# Effect of Ozone on Respiratory Responses in Subjects with Asthma

Jane Q. Koenig

Department of Environmental Health, University of Washington, Seattle, Washington

In the process of understanding the respiratory effects of individual air pollutants, it is useful to consider which populations seem to be most susceptible to the exposures. Ozone is the most ubiquitous air pollutant in the United States, and there is great interest in the extent of susceptibility to this air pollutant. This review presents evidence that individuals with asthma are more susceptible to adverse respiratory effects from ozone exposure than are nonasthmatic individuals under similar circumstances. In studies comparing patients with asthma to nonasthmatic subjects, research has shown increased pulmonary-function decrements, an increased frequency of bronchial hyperresponsiveness in ozone responders, increased signs of upper airway inflammation after ozone exposure, and an increased response to inhaled sulfur dioxide or allergen in the subjects with asthma. Subjects with asthma are indeed a population susceptible to the inhaled effects of ozone. These data need to be considered by regulators who are charged with setting air quality standards to protect even the most susceptible members of the population. They also underline the importance of strategies to reduce human exposure to ambient ozone. — Environ Health Perspect 103(Suppl 2):103–105 (1995)

Key words: ozone, lung function, asthma, susceptibility

## Introduction

Ozone is the most ubiquitous air pollutant in the United States. During 1989, over 66 million individuals lived in areas where the ozone concentration exceeds the National Ambient Air Quality Standard (NAAQS) set by the Environmental Protection Agency. During 1988, which included an abnormally hot summer, over 112 million people resided in areas not meeting the ozone NAAQS. Even more individuals live in nonattainment areas which track ozone data over 3 years. In 1992, 140 million people were estimated to live in ozone nonattainment areas (*1*). Two excellent reviews of the respiratory effects of ozone are available (*2,3*).

Careful dose–response relationships between ozone concentrations and durations of exposure in healthy subjects have shown that 10 to 20% of subjects are more sensitive than average (*4*) and that forced expiratory volume in one second ($FEV_1$) values continue to decrease with lengths of exposure up to 6 hr (*5*). Many studies have failed to show that asthmatic subjects are more sensitive to ozone than healthy subjects. However, careful scrutiny of the literature reveals at least five studies which indicate that asthmatics do show an increased sensitivity to ozone. Silverman (*6*) found consistent decreases in maximal expiratory flow rate in asthmatic subjects exposed to 0.25 ppm $O_3$ for 2 hr. Kreit and co-workers (*7*) reported greater pulmonary function changes in asthmatic subjects than in healthy subjects after exposure to 0.40 ppm $O_3$. (Peak concentrations of $O_3$ in Los Angeles are now in the range of 0.30–0.35 ppm.) Hackney and co-workers reported that more subjects who showed sensitivity to $O_3$ exposure had bronchial hyperresponsiveness (*8*). Additional evidence comes from a study by Aris et al. (*9*) who found that ozone-sensitive subjects had positive responses to a methacholine challenge, whereas matched ozone-insensitive subjects did not. Also, a recent study in our laboratory compared ozone exposures (0.120 and 0.240 ppm) in asthmatic and healthy subjects and found increased markers of inflammation in nasal lavage fluid only in the asthmatics (*10*). These studies will now be discussed in detail.

Silverman demonstrated that subjects with asthma have an exaggerated response to ozone (*6*). This study actually demonstrated an equally important point: within a population of asthmatic subjects there is a heterogeneous response to ozone. The subjects in her study were 17 nonsmoking subjects with asthma who ranged in age from 20 to 71 years (mean age = 41). Five of the subjects were male. They ranged in severity of asthma: 13 had positive skin prick tests, and 12 subjects were using inhaled bronchodilator medication. Each subject was exposed to filtered air or 0.25 ppm ozone for 2 hr while seated at rest in an environmental chamber. As a group, there was not a significant difference in pulmonary response to air or ozone. However, six of the subjects had a greater than 10% decrease in maximum flow rate at 50% of expired vital capacity ($V_{max50}$). In this group of six subjects, there was a mean reduction in $V_{max50}$ of 7% after air exposure and 22% after ozone exposure. Two hours after the end of exposure, mean $V_{max50}$ was still decreased by 30% from baseline values. Four of the six most reactive subjects experienced mild to moderately severe cough, shortness of breath, wheeze, and chest tightness after the ozone exposure. The other two subjects did not have these symptomatic responses. However, no relationship could be established between the response to ozone and clinical indicators of asthma. Therefore, from this study, we are left with the knowledge that some subjects with asthma are especially sensitive to ozone but that clinical tests were not predictive. Also, it is important to note that, since this study was carried out at rest, the effective dose of ozone was small in comparison to that in many studies using exercise protocols.

