disease, particularly of the respiratory tract, has been inferred for centuries. Modern appraisal of this relationship can be considered to have begun at the time of the London smog episode of 1952, although a few antecedent studies and local air pollution disasters (e.g., Donora, Pennsylvania in 1948; Meuse Valley in 1937) can be cited.

In 1952 London was characterized as having multiple emission point sources arising from coal combustion. Coal was used for heating of individual homes as well as for power generation and industry. In December 1952 weather conditions produced a four-day inversion period, which resulted in a marked increase in air pollutant levels. During the smog, and a few days subsequent to it, more than 3000 excess deaths were estimated to have occurred. This galvanized medical authorities in Britain and elsewhere to look very closely into the causes and consequences of air pollution, particularly in relation to coal combustion. The pollutants that were measured were, quite obviously, those that were amenable to analysis with the available technology. This led to a focus on sulfur dioxide and particulates (measured as smokeshade in Great Britain and total suspended particulates in the U.S.). While many studies used the level of these two indices to correlate with observed health effects, it was recognized

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at about the time of the 1952 London disaster that sulfur dioxide and smokeshade were somewhat indirect indicators of the agents responsible for human effects. Since that time, much evidence has accumulated demonstrating that it is a complex of atmospheric products and mixtures of emitted pollutants which play the major causative role in adverse health effects due to fossil fuel combustion products. The group of compounds participating in this process, which will be discussed in more detail below, will be described as the gas-aerosol complex. Although the nature of the available information requires this document to treat this complex in its individual components, it should be kept in mind that it is the interplay of these many components which result in the deleterious human health effects associated with fossil fuel combustion.

Inasmuch as the focus is on coal, this document will stress studies in Great Britain where control of coal combustion effluents has led to a marked improvement in air quality, as well as American studies. Unfortunately, in neither country was there a rigorous attempt to study prospectively the health consequences of the major changes in fuel consumption and emission control that led to the presence of cleaner air. This lack of information is most unfortunate. It is possible to construct a graph depicting the decrease in atmospheric pollution levels in the recent past. Were one able to construct a similar curve showing changes in community health associated with the previous decrease in level of pollutants, it would now be a much simpler proposition to predict what effect, if any, would occur due to increased pollutant levels attendant upon conversion to coal. It is unlikely that retrospective studies in the United States will rectify this serious omission in view of our generally inadequate health statistics base. There is, however, the possibility, worthy of exploration, that pertinent information concerning the effect of decreasing coal use on human health could be obtained by a study of the more complete British health records. As an obvious corollary, a careful study of the effect of reinstitution of coal use should begin as soon as possible before the actual switchover occurs, and continue for some time afterwards. While such a study would be relatively expensive relative to the current funding level for studies of environmentally caused health effects, it is extremely cheap compared to the multibillion dollar impacts arising from decisions concerning the energy program.

It is assumed that those reading this review are reasonably knowledgeable concerning the biomedical effects of pollutants, the inherent limitations of the various types of toxicological studies, and the need for confirmatory information from differing approaches. A number of reviews describing the health effects of air pollutants have been published in recent years. These should be consulted for detailed information beyond the scope of this document (1-4).

The subject of health effects of photochemical oxidants will not be discussed in this review, although one of the precursors of these pollutants, oxides of nitrogen (NOx), will be increased by the proposed switch from oil to coal. It is difficult to assess the effect of increased NOx emissions on photochemical oxidant levels because of the complicated time-dependent set of reaction mechanisms leading to the formation of oxidants.

**Constituents of the Gas-Aerosol Complex**

The constituents of the gas-aerosol complex derived from stationary source fossil fuel combustion are usually subdivided into particles and gases (the major gases being sulfur oxides and nitrogen oxides). The subject of airborne particles has recently been reviewed by a panel of the National Academy of Sciences (1). Of importance is that the particles formed as a result of fossil fuel combustion tend to be in the respirable size range (i.e., <1 μm). The major anionic components of toxicological importance are sulfates and nitrates, and perhaps sulfites and nitrates as well. These are predominantly products formed in the atmosphere from reactions of the emitted gases (i.e., secondary products). More information about the levels of the associated cations is becoming available. These cations include trace levels of various metal elements, ammonium ions, and protons (hydrogen ions). The effects arising from trace elements are considered in a separate document.

Sulfur in fossil fuel is converted mainly into sulfur dioxide during combustion, although a small percentage is emitted directly as sulfate. Sulfur dioxide is a highly soluble gas which exists in solution, either as hydrated SO2 or as the sulfite or bisulfite ion, depending upon pH. Two general processes associated with polluted atmospheres act to convert sulfur dioxide to sulfate aerosols. In the presence of various trace elements, SO2 absorbed into aqueous aerosols is catalytically oxidized to H2SO4 (sulfuric acid). This process is highly dependent upon humidity, temperature, the type and quantity of trace elements present, and the pH of the aerosol. The second general pathway for the formation of atmospheric sulfates is through a photochemical process in which the action of sunlight on hydrocarbons and oxides of nitrogen generates species capable of oxidizing SO2. The complexity of both of these processes requires emphasis. There is a potentially large variety of dif-
fert sulfate formed depending upon the cations. These sulfates have a wide range of physicochemical properties and, presumably, toxicity. Most are in the respirable size range. Further information concerning the mechanisms of formation, the reaction rates, the atmospheric transport, and the dispersion of sulfur oxides is necessary in order to better understand the toxic properties of the aerosols, and in order to attempt to construct successful control strategies. Of particular value would be a determination of the chemical speciation of sulfates present in ambient air. This would allow epidemiological and controlled human exposure studies to focus on those sulfates most likely to be responsible for toxicity. At present, however, there is little reason to expect that any one sulfur oxide will be solely or mainly responsible for the effects of the gas-aerosols complex. It should be kept in mind that sulfur in fuel and the resultant sulfur dioxide, are the precursors of essentially all anthropogenic sulfate oxides.

