# 7

# Human Health Effects of Ozone and Related Photochemical Oxidants

## 7.1  Introduction

In the previous chapter, results of ozone ($O_3$) studies in laboratory animals were presented in order to understand the wide range of potential effects that might occur in exposed human populations and to expand the understanding of the mechanisms of $O_3$ toxicity and the basic exposure-response relationships for $O_3$.  The concept of quantitatively extrapolating results from laboratory animals to humans is further explored in Chapter 8.  Whenever possible, however, risk assessment of pollutants should be based on direct evidence of their health effects in human populations.  Information on human health responses to $O_3$ can be obtained through controlled human exposure studies on volunteer subjects or through field and epidemiological studies of populations that are exposed to ambient air containing $O_3$.  Controlled human studies typically use fixed concentrations of $O_3$ under carefully regulated environmental conditions, whereas realistic $O_3$ exposure conditions occur in field and epidemiology studies, but are more variable.  The primary purpose of all these studies, however, is to obtain exposure-response data for $O_3$.  This chapter will summarize the results of controlled human, field, and epidemiologic studies on the health effects of exposure to $O_3$ that have been published or accepted for publication in the peer-reviewed literature.  Further evaluation of the most important key information from this chapter, as it relates to the rest of the document, will be provided in Chapter 9, where the overall database on $O_3$ health effects is integrated and summarized.

Most of the scientific information selected for review and comment in this chapter comes from the literature published since completion of the previous $O_3$ criteria document (U.S. Environmental Protection Agency, 1986).  Some of these newer studies were briefly reviewed in the supplement to that document (U.S. Environmental Protection Agency, 1992), but more thorough evaluation of these studies is included here.  In order to give a broader overview of the known human health effects of $O_3$, the older literature is summarized, and specific studies whose data were judged to be significant because of their usefulness in deriving the current National Ambient Air Quality Standards (NAAQS) are discussed briefly.  The reader is, however, referred to the more extensive discussion of these key studies in the previous document.  Other, older studies also are briefly discussed in this chapter if they are (1) open to reinterpretation because of newer data or (2) potentially useful as criteria for the $O_3$ NAAQS reevaluation.  To further aid in the development of this chapter, summary tables of the relevant $O_3$ literature are included for each of the major subsections.  In summarizing the

human health effects literature, changes from control are described if they were statistically significant at a probability (p) value less than 0.05.  A specific p value is provided, however, if it aids understanding of the data, particularly trends toward significance, or if major effects need to be emphasized.  Where appropriate, critique of a statistical procedure also is mentioned.

# 7.2  Controlled Human Exposure Studies
## 7.2.1  Pulmonary Function Effects of One- to Three-Hour Ozone Exposures
### 7.2.1.1  Healthy Subjects
*Introduction*

The pulmonary responses observed in healthy human subjects exposed to ambient $O_3$ concentrations consist of decreased inspiratory capacity; mild bronchoconstriction; rapid, shallow breathing pattern during exercise; and subjective symptoms of cough and pain on deep inspiration.  In addition, $O_3$ has been shown to result in airway hyperresponsiveness as demonstrated by an increased physiological response to a nonspecific stimulus.  The decrease in inspiratory capacity results in a decrease in forced vital capacity (FVC) and total lung capacity (TLC) and, in combination with bronchoconstriction, contributes to a decrease in the forced expiratory volume in 1 s ($FEV_1$).  However, it is important to stress that in many of the studies reporting the effects of ambient ranges of $O_3$ concentrations (i.e., <0.3 ppm), the observed decrements in $FEV_1$, to a large extent, reflect decrements in FVC of a similar magnitude (i.e., a decreased inspiratory capacity) and, to a lesser extent, increases in central and peripheral airway resistance ($R_{aw}$).