Hackney and co-workers (*8*) studied responses to ozone in adult subjects in the spring and in the summer in an attempt to understand the adaptive effect of ambient ozone concentrations and to explore the biological basis of individual differences in response to ozone. The subjects were studied over a 1 year period to determine whether individual reactivity persisted for periods of 1-year. Prior to entry into the

This is an updated and expanded version of an article that was presented at the Environmental and Occupational Health Sciences Institute Symposium on Ozone Air Quality and Health Effects held 27–29 May 1992 in Piscataway, New Jersey.

Address correspondence to Dr. Jane Q. Koenig, Department of Environmental Health, SC-34, University of Washington, Seattle, WA 98195. Telephone (206) 543-2026.

study, subjects were screened to determine their response to an ozone challenge. Fifty-nine subjects were screened; the 16 most ozone-reactive and the 16 least reactive were chosen for the study. The mean age was 27 years and the gender ratio was 5:8 females in the nonreactor group and 7:5 females in the reactor group. The exposure to air or 0.18 ppm ozone was carried out in an environmental chamber. The results showed an enhanced response to ozone in the spring (during low ambient ozone) compared to summer (high ozone season). However, individual responses were consistent across seasons. The authors' interpretation was that there was adaptation to ozone during the ozone season which mitigated the response seen in the laboratory. However, there also may have been some interaction between aggravation by pollen during the spring, which was responsible for the enhanced response. From the point of view of this review, the interesting fact is that the ozone-reactive subjects had a history of allergy, mild asthma, or previous evidence of sensitivity to ozone in a controlled laboratory setting. None of the nonreactive subjects had a history of respiratory allergic disease. We can conclude from this study that the subjects with asthma or a predisposition to asthma were significantly more reactive to inhaled ozone than a comparison group of subjects with no signs or symptoms of allergic disease.

A third study, which provides evidence that asthmatic subjects are hyperreactive to ozone, was reported by Kreit and co-workers (*7*). Nine subjects with asthma and nine healthy subjects participated in a study to compare their response to a 2-hr exposure to air or 0.4 ppm ozone in an environmental chamber. Exposure was carried out during intermittent exercise on a cycle ergometer. Subjects were classified as asthmatic if they had a history of chest tightness and wheezing and had been diagnosed as asthmatic by a physician. They also were required to have a positive response to a methacholine challenge test, defined as a 100% increase in baseline airway resistance ($R_{aw}$). The age range was 18 to 34 years in the group with asthma and 19 to 31 in the healthy group. In both groups there were five females and four males. Two of the subjects with asthma were using daily anti-asthma medications; four others used inhaled bronchodilators as needed. Ozone exposure was associated with significant changes in expiratory flow and volume measurements in both groups, although the decrements were greater in the asthmatics [e.g., an average 15% decrease in forced vital capacity (FVC) in asthmatics compared with a comparable 9% decrease in the healthy subjects]. Also, only the subjects with asthma showed a significant post-ozone increase in $R_{aw}$. The protocol for this study included a baseline and post exposure methacholine challenge test, and thus suffers from the potential confounding interaction of the provocation test and the ozone exposure. Nevertheless, this study offers evidence that subjects with asthma are more likely to have exaggerated pulmonary function changes after ozone exposure than are nonasthmatic subjects.

Aris and co-workers (*9*) designed a study to investigate the effects of sequential exposure to acidic fog and ozone on pulmonary function in healthy subjects. To enhance the chance of positive effects, the study design called for recruitment of ozone-sensitive subjects. Ozone sensitivity was determined by a 3- or 4-hr exposure to 0.2 ppm ozone with moderate exercise during 50 min of each hr. Ten ozone-sensitive subjects were chosen for the acidic fog study. Six were male and the age range was 23 to 31 years. The subjects all denied a history of respiratory disease and were not using bronchodilating or anti-inflammatory medications. However when challenged with methacholine, the ozone- sensitive subjects had a mean provocative methacholine concentration of $2.95 \pm 0.80$ mg/ml at which $R_{aw}$ increased by 100% ($PC_{100}$) compared with nonsensitive subjects whose mean $PC_{100}$ was $18.67 \pm 4.54$ mg/ml. These group methacholine responses were significantly different ($p = 0.005$). The authors state that previous studies in their laboratory have established a $PC_{100}$ of 4 mg/ml as the cutoff between normal airway reactivity and bronchial hyperreactivity. From this study, we can conclude that these particular ozone-sensitive subjects had bronchial hyperresponsiveness, which is often predictive of asthma. It cannot be judged whether they are subclinical asthmatics, nonasthmatics with enhanced bronchial reactivity from a previous bronchial irritation, or healthy subjects with a positive response to methacholine. Nevertheless, these interesting data suggest that the 10 to 20% of "healthy" subjects who show responses to ozone may, in fact, have underlying allergic disease which predisposes the bronchial airways to an irritative response to inhaled air pollutants.

