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Epidemiologic Basis for Photochemical Oxidant Standard

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The problem of photochemical oxidant pollution, 98% of which is ozone, is addressed. Ozone itself is not the cause of all adverse effects (e.g., peroxyacetyl nitrites cause eye irritation). The typical sequence in the development of oxidant pollution is an initial increase in nitrous oxide, followed by nitrogen dioxide, followed by ozone. These pollutants can be carried long distances and may have long range effects. Ozone is considered by far the most irritant gas to humans, with effects seen even at extremely low concentrations. Dr. Bates reviewed the initial results of a study of hospitalization in the Niagara Peninsula of Ontario as it related to hourly pollution measurement, noting a relationship between elevated ozone and SO_2 levels and respiratory admissions within 24 hr during the summer months. This is an important preliminary finding, as EPA data indicate that nitrogen oxides are increasing while other pollutants are decreasing.

Introduction

This review will concentrate on environmental epidemiology and will refrain from detailed consideration of animal work in relation to ozone toxicity and review of the complex series of reactions which are now known to lie behind the formation of photochemical oxidants. However, I do wish to stress at the outset that, in my opinion, the animal work, which has indicated that concentrations of ozone as low as 0.1 ppm may interfere with the normal pulmonary defenses of the animal against inhaled pathogenic infection, necessarily has a major role to play in forming a judgment as to the possible hazard involved in breathing such concentrations. Also, I feel it important to stress that photochemical oxidant pollution has some unique features, one of which is that the main constituent, ozone, is not directly emitted, but formed secondarily from other chemicals. Also we now know that ozone may travel at low concentrations across large tracts of countryside. A recent article documents ozone being formed over the Ruhr; having hydrocarbons added to it as it traveled over Rotterdam; and finally causing the highest ambient ozone concentration ever recorded in the south of England. It finally went out over the Atlantic over North Wales (*1*). There are other carefully studied ozone trajectories. This means that populations may be exposed to ozone many miles away from the major source of the photochemical pollutants.

Most of the epidemiological data deal only with ozone, but as this constitutes about 95% of photochemical pollutants and as it is a very irritant gas, it is probably proper at this point of time to concentrate on ozone as the main focus of the standard setting process. What is now a considerable body of human exposure work generally confirms that adverse effects on pulmonary function are recorded in normal people under conditions of light exercise breathing 0.37 ppm of ozone (*2*). We know of no other irritant gas which causes a major disturbance of normal pulmonary function at concentrations as low as 0.000037%. Those responsible for standard setting have to be made aware of the fact that we are dealing, in this instance, with the most irritant gas we know.

Update of Epidemiologic Data

In April 1978, EPA produced its criteria document for ozone and other photochemical oxidants (*3*). This document contained 52 pages of assessment of the epidemiological evidence, and I do not intend to re-review all of this material. Instead, I will concentrate on some observations which are

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not made in that review, and then consider in more detail a number of papers which have appeared since that document was published, which would clearly have an impact on the standard setting process.

The first epidemiological study in relation to oxidant air pollution was that published by Schoettlin and Landau (*4*) in 1961. Although this is only a two-page paper, the study was actually done in the autumn of 1956. There has never been any explanation as to why there was a 5-yr delay between the observations being made and publication and why the publication itself was so short. This work showed that the difference between the mean number of asthmatic patients having attacks on days when the oxidant level exceeded 25 pphm, compared to the mean number of patients having attacks when oxidant was below this level, was significant. However, the authors could not show a multiple correlation between oxidant on a given day, and attacks on that day. This was followed by the much more extensive study of Sterling et al., published in 1966 (*5*), and by a substantial amount of other work reviewed in the epidemiological section of the EPA document.

In an EPA report dated June 1976, French et al. reported on the relationship between asthma attack rates and various pollutants in the Los Angeles region (*6*). For some reason this report was never published in the scientific literature, at least as far as I can determine. The study involved a total of 437 asthmatic patients, selected from hospital clinic records, and records of practicing physicians. Each prospective subject was interviewed by a trained interviewer to obtain information regarding the nature, frequency and severity of asthma attacks. Between April and December 1972, 218 patients were studied, and 219 studied from October 1972 to June 1973. The risk ratio of asthmatic attacks was related only to days with elevations of both sulfur dioxide and ozone. No relationship could be demonstrated to oxidants alone. In the same year, Kurata et al. (*7*) published a multifactorial study of the relationship between asthma attacks and air pollutants in the Los Angeles region. These authors concluded that an apparent elevation in number of attacks in asthmatics when the ozone exceeded 0.28 ppm was to be explained by the over-reporting of increased symptoms in a very small number of subjects. The authors concluded that their data did not indicate any strong association between air pollution and asthma, and they criticized other studies from the standpoint of data analysis when recorded symptoms formed the basis of the studies.