The majority of controlled human studies have been concerned with the effects of various $O_3$ concentrations in healthy subjects performing continuous exercise (CE) or intermittent exercise (IE) for variable periods of time.  These studies have two weaknesses: (1) the failure to detect short-term effects with long-term consequences and (2) their use of small numbers that are not generally representative of the general population.  Controlled human exposure studies of this type have provided the strongest and most quantifiable concentration-response data on the health effects of $O_3$.  As a result of these studies, a large body of data regarding the interaction of $O_3$ concentration (C), minute ventilation ($\dot{V}_E$), and duration of exposure (T) is available.  The most salient observations from these studies are (1) $O_3$ concentration is more important than either $\dot{V}_E$ or T in determining pulmonary responses and (2) normal, healthy subjects exposed to $O_3$ concentrations ⬜0.12 ppm (the level of the current NAAQS) develop significant reversible, transient decrements in pulmonary function if $\dot{V}_E$ or T are increased sufficiently.  There is typically a large intersubject variability in physiologic and symptomatic responses to $O_3$; however, with most individuals these responses tend to be reproducible.  The relationship among response variables such as spirometry, resistance measurements, symptoms, and nonspecific bronchial responsiveness is yet to be fully determined, but the generally weak associations suggest that several response mechanisms may be operant.  In addition, a growing number of studies are beginning to provide insight into the relationship between regional dosimetry (see Chapter 8), mechanisms of pulmonary responses elicited by acute $O_3$ exposure, and tissue level events within the airways.  This type of information promises to provide further insight into the health effects relevance of $O_3$-induced pulmonary responses in determining which individuals are at greatest risk from ambient $O_3$ exposure.

In this section, the effects of acute (single 1- to 3-h) $O_3$ exposures on pulmonary function in healthy subjects are examined by reviewing studies that investigate (1) the $O_3$ exposure-response relationship; (2) intersubject variability, individual sensitivity, and the association between responses; and (3) mechanisms of pulmonary function responses and the relationship between tissue-level events and functional responses. Unless otherwise stated, the term "significant" is used in this section to denote statistical significance at $p < 0.05$. Recent, single $O_3$ exposure studies of greater than 3 h duration are reviewed in Section 7.2.2. These single-exposure, longer duration studies are beginning to provide important insights into the C $\times$ T $\times$ $\dot{V}_E$ interaction related to a significant pulmonary response. Key studies of less than 3 h duration that have contributed to the exposure-response database and other studies that have contributed to a better understanding of $O_3$-induced pulmonary responses in healthy individuals are summarized in Table 7-1. Table 7-1 summarizes studies reviewed in the previous air quality criteria document (U.S. Environmental Protection Agency, 1986), as well as studies published since completion of this earlier document. Not reviewed in this section are studies that examine changes in airway responsiveness induced by $O_3$ inhalation (see Section 7.2.3). All of the studies discussed here used appropriate controls and therefore, for simplicity, the text will not indicate for each study that subjects were also exposed under similar conditions to filtered air (FA [reported at 0 ppm $O_3$]).

### The Ozone Concentration-Response Relationship

*At-Rest Exposures*. No new studies examining the acute effects of a single exposure to $O_3$ concentrations below 1 ppm in resting humans have been published since the 1986 U.S. Environmental Protection Agency (EPA) criteria document (U.S. Environmental Protection Agency, 1986). Seven studies (Young et al., 1964; Bates et al., 1972; Silverman et al., 1976; Folinsbee et al., 1978; Horvath et al., 1979; Kagawa and Tsuru, 1979; König et al., 1980) examining 2-h, at-rest exposures were discussed in the 1986 EPA criteria document (U.S. Environmental Protection Agency, 1986) involving 91 healthy subjects (74 males, 17 females) exposed to $O_3$ concentrations ranging from 0.1 to 1.0 ppm. The lowest concentration at which significant reductions in FVC and $FEV_1$ were reported was 0.5 ppm (Folinsbee et al., 1978; Horvath et al., 1979). Reports of increases in $R_{aw}$ are inconsistent in resting human subjects exposed to $O_3$ concentrations below 1.0 ppm.

*Exposure with Exercise*. Bates et al. (1972) and Hazucha et al. (1973) were the first investigators to examine the effect on pulmonary function responses of increasing ventilation via exercise during $O_3$ inhalation. The IE protocol used consisted of the subjects alternating rest and light exercise on a cycle ergometer at a rate sufficient to double resting $\dot{V}_E$ for 15 min during a period of 2 h.

Hazucha et al. (1973) observed significant decreases in forced expiratory endpoints at 0.37 ppm $O_3$ ($p < 0.05$) and 0.75 ppm $O_3$ ($p < 0.001$), with subjects exposed to 0.75 ppm having the greatest decrements. After exposures, all subjects complained to varying degrees of substernal soreness, chest tightness, and cough. The important findings from these early studies were that the exercise-induced increase in $\dot{V}_E$ accentuated the observed pulmonary response at any given $O_3$ concentration and lowered the minimum $O_3$ concentration at which significant pulmonary responses were observed. Subsequently, the interaction between $O_3$ concentration and $\dot{V}_E$ was examined by using similar IE protocols in which both