A recent study from our laboratory investigated ozone exposures in asthmatics compared to nonasthmatics (*10*). The objective of this study was to determine whether exposure to ambient levels of ozone causes inflammatory or functional changes in the upper or lower airways of asthmatic and nonasthmatic individuals. Ten asthmatic and eight nonasthmatic subjects were exposed to clean air, 120 ppb, or 240 ppb ozone for 90 min during intermittent, moderate exercise using a head dome exposure system (Figure 1). Pulmonary and nasal function and nasal lavage were measured before and after exposure. Pulmonary function measurements included $FEV_1$, total respiratory resistance ($R_T$), FVC, and maximal flow at 50 and 75% of expired vital capacity. Cellular enzymes and biochemical mediators, as well as cell counts, were analyzed from the recovered nasal lavage fluid. No significant changes in pulmonary function or nasal work of breathing in either the asthmatics or nonasthmatic subjects were found. Significant increases in white blood cells from subjects with asthma were detected immediately after exposure to 240 ppb ozone and then again 24 hr after the exposure ($p < 0.05$), indicating a possible biphasic inflammatory response to ambient levels of ozone inhalation. In these subjects, there was also a significant increase in epithelial cells immediately after the exposure ($p < 0.05$). No significant cellular changes were seen in the nonasthmatic subjects. Individual changes in interleukin-8 concentrations were correlated with corresponding changes in white blood cells after exposure to 240 ppb ozone ($r = 0.76$) in the asthmatic subjects. We conclude that these asthmatic individuals are more susceptible to acute inflammatory effects produced by low levels of ozone than the nonasthmatic individuals.

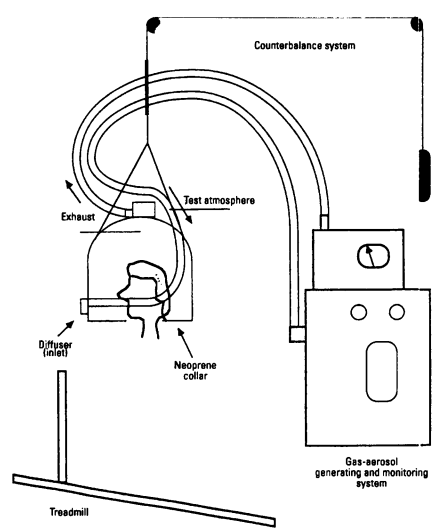


**Figure 1.** A schematic diagram of the head dome system for inhalation of test atmospheres.

## Conclusions

These controlled laboratory data can be put in perspective by considering epidemiologic evidence that ozone aggravates asthma. Over a decade ago, Whittemore and Korn (*11*) reported evidence implicating outdoor air pollution as a factor in aggravation of asthma by showing that daily asthma attacks in asthmatics residing in Los Angeles were strongly associated with daily levels of photochemical oxidants and suspended particulate matter. Bates and Sizto (*12*) studied hospital admissions in Southern Ontario, Canada, serving a population of 7 million and observed increased rates of admissions for asthmatics in the summer, which correlated with both ozone and suspended sulfates. These authors suggest that a general "acid summer haze" may be responsible for air pollutant-induced respiratory effects. Most recently, Cody and associates (*13*) conducted a retrospective study of emergency department visits for asthma during 1988 and 1989 in New Jersey. Their study demonstrated a significant association between the asthma visits and ambient ozone concentrations ($p = 0.0001$). Approximately 14% of asthma visits were associated with the combined variables of temperature and ozone.