In 1977, Kahn (*8*) reported on a study of 80 asthmatic children in the Chicago area. He concluded that weather and pollution were responsible for less than 15% of the variance of asthmatic attacks in these children, but the ozone air pollution data was incomplete. However, the author noted . . . "High O_3 levels were significantly correlated with an increased number of asthmatic attacks, the frequency and amount of medication taken for relief, and the severity." The data in the paper do not permit one to deduce the ozone levels which might be responsible for the increase in attacks. In 1979, Zagraniski et al. (*9*) reported on two groups of subjects studied in New Haven, Connecticut. One group was drawn from telephone company employees, and the other group was from an allergy and asthma clinic. Daily symptom rates were related to the 8-hr meteorological and air pollutant data. These authors did not find any evidence that suspended sulfates were associated significantly with acute adverse health effects, but the photochemical oxidant levels, which ranged up to 0.142 ppm over an 8-hr period, were associated with increasing symptoms. The associations were not stronger than significant at the 5% level, and the authors noted that the level of association between oxidants and adverse health effects was lower than that in the Los Angeles student nurse studies reported in 1974 by Hammer et al. (*10*).

In 1980, Whittemore and Korn (*11*) published a detailed study of the relationship between asthmatic attacks, and oxidants, total suspended particulates and meteorological conditions, in the communities of Santa Monica, Anaheim, Glendora, Thousand Oaks, Garden Grove and Covena, all in the Los Angeles region. Sixteen panels of asthmatics were studied during the years 1972-1975. The criteria for selection of the subjects were carefully described, and air pollution data for the communities were analyzed in detail. The association of increased asthmatic attacks with oxidant levels permitted the authors to compute a risk rate for asthmatic attacks. This showed that when oxidant was increased to about 0.1 ppm, the relative risk was increased from 1 to 1.2, and when the oxidant was above 0.2 ppm, the relative risk rose to 1.4. By comparison, the relative risk ratio for particulates showed that when these rose above 200 $\mu g/m^3$, the relative risk of an asthmatic attack was increased to 1.2 from 1. Their data can also be analyzed to show that the highest significance of association was found in the community with the highest oxidant levels (Glendora). The rigorous nature of the statistical analysis leads one to suggest that this study can

probably be considered as more reliable than most of those which have preceeded it.

Deficiencies in Epidemiological Data

It is an important component of the scientific basis of standard setting to identify data which we know we should have for the standard setting process, but which does not exist. The enumeration of these missing data is not often attempted, but I may draw attention to some of the information which we may hope to secure in future years. The major aspects not yet fully addressed by the epidemiological data seem to me to be the following.

Since we do have some evidence from the experimental laboratory that exposure to ozone during the period of lung growth may influence certain aspects of lung development (*12*), it seems to me to be essential to be reassured that current oxidant levels to which young children are being exposed, are not having an adverse effect on lung growth and development. We have no reliable epidemiological data yet to answer this question.

A second but equally important question is whether long-term residence in ozone concentrations above ambient, produces any long-term changes in pulmonary function. The experimental laboratory has provided evidence that acute exposures to ozone on consecutive days are followed by a diminishing response in terms of bronchial constriction (*13*). But we do not know whether any price is paid for the "adaptation," nor do we know that repetitive exposures are without long-term consequences. This question is being addressed by current epidemiological studies, and it is to be hoped that in a few years we may be in a better position to provide an answer to it.

As noted earlier, the animal experimental data indicate that ozone may interfere with lung defenses against infections. So far, epidemiological studies have mainly dealt with an increase in asthmatic attacks, and we have no information as to whether the occurrence of viral or bacterial respiratory infections is related in any way to ozone exposure. This line of investigation is clearly indicated by the animal experimental data, but has not so far been pursued in detail.

Study of Oxidants in Southern Ontario

I have recently completed a review of the relationship between hospital admissions and pollution levels in Southern Ontario (*14*), and I would like to comment briefly on this, since it illustrates the difficulties of using epidemiological data for standard setting purposes. We have reviewed the admissions data for a group of patients with respiratory disease, including all pneumonias and asthma, from 79 acute care hospitals between Windsor and Peterborough, Ontario. This is a corridor about 250 miles long in which 5.7 million people live. There are approximately 2400 hospital admissions a day, of which approximately 40 are for respiratory conditions in the summer and 70 in the winter. We have air pollution data from 15 sampling stations in this region for the months of January and February, and July and August, for 1974, 1976, 1977 and 1978. It has been known for some time that waves of ozone formed from the large nitrogen dioxide emissions in the midwest of the United States, pass from southwest to northeast across this region during the summer. Concomitant SO_2 concentrations tend to be somewhat higher at the western end of the region than at the eastern end. Ozone levels over the whole period of the study were never higher than 0.17 ppm as an hourly maximum, and were generally much lower than this. We found a highly significant association ($p < 0.1\%$) between the respiratory admissions and ozone levels above 0.06 ppm when averaged as the average daily maxima across all 15 stations. Certain marker conditions such as cerebral hemorrhage showed no relationship to air pollution. There was also an association between respiratory admissions and SO_2 levels, and a slight association with summer temperatures above +22°C.