The nitrogen oxides have usually been considered separately from sulfur oxides and particulates in discussion of health effects of air pollutants. This in part is due to the fact that both stationary source and automotive fossil fuel combustion contribute substantially to atmospheric NOx emissions. In the past, the toxicity of nitrogen oxides has been considered almost solely in terms of nitrogen dioxide. (Nitric oxide, the other major gaseous oxide of nitrogen, does not appear to be toxic at ambient concentrations). Recent information has suggested that aerosols containing nitric acid, organic and inorganic nitrates and nitrites are present in the atmosphere and may contribute to the observed toxicity of the gas-aerosol complex. The evolving evidence suggests a situation analogous to that described above for sulfates, i.e., the presence of nitrates concentrated in the respirable size range, and being derived from atmospheric transformation of gaseous NOx precursors. There is, however, far less information concerning nitrate air chemistry and toxicology than there is for sulfate. The subject of nitrogen oxide formation and toxicity has recently been thoroughly reviewed by an NAS panel (2).

Basic Biomedical Considerations
Respiratory Tract Response to Inhaled Irritants

The human respiratory tract contains a number of relatively effective defenses against inhaled irritants. The nose is particularly efficient in removing those larger particles which impinge upon the nasal turbinates, and also in scrubbing out soluble gases such as sulfur dioxide. Pollutant removal within the nose does not completely preclude pulmonary effects, as there is some evidence which suggests that vagal reflexes, leading to bronchoconstriction, may be initiated by nasal receptors. Breathing through the mouth also effectively removes soluble gases and larger particulates, but to a lesser extent than the nose. Smaller particulates, including most anthropogenic sulfates and nitrates, as well as less soluble gases such as NO2 and O3, more readily penetrate deeply into the respiratory tract. In normal adults, mouth breathing usually occurs during periods of high minute volume when the dose delivered to the lower airways would tend to be highest. Such considerations presumably play a role in the susceptibility of children and individuals with pre-existing cardiorespiratory disease to pollution. Mouth breathing and high minute volumes occur relatively frequently in these population segments.

Acute Exposure. Mucociliary clearance is a cleansing process which results in a flow of mucoid material upwards toward the pharynx. There is unfortunately relatively little information concerning the basic determinants of mucociliary clearance rates or the effects of pollutants on this process. Although some studies have obtained indirect evidence of altered pulmonary clearance rates following exposure to components of the gas-aerosol complex, there is no evidence that usual ambient levels have an effect on this process. Of potential interest are recent animal studies suggesting that repetitive acute exposure to sulfuric acid aerosol during a period of months may lead to an alteration in baseline pulmonary clearance (5). Also of interest is the ability of mucosal secretions to buffer inhaled acid aerosols. This has been highlighted by recent studies suggesting that ammonia may be a constituent of the respiratory tract (6). If neutralization of acid aerosols does prevent toxicity, then it is conceivable that the buffering capacity of the respiratory tract is the basis for a true threshold for the acute effects of acid aerosols, although possibly subject to individual or temporal variability. This is, of course, speculative but represents an intriguing area of potential significance.

The alveolar macrophage is an important component of pulmonary defense. There is some evidence suggesting that the basis for the potentiation of respiratory tract infections by nitrogen dioxide may be an interference in the ability of alveolar macrophage to kill inhaled microorganisms (7, 8). Such evidence is not available for sulfur oxides. More information concerning the effect of inhaled particulates on alveolar macrophage function is needed. A better understanding of the mechanism of the bacteriocidal
mechanisms employed by the macrophage is also required.

The major physiological response to sulfur oxides in controlled short-term human and animal exposure studies is an increase in airway resistance. In animal studies, sulfuric acid aerosol has been shown to be a stronger potentiatior of bronchoconstriction than ammonium sulfate aerosol which is stronger than SO₂ gas (9). The pathways mediating bronchoconstriction, which is generally believed to be the basis for this response, include vagal reflexes set off by receptors located in various parts of the respiratory tract. However, studies have shown that bronchoconstriction can occur even when the vagus nerve has been inactivated. It is hypothesized that humoral factors are capable of acting on airway smooth muscle, or may potentiate the effect of such factors. In vitro studies have shown that acid salts are enhancers of histamine release from cells (10). This bronchoconstrictive response could account for many of the adverse health consequences associated in epidemiological studies with the gas-aerosol complex. Controlled human studies on asthmatics have shown that short-term NO₂ exposure potentiated the bronchoconstrictive effect of carbachol (11).

**Long-Term Exposure.** Studies of the effects of long-term exposure of animals to sulfate aerosol have produced evidence of some effects, but in general, the findings have not been dramatic. Slight bronchial epithelial proliferation, edema and alveolar wall thickening in animals exposed to at least 500 μg/m³ of sulfuric acid has been reported, as has a decrease in CO lung diffusion capacity in beagles continually exposed to H₂SO₄ for up to two years (12).

Monkeys continually exposed to H₂SO₄ levels of 100 μg/m³ for one year have shown no evident lung abnormalities. At H₂SO₄ exposure levels of about 1000 μg/m³ in conjunction with about 500 μg/m³ fly ash particles, bronchiolar wall thickening was observed (13). Occupational studies of workers chronically exposed to H₂SO₄ levels above 10,000 μg/m³ have not indicated excess chronic disease incidence, but have indicated an excess number of acute attacks in those individuals already suffering from chronic respiratory disease, such as bronchitis. These results yield an unclear picture of possible long-term acid sulfate aerosol exposure effects. The real problem is that the underlying biochemistry of the disease etiology is not well understood for sulfates.

Considerably more research is required to definitively pin down the role of individual coal-derived pollutants in the causation of chronic disease. The biomolecular mechanisms must be elucidated as well as the dose-response relationships.

**Individual Variability**

The concept of individual variability in the susceptibility to pollutants is important for understanding the health impact of the gas-aerosol complex. Such variability must be considered to be operative both among different individuals, leading to some members of the population being inherently more vulnerable, and within a single individual at different time periods. Inter-individual differences represent inherited factors, including presumably the reactivity of the bronchial tract to external agents, and acquired factors, such as preexisting cardiorespiratory disease. Intra-individual variability includes such temporal factors as the presence of microbial respiratory tract infection and age. Controlled exposure studies have clearly demonstrated widely differing responses in groups of animals to bronchoconstrictive pollutants. Inasmuch as animals used in these studies generally have a common genetic and environmental heritage, it is not surprising that, based on the few available studies, there appears to be at least as great a variability in human response. A marked variability in human response is also suggested by some epidemiological studies.

Unfortunately, there are as of yet inadequate data to statistically characterize the degree of human variability in response to pollutants. This would be of value in determining the validity of extrapolating results of controlled human exposure studies (which generally utilize a small number of healthy subjects) to high risk populations.