It is not well established whether outdoor air pollution exposure is a risk factor for the development of bronchial hyperresponsiveness or asthma. There is one report that provides evidence that seasonal ozone exposure may cause bronchial hyperresponsiveness. This recent study evaluated the respiratory health, allergic sensitization, and immune response in 218 children from a high ozone community (Group A) and compared them with 281 children from a community with lower ozone levels (Group B) (*14*). Bronchial hyperresponsiveness, measured with a methacholine challenge test, occurred more frequently in the Group A children. Comparison of serum IgE levels showed no difference between the two groups. However, there was a significantly lower helper/suppressor T cell ratio in Group A children. One limitation of this study is the lack of personal exposure assessment. Another study has shown that prior exposure to ozone in a controlled laboratory setting in asthmatic adolescent subjects potentiates the pulmonary function decrements seen after a subsequent sulfur dioxide exposure (*15*). A recent study has shown that a controlled exposure to an ambient concentration of ozone (0.120 ppm) was associated with a significant increase in bronchial responsiveness to allergen challenge (*16*). These studies suggest a relationship between the course of bronchial hyperresponsiveness and personal ozone exposure.

Based on the studies reviewed in this paper, I conclude that subjects with asthma are indeed a population susceptible to the inhaled effects of ozone. These data need to be considered by regulators who are charged with setting air quality standards to protect even the most susceptible members of the population. They also underline the importance of strategies to reduce human exposure to ambient ozone.

### REFERENCES


1. U.S. EPA. National air quality and emissions trends report. Report no. EPA 454/R-93-031. Washington:U.S. Environmental Protection Agency, 1993.
2. Lippmann M. Health effects of ozone. A critical review. J Air Pollut Control Assoc 39:672–695 (1989).
3. Beckett WS. Ozone, air pollution, and respiratory health. Yale J Biol Med 64:167–175 (1991).
4. McDonnell WF, Horstman DH, Hazucha MJ, Seal E Jr, Haak ED, Salaam SA, House DE. Pulmonary effects of ozone exposure during exercise: dose response characteristics. J Appl Physiol 54:1435–1352 (1983).
5. Horstman DH, Folinsbee LJ. Ozone concentration and pulmonary response relationships for 6.6 hour exposures with 5 hours of moderate exercise to 0.08, 0.10, and 0.12 ppm. Am Rev Respir Dis 142:1158–1163 (1990).
6. Silverman F. Asthma and respiratory irritants (ozone). Environ Health Perspect 29:131–136 (1979).
7. Kreit JW, Gross KB, Moore TB, Lorenzen TJ, D'Arcy J, Eschenbacher WL. Ozone-induced changes in pulmonary function and bronchial responsiveness in asthmatics. J Appl Physiol 66:217–222 (1989).
8. Hackney JD, Linn WS, Shamoo DA, Avol EL. Responses of selected reactive and nonreactive volunteers to ozone exposure in high and low pollution seasons. In: Atmospheric Ozone Research and Its Policy Implications (Schneider T, ed). Amsterdam, Netherlands:Elsevier, 311–318; 1989.
9. Aris R, Christian D, Sheppard D, Balmes JR. The effects of sequential exposure to acidic fog and ozone on pulmonary function in exercising subjects. Am Rev Respir Dis 143:85–91 (1991).
10. McBride DE, Koenig JQ, Luchtel DL, Williams PV, Henderson WR Jr. Inflammatory effects of ozone in the upper airways of subjects with asthma. Am Rev Respir Crit Care Med 149:1192–1197 (1994).
11. Whittemore AS, Korn EL. Asthma and air pollution in the Los Angeles area. Am J Public Health 70:687–696 (1980).
12. Bates DV, Sizto R. Air pollution and hospital admissions in Southern Ontario: the acid summer haze effect. Environ Res 43:317–331 (1987).
13. Cody RP, Weisel CP, Birnbaum G, Lioy PJ. The effect of ozone associated with summertime photochemical smog on the frequency of asthma visits to hospital emergency departments. Environ Res 58:184–194 (1992).
14. Zwick H, Popp W, Wagner C, Reiser K, Schmoger J, Bock A, Herkner K, Radunsky K. Effects of ozone on the respiratory health, allergic sensitization, and cellular immune system in children. Am Rev Respir Dis 144:1075–1079 (1991).
15. Koenig JQ, Covert DS, Hanley QS, van Belle G, Pierson WE. Prior exposure to ozone potentiates subsequent response to sulfur dioxide in adolescent asthmatic subjects. Am Rev Respir Dis 141:377–380 (1990).
16. Molfino NA, Wright SC, Katz I, Tarlo S, Silverman F, McClean PA, Szalai JP, Raizenne M, Slutsky AS, Zamel N. Effect of low concentrations of ozone on inhaled allergen responses in asthmatic subjects. Lancet 338:199–203 (1991).