# Table 7-1.  Controlled Exposure of Healthy Human Subjects to Ozone[a]

| Ozone Concentration[b] | | Exposure Duration and Activity | Exposure Conditions | Number and Gender of Subjects | Subject Characteristics | Observed[c] Effect(s) | Reference |
|---|---|---|---|---|---|---|---|
| ppm | μg/m | | | | | | |
| *Healthy Adult Subjects at Rest* | | | | | | | |
| 0.25<br>0.50<br>0.75 | 490<br>980<br>1,470 | 2 h | NA | 8 M<br>5 F | Young, healthy adults, 21 to 22 years old | FVC decreased with 0.50- and 0.75-ppm O$_3$ exposure compared with FA; 4% nonsignificant decrease in mean V̇O$_{2max}$ following 0.75 ppm O$_3$ compared with FA exposure. | Horvath et al. (1979) |
| 0.37<br>0.50<br>0.75 | 726<br>980<br>1,470 | 2 h | NA | 20 M<br>8 F | Young, healthy adults, 19 to 29 years old | Decrease in FEV$_1$, V$_{25\%VC}$, and V$_{50\%VC}$ with 0.75 ppm O$_3$ exposure compared to FA. | Silverman et al. (1976) |
| 0.50 | 980 | 2 h | NA | 40 M | Young, healthy adults, 18 to 28 years old | Decrease in forced expiratory volume and flow. | Folinsbee et al. (1978) |
| *Healthy Exercising Adult Subjects* | | | | | | | |
| 0.08<br>0.10<br>0.12<br>0.14<br>0.16 | 157<br>196<br>235<br>274<br>314 | 2 h IE (4 × 15 min at V̇$_E$ = 68 L/min) | Tdb = 32 °C<br>RH = 38% | 24 M | Young, healthy adults, 18 to 33 years old | No significant changes in pulmonary function measurements. | Linn et al. (1986) |
| 0.10<br>0.15<br>0.20<br>0.25 | 196<br>294<br>392<br>490 | 2 h IE (4 × 14 min treadmill at mean V̇$_E$ = 70.2 L/min) | Tdb = 22 °C<br>RH = 50% | 20 M | Young, healthy NS, 25.3 ± 4.1 (SD) years old | FVC, FEV$_1$, FEF$_{25-75\%}$, SG$_{aw}$, IC, and TLC all decreased with (1) increasing O$_3$ concentration, and (2) increasing time of exposure; threshold for response was above 0.10 ppm but below 0.15 ppm O$_3$. | Kulle et al. (1985) |
| 0.12<br>0.18<br>0.24 | 235<br>353<br>470 | 1 h competitive simulation exposures at mean V̇$_E$ = 87 L/min | Tdb = 23 to 26 °C<br>RH = 45 to 60% | 10 M | 10 highly trained competitive cyclists, 19 to 29 years old | Decrease in FVC and FEV$_1$ for 0.18- and 0.24-ppm O$_3$ exposure compared with FA exposure; decrease in exercise time for subjects unable to complete the competitive simulation at 0.18 and 0.24 ppm O$_3$, respectively. | Schelegle and Adams (1986) |
| 0.12<br>0.18<br>0.24<br>0.30<br>0.40 | 235<br>353<br>470<br>588<br>784 | 2.5 h IE (4 × 15 min treadmill exercise [ V̇$_E$ = 65 L/min]) | Tdb = 22 °C<br>RH = 40% | 20 M<br>22 M<br>20 M<br>21 M<br>20 M<br>29 M | Young, healthy adults, 18 to 30 years old | Significant decrease in FVC, FEV$_1$, and FEF$_{25-75\%}$ at 0.12 ppm O$_3$; decrease in V$_T$ and increase in f and SR$_{aw}$ at 0.24 ppm O$_3$. | McDonnell et al. (1983) |

## Table 7-1 (cont'd). Controlled Exposure of Healthy Human Subjects to Ozone[a]

| Ozone Concentration[b] | | Exposure Duration and Activity | Exposure Conditions | Number and Gender of Subjects | Subject Characteristics[c] | Observed Effect(s) | Reference |
|---|---|---|---|---|---|---|---|
| ppm | $\mu$g/m | | | | | | |

