Examining Acute Health Outcomes Due to Ozone Exposure and Their Subsequent Relationship to Chronic Disease Outcomes

Bart D. Ostro

Air Pollution Epidemiology Unit, California Office of Environmental Health Hazard Assessment, Berkeley Way, Annex 11, Berkeley, CA 94704

Current evidence indicates that individuals exposed to short term elevations in ambient ozone may experience both upper and lower respiratory effects. Some respiratory symptoms and spirometric changes are mild and reversible in nature, while others involve more severe outcomes, including hospital admissions and emergency room visits. However, many questions remain about the effects of acute ozone exposure and the implications of this exposure for chronic disease outcomes. For example, the identification of sensitive subgroups, the delineation of the entire spectrum of health effects due to exposure to ozone, the potential synergy between viral infections and ozone exposure, and the nature of adaptation to ozone are not well characterized. In addition, studies that examine the association between acute responses to ozone and potential biological indicators of a chronic disease process would be desirable. This paper serves to provide an overview of the types of epidemiologic studies that may be appropriate and factors to consider in addressing these questions. — Environ Health Perspect 101(Suppl 4):213-216 (1993).

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Introduction

Previous epidemiologic and field studies have examined the effects of ozone on several different acute health outcomes, including incidence of asthma attacks, hospital admissions, emergency room visits, cough and other respiratory symptoms, changes in lung function, and decreased exercise performance. Controlled chamber studies of exercising adults have recorded the occurrence of respiratory symptoms, spirometric changes, and effects on bronchial reactivity of 1, 2 or 7 hr ozone exposures. Taken together, such studies indicate that individuals experience both upper and lower respiratory symptoms, apparently of a mild and reversible nature, in response to current ambient levels of ozone. However, at this time, many questions remain about the health effects of acute ozone exposure. For example, the existence of a sensitive subpopulation, the role of respiratory infection prior to exposure, the effects of ozone on allergic response, the interactions between ozone and other pollutants or aeroallergens, the relevant averaging time for ozone exposure, the relationship between exposure and response, the lowest level at which effects are observed, and the role of averting behavior all are not well characterized at this time. In addressing these uncertainties, several factors need to be considered, including: a) How representative are the groups that have been and are being studied in relation to the general population? b) What acute health outcomes should be examined? c) Which acute health outcomes, if any, indicate the existence of a chronic disease process? d) What is the nature of adaptation to ozone exposures over time? e) How should ozone dose be measured to better represent actual exposures? f) What confounders and effect modifiers need to be incorporated into any analysis of ozone effects? and g) What study design is most appropriate for examining the acute effect of ozone?

This paper provides an overview of the types of epidemiologic studies that may be useful and factors to consider when addressing these questions. It begins with a brief survey of previous epidemiologic studies of the acute effects of ozone.

Previous Epidemiologic Studies

Existing epidemiologic studies provide an incomplete picture of the acute health effects of ozone. To date, panel studies, which incorporate both cross-sectional and time-series components, have focused on selected groups that include asthmatics and female student nurses in Los Angeles. Studies of asthmatics (1,2) suggest that moderate levels of air pollution, including ozone, result in an increase in the exacerbation of asthma. However, these studies can examine the response for only a small subset of asthmatics. In addition, questions about the role of medication, exercise, averting behavior, indoor exposures, and viral infections remain. Also, in these studies, asthmatics who reported only a small number of symptoms during the survey period were dropped from the sample because of the statistical methods employed (i.e., individual-level logistics would not reach convergence). Studies of female nurses in Los Angeles (3-5) explored the relationship of daily oxidant (rather than ozone) concentrations to daily symptoms that included cough, chest discomfort, sore throat, and eye irritation. These studies suggest that eye irritation, cough, and chest discomfort are related to daily exposure to oxidants.

Evidence of morbidity from acute ozone exposure also is provided from studies of hospital admissions. For example, in southern Ontario, Canada, Bates and Szeto (6) reported a relationship between hospital admissions and higher concentrations of the existing “summer haze” consisting of ozone and sulfur compounds. Because of high covariance among the various pollutants, however, it is difficult to determine the extent of an independent effect of ozone. Wayne and Wehrle (7) showed that high oxidant (and particulate matter) levels were associated with decreased athletic performance among high school students in Los Angeles.

Analysis of large, cross-sectional datasets also provides some evidence of acute health effects of ozone exposure. For
example, analyses of the National Health Interview Survey, an individual-level survey of 50,000 households conducted by the National Center for Health Statistics, suggest an association between ozone and respiratory symptoms causing minor restrictions in activity (8, 9).

Several field studies have examined the impact on lung function of daily ozone exposure. Study groups have included children in summer camps in New Jersey and in the San Bernardino mountains of California (10–12), and healthy, exercising, nonsmoking adults in New York (13). These studies indicate a dose-dependent relationship between ozone and lung function parameters, including FEV₁ and peak flow. However, the implications of these small changes in lung function for either acute symptoms or chronic respiratory effects are uncertain. Of note, the measured changes in pulmonary function were greater than those predicted from comparable levels of ozone administered in controlled chamber studies, suggesting that chamber studies do not accurately represent effects of the mix of exposures experienced by the general public.