Although we have not yet completed our analysis, it seems fair to conclude that the strong association with pollution levels can be interpreted to mean that existing air pollution levels in this region are already responsible for increases in hospital morbidity. We do not yet know which age groups are particularly affected, nor whether the effect is in relation to respiratory infections as well as asthma, but future analysis will throw light on these questions. The major relationship exists in summer, when the ozone levels are high enough to reach the criterion which we established to trace the association.

It will be important to confirm that in succeeding years the relationship continues to hold. We anticipate that the study will be stronger than it is at the moment when the data for 1979 and 1980 have been added to it. Because of the large geographic area involved, it is not possible to make any precise estimate of the relationship between the increased hospital admissions and specific pollutant levels, except in a very general sense. I

do not intend to discuss this study in detail until it has been fully published in a refereed scientific journal (in accordance with the normal traditions of standard setting discussions), but I intend to use my experience with this study to draw some conclusions.

Conclusions

It seems obvious that there is no substitute for epidemiologic studies of human morbidity as part of the standard setting process. If one regards the setting of a standard as the enunciation of a scientific hypothesis (which I think is a perfectly permissible way to look at standard setting), then attempts to prove the hypothesis false are very necessary. The major difficulty is getting a precise indication of the significant levels of different pollutants. The reasons for this are the following.

Without personal dosimetry, which in the case of many pollutants such as ozone is impossible, there will always be ambiguity in relation to level of exposure and effect.

An additional difficulty is the necessity of studying very large populations if one is concerned with variations in hospital admission rate for respiratory diseases. To deduce the significant variance around a number much less than 40 per day is difficult; on the basis of our study this seems to necessitate a population in excess of 5 million people in the study group. This fact also leads to uncertainty in relation to pollutant exposure level since the geographical area is likely to be extensive to permit one to study such a large population.

A third factor is the possible effect of combinations of pollutants. In the case of ozone, there is evidence which is somewhat conflicting, that ozone and SO_2 may be particularly irritant (*15*). This means that it may be difficult to arrive at a conclusion as to precise combinations of pollutants which are driving the variations in hospital morbidity.

Epidemiologic studies based on an attack rate of asthmatic attacks are never easy to interpret, unless some individual has seen such a patient when the situation is alleged to be worse. In this respect at least, a hospital admission requires a decision by a physician that the patient should be managed in a hospital setting, and this, therefore, is stronger evidence of effect than are symptoms noted by the patient.

The Japanese symptomatology data in respect to ozone has been well summarized elsewhere (*3*), but there is interpretational difficulty in respect to the reporting of symptoms as between different populations with different backgrounds.

Field epidemiological studies, which actually measure pulmonary function on a continuing basis, no doubt provide a sharper basis of comparison, but these also have their interpretation problems. The standardization of equipment and the continuing reliability of observations over periods of years make this type of study difficult to organize and also extremely expensive.

Having in mind these reservations, I would like to conclude by noting what to me seem to be the present circumstances in respect of epidemiological data and the standard for ozone, which was recently changed in the United States from 0.08 ppm as an hourly maximum to 0.12 ppm. No doubt this decision was necessary for economic purposes, but those responsible for the standard should be made fully aware of the following circumstances: (1) A standard of 0.12 ppm in the light of present epidemiological data is without a safety margin in respect of aggravation of asthmatic attacks in the general population. (2) We do not yet know whether such an oxidant level produces increasing morbidity on its own, or whether it is this level in the presence of other pollutants which is important. The possibility of such interaction would normally lead one to build in a larger safety factor in the case of ozone. (3) We lack important epidemiological evidence on the possible long-term effects on the lung and, most particularly, on whether the experimental evidence of effect during lung development should indicate to us the importance of restricting ozone exposure during the first nine years of life. The existence of this possibility should lead to a larger safety factor being adopted than would be the case simply in relation to the data concerning adult morbidity.

Epidemiologic data are ideal for telling us whether or not existing levels of pollutants are or are not having any impact on human morbidity. It seems to be clear from the existing evidence that the epidemiologic information we now have on photochemical pollutants shows that this is the case. Epidemiologic evidence is much less satisfactory in providing a guideline for the levels of pollutants which are dangerous, and also for combinations of pollutants which may be important in determining effects. In the light of all the information we have, however, it seems quite clear to me that there is a smaller safety factor built in to the present photochemical standard, than for any other pollutant to which the public is currently exposed.

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