*Healthy Exercising Adult Subjects (cont'd)*

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 0.12 | 235 | $2 \times 2.5$ h IE | Tdb = 22 °C | 8 M | Young, healthy | Pulmonary function variables $SR_{aw}$ and $\dot{V}_E$ were not | McDonnell et al. (1985b) |
| 0.18 | 353 | ($4 \times 15$ min | RH = 40% | 8 M | adults, 18 to | significantly different in repeat exposures, indicating that | |
| 0.24 | 470 | treadmill | | 5 M | 30 years old | the response to 0.18 ppm $O_3$ or higher is reproducible. | |
| 0.30 | 588 | exercise | | 5 M | | | |
| 0.40 | 784 | [ $\dot{V}_E$ = | | 6 M | | | |
| | | 35 L/min/m² | | | | | |
| | | BSA]). | | | | | |
| | | Exposure | | | | | |
| | | separated by | | | | | |
| | | 48 $\pm$ 30 days | | | | | |
| | | and 301 | | | | | |
| | | $\pm$ 77 days | | | | | |
| 0.12 | 235 | $2 \times 2.5$ h IE | Tdb = 22 °C | 290 M | Young, healthy | $O_3$ concentration and age predicted $FEV_1$ decrements; it was | McDonnell et al. (1993) |
| 0.18 | 353 | ($4 \times 15$ min | RH = 40% | | adults, 18 to | concluded that age is a significant predictor of response | |
| 0.24 | 470 | treadmill | | | 32 years old | (older subjects being less responsive to $O_3$). | |
| 0.30 | 588 | exercise | | | | | |
| 0.40 | 784 | [ $\dot{V}_E$ = | | | | | |
| | | 35 L/min/m² | | | | | |
| | | BSA]) | | | | | |
| 0.12 | 235 | 2.5 h IE | Tdb = 22 °C | 17 WM/15 BM/15 WF/ 15BF | Young, healthy | Decreases in $FEV_1$ for all levels of $O_3$ as compared with | Seal et al. (1993) |
| 0.18 | 353 | ($4 \times 15$ min | RH = 40% | 15 WM/15 BM/15 WF/ 16BF | whites and | FA; increase in $SR_{aw}$ with 0.18 ppm $O_3$ and greater | |
| 0.24 | 470 | treadmill | | 15 WM/17 BM/17 WF/ 15BF | blacks, 18 to | compared with FA; black men and women had larger $FEV_1$ | |
| 0.30 | 588 | exercise | | 16 WM/15 BM/17 WF/ 16BF | 35 years old | decrements than white men, and black men had larger $FEV_1$ | |
| 0.40 | 784 | [ $\dot{V}_E$ = | | 15 WM/15 BM/15 WF/ 15BF | | decrements than white women. | |
| | | 25 L/min/m² | | 15 WM/15 BM/15 WF/ 15BF | | | |
| | | BSA]) | | | | | |
| 0.12 | 235 | 1 h CE | Tdb = 31 °C | 15 M | Highly trained | Decrease in $\dot{V}_{Emax}$, $VO_{2max}$, $V_{Tmax}$, work load, ride time, | Gong et al. (1986) |
| 0.20 | 392 | (mean $\dot{V}_E$ = | | 2 F | competitive | FVC, and $FEV_1$ with 0.20 ppm $O_3$ exposure during | |
| | | 89 L/min) | | | cyclists, 19 to | maximal exercise conditions, but not significant with | |
| | | | | | 30 years old | 0.12 ppm $O_3$ exposure, as compared to FA exposure. | |