**Physicochemical Characteristics of Pollutants in Relation to Respiratory Response**

Studies in animals exposed to defined components of the gas-aerosol complex have clearly demonstrated that there is a marked difference in the ability of individual pollutants or combinations to elicit an acute bronchoconstrictive response. This is particularly evident in the series of studies performed by Amdur and her colleagues on guinea pigs (9, 14). The physicochemical characteristics which appear to be particularly significant are size, solubility, pH, and chemical reactivity. For example, particles in the respirable (< 1 μm) size range appear to exert a greater bronchoconstrictive response than larger particles given a similar mass concentration. Many aerosols of the appropriate size are, however, inert with respect to bronchoconstriction. In some cases the absence of response appears to be due to lack of "chemical reactivity" (e.g., NaCl), in others it is due to the relative insolubility of the compound which
presumably allows clearance before any chemical reaction can occur. The pH of the aerosol also is of importance. In general, the greater the acidity, the higher the likelihood of a bronchoconstrictive response. More information is needed on the role of particle shape and hygroscopicity in determining regional airway deposition and subsequent bronchoconstrictive impact (15).

Knowledge concerning the role of these physicochemical characteristics in mediating airway response to aerosols has been of great value in understanding pollution effects and predicting response. Simple manipulations of these parameters does not, however, totally explain the response of guinea pig airways to inhaled irritants. A better basic understanding of the biochemistry underlying the physiology of airway response would be of great value. Another research area of related importance is the determination of the responsiveness of the human respiratory tract to these pollutants. Such studies would consist of short-term acute exposures with the aim of establishing a hierarchy of responsiveness to individual components of the gas-aerosol complex, as well as determining appropriate no-effect levels. In addition, more information is required concerning potential synergistic interactions of these air contaminants. In particular, animal studies of sulfur dioxide effects in the presence of inert respirable particles and photochemical pollutants including ozone, NO₂, and organic irritants such as acrolein should be extended to man.

Observed Health Effects of the Gas-Aerosol Complex in Humans

Mortality

There is no question that exposure to past ambient levels of the gas-aerosol complex has led to increased mortality during acute air pollution episodes. Those individuals who died during such episodes were mainly the elderly, the infirm, and, in some episodes, the very young. Controversy does exist concerning the extent, if any, to which current pollutant levels are responsible for daily variations in mortality. To study this problem it is necessary to carefully adjust for many variables, including meteorological and seasonal effects.

In recent years a number of investigators have evaluated New York City mortality data in relation to air pollution levels (16-21).

The studies are in general agreement as to the existence of a residual variation in daily mortality that is explainable by pollution levels. There is, however, a lack of consensus concerning whether the effect correlates more strongly with sulfur dioxide or total suspended particulates. This is not surprising in view of the interrelationship of these two measures of the gas-aerosol complex. There is also controversy concerning the interpretation of these studies: the results of one investigation suggesting little or no threshold for the association of mortality with sulfur dioxide levels (20), while a more recent analysis (21) reports no change in the excess mortality associated with pollution during a period in which there was substantial improvement in ambient sulfur dioxide levels.

A deficiency in most of these investigations, as well as air pollution-related epidemiological studies in general, is the use of only one monitoring station to characterize the pollutant exposure of a large population. This adds to the uncertainty of the results. It should be noted that studies of daily mortality in relation to daily air pollution levels are unlikely to discover a life-shortening effect that is due to the causation of a chronic disease by these air pollutants.

Morbidity

Acute Effects. There are literally dozens of types of adverse health effects which have been reported to be associated with inhalation of the gas-aerosol complex or its components. For many of these effects (e.g., behavioral, immune) the information is inconclusive or at best, peripheral. Epidemiologic studies of respiratory tract effects of these pollutants have utilized a variety of different measured parameters. These studies have tended to focus on population groups believed to be at high risk for pulmonary effects, including children, asthmatics, the elderly, and individuals with pre-existing cardiorespiratory disease.

The impact of air pollutants on children has been studied extensively [see for example reviews by the American Academy of Pediatrics (22), Wehrle and Hammer (23), and NAS (4)]. A relation between the gas-aerosol complex and lower respiratory illness has been established. Epidemiological studies in Great Britain, including evaluation of up to 10,000 individuals, have reasonably clearly demonstrated an effect of air pollution on bronchitis incidence (24-26).

Of particular interest are two studies in which cohorts were evaluated at varying time intervals. In a study of 5-year-olds living in four different areas, the incidence of chronic cough correlated well with existing air pollution levels, and there was a significant decrease in pulmonary function in the residents of
the most polluted area during the first study period. Four years later, in 1969, these same children were restudied. During this period there had been a marked improvement in air pollution levels (45-80% decrease in smokeshade; 10-25% decrease in sulfur dioxide) with an abolition of the pollutant gradient between the four areas. Appreciable decreases in observed respiratory effects were observed and there were no longer differences between the areas (27, 28). Another study of a cohort of children born in 1946 noted an association of the history of lower respiratory tract infection with air pollution (25). When this group was thoroughly evaluated at age 20, cigarette smoking was found to be the dominant factor in the presence of respiratory symptoms, while air pollution had at most a minimal effect. Other British and American studies have reported a lesser prevalence of respiratory problems in association with improvement of air quality (29-31).

Studies in the United States and elsewhere, including the CHESS studies (32), have evaluated the association of sulfur oxides and particulates with childhood respiratory tract illness. With some exceptions, lower respiratory tract illness has been positively correlated with those pollutants at levels somewhat above the current U.S. standards, but not at lower levels. Studies of childhood pulmonary function in relation to sulfur oxides and particulates have shown less consistent results.

Ambient levels of nitrogen dioxide have been implicated in the potentiation of upper respiratory tract infection in children and their families. This is in contrast to sulfur oxides which, while clearly associated with lower respiratory tract bacterial illness, have not been consistently found to be associated with upper respiratory viral infections. Epidemiological evidence of a relationship between NOx and respiratory infection was noted in school children and their families in a study performed in Chattanooga (33). This took advantage of a relatively unique point source of nitrogen dioxide. Replication of this study, which is a major base of the U.S. air quality standard, would be of great value, but is difficult due to the entanglement of nitrogen dioxide with other pollutants in most areas. Recent studies demonstrating relatively high nitrogen dioxide levels in kitchens with gas as compared to electric stoves (34, 35) may provide a basis for re-evaluation of the epidemiological association of nitrogen dioxide with respiratory tract infection.