Representativeness of Previous Findings

It is uncertain whether the existence and magnitude of these same acute health effects related to air pollution can also be expected to occur for the population as a whole. For example, it is unclear whether the effects exist only for those people receiving a high effective dose of ozone (ozone concentration x duration of exposure x ventilation rate), such as children at play or adults vigorously exercising, or for people who may be particularly vigilant about reporting changes in health status (i.e., student nurses or asthmatics). To date, epidemiologic studies have used 1-hr maximum concentrations of ozone as the averaging time; no study has examined, for example, the impact of 7-hr daily averages of ozone. Mismeasurement of exposure would result in lower detection of an effect of air pollution. Thus, current evidence does not clearly indicate the entire range and severity of effects and whether they are related to exposure to ozone alone or to a more complex mix of pollutants. While setting ambient air quality standards requires only the determination of concentrations that cause effects in a subpopulation, comprehensive policy analysis necessitates an understanding of the true scope of the health and economic impacts of air pollution.

Measures of Acute Effects

Given the uncertainties cited above, additional studies of acute exposure experienced by the general population are warranted. The full spectrum of potential health outcomes should be explored, from relatively minor and reversible outcomes, such as respiratory irritation and pulmonary function changes, to exacerbations of existing chronic respiratory disease, incidence and duration of respiratory infections, physician and hospital visits, and mortality. If pulmonary function changes are utilized as an end point, their relevance to acute symptoms and chronic outcomes should be explored.

In examining the effects of ozone, it would be particularly useful to consider the coherence (i.e., the joint occurrence) of multiple health end points within or across sample sites. The observance of a continuum of effects would lend credibility to the epidemiologic approach and findings. Thus, if an association between ozone exposure and emergency room visits is found, one should also be able to detect, under similar ambient conditions, an association between ozone exposure and less severe outcomes. Such an examination would involve, for example, the collection of individual-level data on symptoms along with group-level data on hospital admissions and emergency room visits within a given catchment area. Another option would be to recruit individuals making respiratory-related emergency room visits for a subsequent study of acute respiratory symptoms.

Relating Acute and Chronic Effects

Because of the difficulties inherent in conducting long-term epidemiologic studies, few studies have attempted to relate chronic exposure to ozone to subsequent health effects. Some studies compare two or three different cities and statistically relate the differences in respiratory symptoms or pulmonary function to the general ambient air pollution levels observed in those cities (14). These cross-sectional studies typically suffer from several shortcomings, including imprecise or unmeasured pollution exposure during and prior to the study and the lack of information on commuting patterns, income and education, health habits and practices, and averaging behavior. Nevertheless, the findings of these studies suggest that the development of chronic disease may be associated with long-term exposure to ozone.

An understanding of the implications of acute health outcomes and exposures for the development of chronic disease continues to be of particular importance. Animal studies indicate that ozone exposure may result in increased fibroblast or collagen in the lung, which may indicate a chronic disease process. Devlin (15) presents a more complete discussion of the status and use of various indicators of chronic disease. Study designs that examine the link between acute exposures and biological markers of chronic disease would be an important contribution to the understanding of the effects of ozone. Such a study would investigate the extent to which biochemical changes indicative of a chronic disease process are associated with changes in lung function, airway reactivity, or symptomatology in a cohort of individuals exposed to a mix of pollutants including ozone.

Research by Ostro et al. (16) demonstrated that a quantitative relationship exists between changes in FEV₁ and reports of both mild and moderate lower respiratory symptoms. Ideally, associations between these acute health end points and assays that indicate lung damage could also be examined with respect to the potential for chronic disease. This effort could be part of a general study linking ozone to acute respiratory effects among, for example, a panel of healthy individuals. Individual-level regression analysis could be used to differentiate levels of response to ozone. This would facilitate subsequent comparisons of those individuals who are most responsive to ozone with those who have little or no response. Between these two distinct groups, it may be easier to differentiate biochemical indicators that are believed to be indicators of a chronic disease process. Investigators could examine the length and level of ozone exposure necessary (if it relates at all) before biochemical signs of chronic disease occur. This may entail simultaneous long-term cohort studies in parts of the county experiencing different patterns of peak and long-term ozone concentrations.

Adaptation

Another issue that deserves consideration within the context of epidemiologic studies of acute health effects is that of adaptation. Some clinical studies indicate that repeated daily exposures to ozone cause reduced functional and symptomatic responses (17). However, this has not been examined epidemiologically, particularly among individuals with moderate or severe preexisting respiratory disease. Also, there is uncertainty about the duration of the attenuation after
whether the inflammatory process continues in human lungs even with adaptation.