There is some controversy concerning the susceptibility of asthmatics to the gas-aerosol complex. Basic biomedical considerations lead to a strong suspicion that individuals with a hyperactive bronchoconstrictive response should be particularly sensitive to inhaled air contaminants. There are a number of epidemiological studies which appear to support this contention, as well as the recent controlled human study on NO2 and carbachol (11). The epidemiological studies are, however, open to various degrees of criticism which appear to reflect the fact that asthmatics are a particularly difficult group to study. It is difficult to obtain a large study population, and there are numerous confounding variables, particularly meteorological and seasonal factors, which complicate interpretation of the effects of air pollutants.

The retrospective observation that 87.6% of asthmatics reported respiratory symptoms during the Donora air pollution disaster (36), as compared to 42.7% of the general population, indicates that asthmatics do respond adversely to air pollution. The question at present, which is similar for other susceptible populations, is to what extent do current or foreseeable pollutant levels produce asthma attacks. Relatively low level effects were reported in the CHESS studies and in an EPA study performed in New Cumberland, West Virginia (37). The latter is one of the few U.S. studies of effects due to an uncontrolled coal-fired power plant. These studies have been heavily criticized, mainly on the basis of the data collection and analysis techniques which were used (38). At present, it would appear warranted to place a relatively wide error band around any extrapolation relating potentiation of asthma attacks to current or projected levels of stationary source fossil fuel combustion products.

It should be emphasized that asthma attacks represent an acute effect, and are therefore particularly significant during high short-term peak levels of pollutants. The causation of the basic underlying effect leading to classical allergic asthma does not appear to be related to chronic pollutant exposure. The relation of air pollution to asthma attacks has been the subject of a number of reviews (4, 39, 40).

Exacerbation of pre-existing cardiorespiratory disease has been clearly demonstrated to be a consequence of exposure to the gas-aerosol complex. Controlled animal and human exposure studies have suggested that bronchoconstriction is the basis for the observed acute effects. There may also be an element of pollutant-induced increased mucous production leading to worsening of disease, particularly in the chronic bronchitic.

Numerous epidemiological studies have focused on individuals with chronic pulmonary disease (chronic bronchitis, emphysema, and nomenclature variants thereof). Diary studies of this group (in Britain) readily demonstrated an association of worsening symptoms with short-term pollution.
levels. This has recently been less evident following institution of control measures leading to a marked abatement in particulate levels and lesser decreases in sulfur dioxide (29, 30, 41, 42).

Similar studies in the United States have produced somewhat contradictory results. For example, Burrows et al. (43), found little or no correlation of sulfur dioxide levels in Chicago with daily symptoms of patients with chronic respiratory disease, although Carnow et al. (44), using a similar, but somewhat more extensive approach in Chicago, reported that symptoms were related to sulfur dioxide levels extending down to the range of the current air quality standard. The CHESS program has utilized panels of elderly subjects, with and without chronic cardiopulmonary disease, to study daily pollution effects (32). While a positive correlation with current ambient sulfate levels was reported, the high dropout rate and other technical difficulties complicated interpretation of these results.

**Chronic Effects.** The bulk of the studies discussed above deal with the ability of the inhaled gas-aerosol complex to produce acute disease or an acceleration of an already existing chronic disorder. The present section focuses on the possibility that long-term inhalation of these pollutants may act to cause the production of chronic disease, particularly chronic respiratory disease. The potential impact of a role for air pollutants in the causation of chronic respiratory disease may perhaps be greater than that of acute disease. It is, however, a more difficult problem to study. Evaluation of day-to-day variations of pollutants in relation to health effects does not provide any direct information. Nor are usual prospective studies of value in a situation where it may require many decades of exposure for the development of measurable chronic damage.

Studies approaching this problem have generally utilized a geographic comparison in which the prevalence of chronic respiratory disease among a population in a polluted area is compared to the prevalence in a nonpolluted area. In order to make such a comparison successfully it is necessary that the populations in the study areas be as similar as possible in other respects. The major confounding variable in such studies is the extent of cigarette smoking, which is the most important causative factor in chronic respiratory disease. Other factors, particularly occupation, but also life style and social class, could conceivably play a role in the causation of chronic respiratory disease and should be evaluated in the study design.

Using such measures as death rates, reason for disability, and questionnaires concerning cough and sputum production, many studies have clearly demonstrated a higher prevalence of chronic respiratory disease in polluted areas. When originally studied in the 1950's, air pollution appeared to account for a substantial proportion of the total incidence and disability due to chronic bronchitis in Britain. A relation of air pollution to the prevalence of respiratory disease has also been noted in American and Canadian studies. The largest American study of this type was performed by CHESS in various parts of the country by use of a self-administered questionnaire (32). There was a reasonable consistent finding of a higher prevalence of chronic respiratory disease in the more polluted communities. This is among the least controversial of the CHESS findings. However, inasmuch as the observed effect presumably represents long-term exposure to air pollution, including the much higher levels of the past, the data cannot readily be used to estimate effects due to current ambient levels. It would be useful to analyze subsequent years of the CHESS studies to determine whether there was a decrease in the prevalence of chronic respiratory disease which parallels the previous fall in air pollution levels.

A study comparing the prevalence of histologically determined emphysema prevalence on autopsy subjects showed that the disease was three times as prevalent among nonsmokers in St. Louis as in Winnipeg, Canada (45). The variable used to explain the difference was fossil-fuel combustion product derived air pollution. No specific substances were correlated with the disease, rather only total emissions of SO₂, particulates, and NO₂.

There is the possibility that components of the gas-aerosol complex might play a causative role in the increased levels of lung cancer observed in urban areas. Bisulfite has been shown to be mutagenic in a number of systems, presumably by deaminating cytosine (46, 47). It is, however, questionable whether this reaction can occur at physiological pH. Tumor formation in animals exposed to sulfur dioxide has been reported, most notably in a study demonstrating higher levels of lung tumors in animals exposed to sulfur dioxide and benzpyrene as compared to benzpyrene alone (48). In conjunction with arsenic exposure, sulfur dioxide exposure appeared to increase the risk of lung cancer in smelter workers (49). Nitrogen oxides have also been suggested to be potential carcinogens, mainly based on reactions with other agents which might form nitrosamines which are known to be very potent carcinogens (50). Recent studies have demonstrated that these reactions can take place in polluted atmospheres, especially during the nighttime hours.

While further research concerning the possible mutagenic effects of components of the gas-aerosol
complex would be of interest, it is unlikely to provide information in the near future specifically applicable to human exposure.

Dose-Response Analyses

The estimation of human dose response to the gas-aerosol is an arcane art. The major difficulties are derived from the dose side of this equation. The most commonly measured pollutant, sulfur dioxide, is an indicator of varying reliability of the entire gas-aerosol complex. To complicate the problem, sulfur dioxide is also a major precursor of more toxic components and its own toxicity can vary depending on its combination with other pollutants. This multiple role for sulfur dioxide is the basis for the apparent discrepancy between epidemiological studies and controlled human and animal exposure experiments, the latter requiring much higher levels of sulfur dioxide in clean air in order to observe effects. The common methods of particulate measurement are also only indirectly related to those agents actually causing adverse effects. In addition, one must carefully disentangle the effects of other variables (e.g., cigarette smoking, weather, and occupation) from those due to pollution. There is accordingly an essentially inherent degree of uncertainty in the assigned dose for each level of response. There are also difficulties in the measurement of response, including adequate characterization of populations, the validity of measuring techniques, and the selection of subjects for study. These problems are compounded by the requirement for multiple points in the plotting of a dose-response curve.

There are a number of complex statistical techniques which have been developed or refined in recent years to handle the variables in individual studies and to formulate dose-response curves. There is, however, a crossover point at which the uncertainty caused by the multiplicity of pollutants and other variables is replaced by uncertainty about the validity of the complex statistical procedures used to disentangle these variables. Furthermore, there is no consensus in the scientific community concerning where this crossover point is located.

Dose-response information can be more simply derived from controlled human exposure experiments involving defined responses to measured doses. The major drawback of this approach, as is evident in the case of sulfur dioxide, is that the exposure does not replicate the complex mixture present in urban air. In addition, it is difficult to study the response of susceptible populations. Animal exposure experiments, although advantageous in other ways, suffer the same limitations with the added drawback of interspecies differences.

The above caveats should be kept in mind when considering the available literature concerning the effects of the gas-aerosol complex. Among the more frequently quoted studies is that of Lave and Seskin (51) who in 1970 estimated that a 50% production in all urban air pollution would result in a 25-50% decrement in the excess urban mortality and morbidity from bronchitis, 25% of lung cancers, 25% of respiratory disease, 10% of cardiovascular morbidity and mortality, as well as a 15% decrement in the overall prevalence rate. These figures have been utilized by a number of other authors as the basis for further calculations. It should be emphasized that the analysis refers to all air pollutants and is applicable to the increment of these effects observed in urban areas.

A frequently employed data set for extrapolating the effects of various levels of stationary source fossil fuel combustion products is derived from use of the CHESS studies (32). These studies have been the subject of much controversy, including a generally critical congressional review as well as frequent criticism by other researchers. The CHESS dose-response estimations were based on measured levels of atmospheric sulfates. As pointed out by the authors, they clearly represent a first approximation containing a large degree of uncertainty. It should be noted that the major reason for extrapolating a dose response curve from the original CHESS data was a need for making regulatory decisions based on presently available evidence. This remains true today.

Among the subsequent analyses, using the CHESS extrapolations, is a report by the National Academy of Science to the U.S. Senate Public Works Subcommittee (4) in which the impact of alternate fuel use strategies was evaluated. This includes estimates for the health impacts associated with individual plants depending on siting. A series of studies of a similar nature have been performed at Brookhaven National Laboratory including estimation of mortality due to coal utilization. The authors clearly indicate that their model is greatly simplified due to the lack of solid baseline data from which to calculate the health effects of coal combustion products. Specific criticisms of their approach include the use of a non-threshold model (based on Lave and Seskin) which employs an annual average pollutant dose to impute mortality rather than short-term peak levels; the lack of characterization of populations at risk; and assumed constant sulfur dioxide oxidation rates. In order to improve the validity of these predictive models it is necessary to develop more accurate dose-response functions based on appropriate averaging times for the pollutant dose. In addition, better means of predicting the levels of secondarily formed pollutants would be of value.
Summary of Issues

It does not appear possible to readily subdivide the issues concerning health effects of the gas-aerosol complex into those for which there is a consensus of opinion and those for which there exist uncertainties or controversy. There is no concrete borderline where reasonable men may or may not differ. Rather, there is a continuum ranging from questions for which the answer appears certain, to where there is disagreement as to even how to phrase the question. Following are a partial list of issues that appear pertinent to the problem of health effects due to the gas-aerosol complex. Inherent in such an exercise is the author's judgment concerning what are the issues of particular importance, what are the bounds of reasonable differences in interpretation of existing data, and which are the areas where further information, in the relatively near future, is likely to be of crucial importance.

Can the Gas-Aerosol Complex Derived from the Combustion of Coal Produce Acutely Harmful Effects in Man? The answer to this question is a definite yes. Past experience in the United States, Great Britain, and elsewhere, provides more than ample evidence that atmospheric sulfur oxides and particulates are causally related to adverse health effects. These include increased mortality, particularly during prolonged periods of atmospheric inversion. This situation affects mainly the very young, the old and the ill. Also included is an increased morbidity inclusive of exacerbation of preexisting cardiorespiratory disease and potentiation of lower respiratory tract infection, and, more than likely, the production of asthmatic attacks in susceptible individuals.

Can the Gas-Aerosol Complex Derived from the Combustion of Coal Produce Chronic Disease in Man? There is reasonably good evidence that long-term exposure to these pollutants can play a causative role in the production of chronic respiratory disease. Supporting this hypothesis is evidence indicating a higher prevalence of chronic respiratory disease in polluted areas that does not appear to be accounted for by differences in cigarette smoking rates, occupational exposure or other confounding variables. There are, however, differences of opinion concerning the interpretation of these data and it would not be unreasonable to state that the hypothesis is unproven. In the judgment of this author, the scientific evidence that long-term exposure to stationary source fossil fuel combustion products can be involved in the causation of chronic respiratory disease appears compelling. This assumption would also appear to be in keeping with a prudent public health point of view. There is far less evidence that nonorganic coal combustion products may cause cancer. Such a hypothesis is supported primarily by basic research indicating that derivatives of sulfur dioxide and nitrogen dioxide could produce mutagenic effects, and by epidemiological evidence indicating a higher incidence of lung cancer in urban areas. Much more research is required to assess the relation of the basic research findings concerning mutagenesis to human cancer. In respect to the epidemiological evidence, if it in fact reflects a causative role of air pollution in urban lung cancer, the evidence at present more strongly supports a role for organic fossil fuel combustion products.