From a study design perspective, the examination of adaptation may necessitate repeated administrations of a survey instrument and physical measurements within and across seasons at the same and possibly other locations. Adaptation can also be explored by focusing on certain periods within the ozone season (e.g., during consecutive high ozone days, after a one day spike at the beginning and the end of the season, etc.) and examining the severity of response during these times. By considering different locations and seasons, researchers could begin to determine the differential impact of peak versus longer term cumulative ozone exposure on adaptation. It would also be of interest to test for a difference in acute response among a group that has lived in a polluted area over a long period of time and a group that has a long residential history in a relatively low pollution area.

**Exposure**

Readings from fixed-site monitors should be adjusted, to the best extent possible, to refine exposure estimates by including factors such as study participants’ time spent outside; use of air conditioning; and the time, location, and intensity of exercise or other heavy exertion. Until now, few epidemiologic studies have collected or used such information to improve the measurement of exposure. It would be useful to know which, if any, of these factors actually make a difference in the estimated pollution effect. For example, it may be more effective to have broad indicators about the time, location, and level of exercise for a 3- to 6-month period than very detailed (e.g., every 15 min) time-activity diaries for only short periods of time. Likewise, it may be sufficient to have information on simply whether a gas stove or air conditioner was used on a given day (or even if one is in the house) rather than exactly when and how long these appliances were used and the precise location of the survey respondents. The less detailed questions will facilitate longer study periods and perhaps larger sample sizes. With this information, subsequent research efforts could make better use of survey resources, and could improve and streamline survey instruments.

An additional issue relating to ozone exposure is the appropriate length of the averaging time. Because the acute toxicity of ozone appears to be dose-related and because people spend more time outdoors on the sunny days that favor ozone formation, it has been proposed that the ambient air quality standard for ozone incorporate a longer averaging time (18). Several studies indicate that exposures of 7 hr at concentrations as low as 0.08 ppm ozone elicit respiratory symptoms and significant decrements in pulmonary function (19,20). Therefore, measurement of ozone concentrations as both 1-hr daily maximum and longer-term daily averages, especially in areas where these measures are not highly correlated (i.e., where there is a large peak to mean ratio), would be useful.

**Confounders and Effect Modifiers**

Survey research methods for collection of relevant data should be developed to account for such potential confounders or effect modifiers as temperature and humidity, active and passive smoking, and use of gas stoves and air conditioners. In evaluating ozone effects, it is important to collect and evaluate data on pollen and on other ambient pollutants including, but not limited to, fine and inhalable particulates, sulfates, nitrates, and acidic aerosols. Because of high correlation among these pollutants at certain locations during certain seasons, it may be necessary to examine multiple sites or conduct repeated sampling at a given site to ascertain the impacts of individual pollutants.

Recent clinical evidence indicates that prior exposure to ozone enhances the subsequent response to sulfur dioxide (21) and may increase sensitivity to aeroallergens (22). Therefore, exposure information on other ambient pollutants and aeroallergens on days prior to and subsequent to the ozone exposure should be explored and developed. Seasonal influences can be minimized by careful selection of criteria in the study design. This may necessitate either the completion of the study within a given season across many different sites or the continuation of a study into several different seasons within a given study site. For study samples with known disease and high health awareness (e.g., asthmatics), it also may be important to identify behavior that is adopted to avoid effects from exposure to pollution or other potential irritants (i.e., averting behavior). This may include data on medication, changes in exercise or activity, reduction in the amount of time spent outdoors, or the use of filters or air conditioning. Likewise, it would be useful to collect and use information on study participants’ respiratory infections. This would facilitate a test of interactive effects with ozone, since various respiratory viruses cause prolonged bronchial hyperresponsiveness (23). Most chamber studies deliberately exclude individuals with respiratory infections. However, these individuals may be particularly vulnerable to the effects of air pollution.

**Study Design**

Research on acute effects should focus on study designs, such as the use of panel data, that minimize the potential for confounding and omitted variables. With panel data, the collection of health and exposure data for many individuals over time enables the use of analytical techniques where individuals serve as their own statistical controls. It would be useful to develop panels from one source when possible (e.g., one medical practice) to minimize reporting or demographic differences and differences in diagnostic and treatment patterns. In addition, the concurrent analysis of healthy individuals with those with chronic respiratory disease may be useful. Panel data can be used to explore changes on both an individual and group level. On an individual level, the panel can be used to examine the relationship between individual response rates to ozone (based on individual-level analysis) and other factors such as the existence and severity of disease, allergic status, the indoor environment, or the health awareness and practices. It would be useful to use multiple sites for this study design. This would aid in determining factors unique to each study population or location (e.g., pollen, allergies, weather, and pollutant mixtures) that may affect the baseline rate of disease and the response to air pollution as well as the reproducibility of the effect.

Despite administrative and subject recruitment costs, there are several distinct advantages to large-scale studies. For example, these studies have greater ability to detect an effect (i.e., statistical power) among a population if one truly exists. Also, with a larger and more heterogeneous sample comes the ability to stratify the sample and thereby enhance the likelihood of identifying sensitive subgroups, differential responses to air pollution, and interactive effects between air pollution and other risk factors. It may be useful to obtain and use more detailed data for a subset of the entire group to improve exposure estimates and determine the existence and degree of the effect of exposure misclassification.
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