To What Extent Does the Available Information Permit Accurate Prediction of the Adverse Health Consequences Due to Given Levels of Coal Combustion? There is ample historical evidence that ambient levels of stationary source fossil fuel combustion products have produced serious health effects in exposed populations. This is particularly true for situations in which there were relatively high pollutant concentrations. In recent years there has generally been a decrease in ambient levels of most of these pollutants, exclusive of nitrogen oxides whose emissions have continued to increase. The extent to which present ambient levels of the gas-aerosol complex produce adverse health consequences is a matter of controversy. Reasonable interpretations of the data range from no, or negligible, pollutant effects at present, to the position that any level of the gas-aerosol complex is capable of producing harm.

These widely differing interpretations reflect uncertainties concerning the validity of the existing data. As described above, there have been a number of dose-response estimations performed in recent years. They have been based for the most part on data developed by the CHESS program. This controversial program contains the most comprehensive attempt to establish the levels of measurable components of the gas-aerosol complex which produce adverse health effects. There are other studies which provide information useful for approximating a dose-response curve. These, however, are few in number and are derived from different countries, laboratories, scientific approaches, and circumstances. This greatly complicates the problems of extrapolation and leads to the necessity of assigning a relatively high degree of uncertainty to any derived dose-response curve. Accordingly, if the CHESS data are interpreted as being meaningless, one is left with a very wide range of possible interpretations, particularly concerning the effects of current ambient pollutant levels and those likely to be achieved with the proposed conversion of power plants to coal.

If the CHESS data are accepted as being pertinent,
there are then a number of analyses based on these data which can provide dose-response estimations useful for estimating health effects due to the gas-aerosol complex. One of the more extensive analyses is that of the Natural Academy of Science discussed above. It has the advantage of providing data for individual power plants located at various distances from urban populations. This author participated in the health effects aspects of the NAS analysis and estimated that a reasonable error-band for the dose-response curve for sulfate used in the computations ranged from an underestimation by a factor of two to an overestimation by a factor of 10. There appears to be no new information justifying a change in this conclusion.

It is also unlikely that any newly instituted research effort will provide information which will substantially change the boundaries of this analysis or the certainty of any prediction of dose-response before the anticipated switchover of utilities from oil and gas to coal. There is, however, every reason to begin such future studies as soon as possible, and preferably in conjunction with any fuel conversion efforts, so as to provide information pertinent to determining the extent to which further conversion affects air quality and public health.

There is one source of information pertinent to this problem which could be available within the near future. This is the remaining unanalyzed portions of the CHESS program. Only the first, and part of the second year of this five-year program have been completely analyzed. Many, although not all, of the criticisms of this program reflected problems inherent in the institution of a complex epidemiological study. Some of these were rectified in subsequent study years. If the findings in the latter years of the CHESS study replicate the initial findings, this would lend a great deal of credence to the derived dose-response formulations. The converse would also be true. Accordingly, a rapid and thorough analysis of the remaining CHESS data, preferably by those not intimately connected with the study or its criticism, could be of great value.

To What Extent Are Average Pollution Levels and Average Human Response Predictors of the Health Impact of the Gas-Aerosol Complex in a Population? It is misleading to consider average pollution levels and average response in the formulation of control strategies. There is a large degree of variability in the response of humans to air pollutants. In general, regulatory actions in this country have specified that the most sensitive groups should be protected. Accordingly, there is a particular need for information concerning the effect of the gas-aerosol complex on susceptible individuals. Information on this subject has been obtained in epidemiological studies, although this is very often complicated by problems in obtaining sufficient numbers of individuals for study and for appropriate control groups. Controlled human exposure studies of susceptible individuals have only rarely been performed. This is in part due to ethical considerations. Even when ethically appropriate, the performance of these studies is often hampered by the spectre of litigation which makes university review boards reluctant to permit such studies. Unless some answer to this problem is forthcoming, perhaps through federally guaranteed insurance, it is unlikely that information pertinent to the understanding of human variability will be attained in the near future.

Short-term peak pollutant levels are obviously most important in reference to causation of acute effects. It should be emphasized that prolonged meteorological inversions which have the capacity for developing highest pollution levels may occur at intervals of only every few years. Inasmuch as these episodes represent the greatest potential for acute effects, these infrequent occurrences should be considered as a major basis for determination of appropriate control strategies. Such an approach does not substantially differ from that of assignment of flood plain areas based on the concept of the "100 year flood."

What is the Relative Impact on Health of the Gas-Aerosol Mixture Present in the Local Area of a Power Plant Fueled by Coal, Compared to the Gas-Aerosol Mixture Present after Long-Range Transport of Power Plant Emissions? A number of processes act to modify the components of power plant emissions as they travel downwind. These are discussed in detail above. In general, the emitted gases are oxidized to acidic aerosols which appear to be of greater potential harm than the parent compounds. Presumably buffering substances, such as NH₃, are also added over time and these may alter the potential toxicity of the gas-aerosol complex. Obviously, dispersal of the plume over distance leads to a dilution in pollutant concentrations. In areas such as the Northeast, there may, however, be additive effects from multiple point sources.

The importance of this issue lies in its pertinence to decisions concerning which electric power plants should be converted from oil to coal. If, as has generally been assumed, the local effects predominate by virtue of higher concentrations, then clearly the extent of the adverse health impact of a given level of coal combustion would be proportional to the density of the local population. This effect would be magnified by the fact that existing air pollution levels tend to be highest in dense urban areas. Therefore,
by virtue of having both a larger number of susceptible individuals and higher baseline levels of air pollution, the larger American cities would appear to be most at risk from the proximal effects of converting utilities from oil to coal.

The more distant impact of emissions following long-term transport is pertinent to regional rather than local siting of coal-fired power plants. Two densely populated areas deserve special attention in this regard: the Northeast because of the high concentration of electric utilities and the prevailing wind pattern which tends to bring in power plant effluents from the Midwest and Southeast; and Southern California where coal combustion emissions would interact with an exceptionally active atmospheric photochemical process.

Very recently there has been a great deal of study characterizing both the short-range and long-range components of power plant effluents. These are exceptionally important investigations which, in conjunction with appropriate epidemiological and controlled human exposure studies, should provide the basis for understanding the potential local and distant impact of the gas-aerosol complexes derived from stationary source fossil fuel combustion. Most unfortunately, these extensive air monitoring programs are not accompanied by epidemiological studies. This lack of coordination of the national effort must be avoided in the future.

Are the Current Air Quality Standards for Sulfur Dioxide, Total Suspended Particulates, and Nitrogen Dioxide Adequate to Protect against the Health Consequences of the Gas-Aerosol Complex? These standards have been reviewed by a number of scientific panels in recent years. In general, there has been a consensus supporting no change in the present standards but noting the many uncertainties in the state of knowledge underlying the standards. The standards are recognized as being somewhat indirect measures of the totality of combustion products actually producing harm. There have thus been calls for research directed at providing a standard which more accurately reflects the gas-aerosol complex. Preliminary standards for sulfates have been adopted by a number of states. There is still, however, inadequate information concerning the toxicity of individual sulfates to permit a national standard to be set. For instance, there is some question as to whether the relatively high sulfate levels in Southern California may consist mostly of ammonium sulfate and, conceivably, have less of a toxic potential than the lower levels of sulfates in other areas of the country, which may be in the form of sulfuric acid aerosols.

Another type of uncertainty due to the somewhat indirect measures used for the air quality standards arises whenever the mixture of components in the gas-aerosol complex is altered. Inasmuch as these standards were based on past epidemiologic studies reflecting previous air mixtures, they may not be completely applicable to new circumstances. As an example, total suspended particulates include both respirable and nonrespirable sized particles. It is conceivable that a control measure which successfully removed only the larger particles might masquerade as an effective abatement procedure while in fact there would be no real change in the health effects on which the standard is based. Although the current standards are generally adequate and useful, these considerations indicate the need for further research into the components responsible for adverse health effects, and illustrate the importance of intelligent application of available information to air pollution control strategies.

With regard to nitrogen oxides, recent studies emphasizing the effects of peak NO₂ levels suggest the need for a short-term standard. Further information concerning the effects of nitric acid and suspended nitrates is required. These considerations pertaining to oxides of nitrogen are especially important, because of the expected continuing increase of NOₓ emissions, and the fact that presently existing coal-fired combustion sources cannot readily control NOₓ emissions, with the possible exception of fluidized bed combustion technology.

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REFERENCES

1. National Academy of Sciences. Airborne Particles. Subcommittee on Airborne Particles Committee on Medical and Biologic Effects of Environmental Pollutants, National Research Council, NAS, Washington, D.C., 1977.
2. National Academy of Sciences. Nitrogen Oxides. Committee on Medical and Biologic Effects of Environmental Pollutants, NAS, Washington, D.C., 1977.
3. National Academy of Sciences. Sulfur Oxides. Committee on Sulfur Oxides, NAS, Washington, D.C., 1978.
4. National Academy of Sciences. Air Quality and Stationary Source Emission Control. Committee on Public Works, United States Senate, Serial #94-4, U.S. Government Printing Office, Washington, D.C., 1975.
5. Lippman, M. Effects of short-term exposure sulfuric acid and ammonium sulfate. Am. Ind. Hyg. Assoc. J. 39: 275 (1978).
6. Larson, T. V., Covert, D. S., Frank, R., and Charlson, R. J. Ammonia in the human airways: neutralization of inspired acid sulfate aerosols. Science 197: 161 (1977).
7. Ehrlich, R. Effect of nitrogen dioxide on resistance to respiratory infection. Bacteriol. Rev. 30: 604 (1966).
8. Goldstein, E., Lippert, W., and Warshauer, D. Pulmonary alveolar macrophage. Defender against bacterial infection of the lung. J. Clin. Invest. 54: 519 (1974).
9. Amdur, M. O. Aerosols formed by oxidation of sulfur dioxide. Review of their toxicology. Arch. Environ. Health 23: 459 (1971).
10. Charles, J. M., and Menzel, D. B. Ammonium and sulfate ion release of histamine from lung fragments. Arch. Environ. Health 30: 314 (1975).
11. Oremek, J., Gayrard, P., and Grimaud, C. Effet d'une exposition brève à de faibles doses de NO2 sur la sensibilité bronchique de sujets asthmatiques. Lille Med. 21: 646 (1976).
12. Lewis, T. R., Moorman, W. J., Ludmann, W. F., and Campbell, K. I. Toxicity of long-term exposure to oxides of sulfur. Arch. Environ. Health 26: 16 (1973).
13. Alarie, Y., et al. Long-term exposure to sulfur dioxide, sulfuric acid mist, fly ash, and their mixtures. Results of studies in monkeys and guinea pigs. Arch. Environ. Health 30: 254 (1975).
14. Amdur, M. O. The long road from Donora. 1974 Cummings Memorial Lecture. Amer. Ind. Hyg. Assoc. J. 35: 589 (1974).
15. McJilton, C., Frank, R., and Charlson, R. Role of relative humidity in the synergistic effect of a sulfur dioxide-aerosol mixture on the lung. Science 182: 503 (1973).
16. Glasser, M., and Greenburg, L. Air pollution, mortality, and weather. New York City, 1960-1964. Arch. Environ. Health 22: 334 (1971).
17. Hodgson, T. A., Jr. Short-term effects of air pollution on mortality in New York City. Environ. Sci. Technol. 4: 589 (1970).
18. Lebowitz, M. D., and Fairchild, F. A. The effects of sulfur dioxide and As influenza virus in pneumonia and weight reduction in mice. An analysis of stimulus-response relationships. Chem. Biol. Interact. 7: 317 (1973).
19. Schimmel, H., and Greenburg, L. A study of the relation of pollutants to mortality. New York City, 1963-1968. J. Amer. Pollut. Control Assoc. 22: 607 (1972).
20. Buechley, R. W., Rigan, W. B., Hassellblad, V., and Van Bruggen, J. B. SO2 levels and perturbations in mortality. A study in the New York-New Jersey metropolis. Arch. Environ. Health 27: 134 (1973).
21. Schimmel, H., and Murawski, T. J. SO2 — Harmful pollutant or air quality indicator? J. Air Pollut. Control Assoc. 25: 739 (1975).
22. American Academy of Pediatrics, Committee on Environmental Hazards Pediatric aspects of air pollution. Pediatrics 46: 637 (1970).
23. Wehrle, P. F., and Hammer, D. I. Summary Report: Illness of Children. Presented at American Medical Association Air Pollution Medical Research Conference, San Francisco, California, December 5-6, 1974.
24. Colley, J. R. T., and Reid, D. D. Urban and social origins of childhood bronchitis in England and Wales. Brit. Med. J. 2: 213 (1970).
25. Douglas, J. W. B., and Waller, R. W. Air pollution and respiratory infection in children. Brit. J. Prev. Soc. Med. 20: 1 (1966).
26. Holland, W. W., Halil, T., Bennett, A. E., and Elliott, A. Factors influencing the onset of chronic respiratory disease. Brit. Med. J. 2: 205 (1969).
27. Lunn, J. E., Knowelden, J., and Handyside, A. J. Patterns of respiratory illness in Sheffield infant schoolchildren. Brit. J. Prev. Med. 21: 7 (1967).
28. Lunn, J. E., Knowelden, J., and Roe, J. W. Patterns of respiratory illness in Sheffield junior schoolchildren. A follow-up study. Brit. J. Prev. Soc. Med. 24: 223 (1970).
29. Emerson, P. A. Air pollution, atmospheric conditions and chronic airway obstruction. J. Occup. Med. 14: 635 (1973).
30. Lawther, P. J., Waller, R. E., and Henderson, M. Air pollution and exacerbations of bronchitis. Thorax 25: 525 (1970).
31. Ferris, B. G., Jr., Higgins, I. T. T., Higgins, M. W., and Peters, J. Chronic nonspecific respiratory disease in Berlin, New Hampshire, 1961 to 1967. A follow-up study. Am. Rev. Respir. Dis. 107: 110 (1973).
32. U.S. Environmental Protection Agency, Office of Research and Development. Health Consequences of Sulfur Oxides: A Report from CHESS, 1970-1971. EPA-750/1-74-004. pp. 428. U.S. Government Printing Office, Wash. D.C. (1974).
33. Shy, C. M., Creasen, J. P., Pearlman, M. E., McClain, K. E., Benson, F. B., and Young, M. M. The Chattanooga school children study: Effects of community exposure to nitrogen dioxide. II. Incidence of acute respiratory illness. J. Air Pollut. Control Assoc. 20: 582 (1970).
34. Palmes, E. D., Tomczyk, C., and DiMattio, J. Average NO2 concentrations in dwellings with gas or electric stoves. Atmos. Environ. 11: 869 (1977).
35. Melia, R. J. W., et al. Differences in NO2 levels in kitchens with gas or electric cookers. Atmos. Environ. 12: 1379 (1978).
36. Ciocco, A., and Thompson, D. J. A follow-up of Donora ten years after: Methodology and findings. Am. J. Pub. Health 51: 155 (1961).
37. Cohen, A. A., Bromberg, S., Bueckley, R. W., Heidenscheit, L. T., and Shy, C. M. Asthma and air pollution from a coal-fueled power plant. Am. J. Pub. Health 62: 1181 (1972).
38. Electric Power Research Institute. Evaluation of CHESS: New York asthma data 1970-71. Vol. 1, May (1977).
39. Zweiman, B., Slavin, R. G., Feinberg, R. J., Falliers, C. J., and Aaron, T. H. Effects of air pollution on asthma: A review. J. Allergy Clin. Immunol. 50: 305 (1972).
40. Thomas, O. C., and McGovern, J. P. Air pollution and respiratory allergic disease. Southern Med. J. 65: 1453 (1971).
41. Fletcher, C. M., et al. A five-year prospective field study of early obstructive airway disease, pp. 249-252. In: Current Research in Chronic Respiratory Disease. (Proceedings, Eleventh Aspen Emphysema Conference, Aspen, Colorado, June 12-15, 1968), U.S. Department of Health, Education, and Welfare, Public Health Service, Publication No. 1879, U.S. Government Printing Office, Washington, D.C., 1979.
42. Howard, P. The changing face of chronic bronchitis with airways obstruction. Brit. Med. J. 00: 89 April 13, 1974.
43. Burrows, B., Kellog, A. L., and Buskey, J. Relationship of symptoms of chronic bronchitis and emphysema to weather and air pollution. Arch. Environ. Health 16: 406 (1968).
44. Carnow, B. W., Lapper, M. H., Shekelle, R. B., and Stamler, J. Chicago air pollution study. SO2 levels and acute illness in patients with chronic bronchopulmonary disease. Arch. Environ. Health 18: 768 (1969).
45. Zeidberg, L. D., Prindle, R. A., and Landau, E. The Nashville air pollution study. III. Morbidity in relation to air pollution. Am. J. Public Health 54: 85 (1964).
46. Mukai, F., Hawryluck, I., and Shapiro, R. The mutagenic specificity of sodium bisulfite. Biochem. Biophys. Res. Commun. 39: 983 (1970).
47. Shapiro, R., Servis, R. E., and Welcher, M. Reactions of uracil and cytosine derivatives with sodium bisulfite. A specific deamination method. J. Am. Chem. Soc. 92: 422 (1970).
48. Laskin, S., Kuschner, M., and Drew, R. T. Studies in pulmonary carcinogenesis. In: Inhalation Carcinogenesis (AEC Symp. Series 18), M. G. Hanna, J. P. Nettesheim, and J. R. Gilbert, Eds. U.S. Atomic Energy Commission Division of Technical Information, Oak Ridge, Tenn., 0000, pp. 321-350.
49. Lee, A. M., and Fraumeni, J. F. Jr., Arsenic and respiratory cancer in man: An occupational study. J. Nat. Cancer Inst. 42: 1045 (1969).
50. Fishbein, L. Atmospheric mutagens. I. Sulfur oxides and nitrogen oxides. Mutat. Res. 32: 309 (1976).
51. Lave, L. B., and Seskin, E. P. Air pollution and human health. The quantitative effect, with an estimate of the dollar benefit of pollution abatement is considered. Science 169: 723 (1970).