## Table 7-1 (cont'd). Controlled Exposure of Healthy Human Subjects to Ozone[a]

| Ozone Concentration[b] | | Exposure Duration and Activity | Exposure Conditions | Number and Gender of Subjects | Subject Characteristics | Observed Effect(s) | Reference |
|---|---|---|---|---|---|---|---|
| ppm | $\square$g/m | | | | | | |
| *Healthy Exercising Adult Subjects (cont'd)* | | | | | | | |
| 0.16<br>0.24<br>0.32 | 314<br>470<br>627 | 1 h CE (mean $\dot{V}_E$ = 57 L/min) | Tdb = 32 $\square$C<br>RH = 42 to 46% | 42 M<br>8 F | Competitive bicyclists, 26.4 $\pm$ 6.9 (SD) years old | Small decrements in $FEV_1$ at 0.16 ppm with larger decrements at 0.24 ppm $O_3$. | Avol et al. (1984) |
| 0.20 | 392 | 4 h IE<br>(4 × 50 min cycle ergometry or treadmill running [ $\dot{V}_E$ = 40 L/min]) | Tdb = 20 $\square$C<br>RH = 50% | 11 M<br>3 F (FA exposure);<br>9 M<br>3 F ($O_3$ exposure) | Adult, healthy NS, 19 to 41 years old | Decrease in FVC, $FEV_1$, $V_T$, and $SR_{aw}$ and increase in f with $O_3$ exposure compared with FA; total cell count and LDH increased in isolated left main bronchus lavage and inflammatory cell influx occurred with $O_3$ exposure compared to FA exposure. | Aris et al. (1993a) |
| 0.20<br>0.30 | 392<br>588 | 30 to 80 min CE cycle ergometry ( $\dot{V}_E$ = 33 or 66 L/min) | Tdb = 20 to 24 $\square$C<br>RH = 40 to 60% | 8 M | Aerobically fit, 22 to 46 years old | $O_3$ effective dose was significantly related to pulmonary function decrements and exercise ventilatory pattern changes; multiple regression analysis showed that $O_3$ concentration accounted for the majority of the pulmonary function variance. | Adams et al. (1981) |
| 0.20<br>0.35 | 392<br>686 | 1 h CE or competitive simulation (mean $\dot{V}_E$ = 77.5 L/min) | Tdb = 23 to 26 $\square$C<br>RH = 45 to 60% | 10 M | Well-trained distance runners, 19 to 31 years old | Decrease in FVC, $FEV_1$, and $FEF_{25-75\%}$ with 0.20 and 0.35 ppm $O_3$ exposure compared with FA; $V_T$ decreased and f increased with continuous 50-min $O_3$ exposures; three subjects unable to complete continuous and competitive protocols at 0.35 ppm $O_3$. | Adams and Schelegle (1983) |
| 0.21 | 412 | 1 h CE (75% $\dot{V}O_{2max}$) | Tdb = 19 to 21 $\square$C<br>RH = 60 to 70% | 6 M<br>1 F | Well-trained cyclists, 18 to 27 years old | Decrease in FVC, $FEV_1$, $FEF_{25-75\%}$, and MVV with 0.21 ppm $O_3$ compared with FA exposure. | Folinsbee et al. (1984) |
| 0.21 | 412 | 1 h CE cycle ergometry (mean $\dot{V}_E$ = 80 L/min) | Tdb = 22.5 $\square$C<br>RH = 58.8% | 14 M<br>1 F | Highly fit endurance cyclists, 16 to 34 years old | No significant differences in the effects of albuterol on metabolic data, pulmonary function, airway reactivity, and exercise performance vs. placebo; decrease in $\dot{V}_{Emax}$ during $O_3$ conditions. | Gong et al. (1988) |
| 0.25 | 490 | 1 h CE (mean $\dot{V}_E$ = 63 L/min) | Tdb = 20 $\square$C<br>RH = 70% | 19 M<br>7 F | Active nonathletes | FVC, $FEV_1$, and MVV all decreased with 0.25 ppm $O_3$ exposure compared with FA. | Folinsbee et al. (1986) |
| 0.25 | 490 | 1 h CE cycle ergometer ( $\dot{V}_E$ = 30 L/min/m² BSA) | NA | 5 M<br>2 F | Young, healthy NS, 22 to 30 years old | 12.4% decrease in $FEV_1$. Significant elevation of substance P and 8-epi-$PGF_{2\square}$ in segmental airway washing, but not bronchoalveolar lavage fluid. | Hazbun et al. (1993) |

## Table 7-1 (cont'd).  Controlled Exposure of Healthy Human Subjects to Ozone[a]

| Ozone Concentration[b] | | Exposure Duration and Activity | Exposure Conditions | Number and Gender of Subjects | Subject Characteristics | Observed Effect(s) | Reference |
|---|---|---|---|---|---|---|---|
| ppm | $\mu$g/m^{3} | | | | | | |
| **Healthy Exercising Adult Subjects (cont'd)** | | | | | | | |
| 0.30 | 588 | 1 h CE cycle ergometry (mean $\dot{V}_E$ = 60 L/min) | NA | 5 M | Normal | Decrease in FVC and FEV$_1$ and increase in SR$_{aw}$ 1 h post-O$_3$ exposure; increase in percent PMNs at 1, 6, and 24 h post-O$_3$ exposure compared with FA in first aliquot "bronchial" sample.  PMNs peaked at 6 h post-O$_3$ in "bronchial" sample.  Percent PMNs elevated at 6 and 24 h post-O$_3$ in pooled aliquots. | Schelegle et al. (1991) |
| 0.30 | 588 | 1 h CE cycle ergometry ( $\dot{V}_E$ = 60 L/min) and 2 h IE cycle ergometry ( $\dot{V}_E$ = 45 to 47 L/min) | Tdb = 21 to 25 °C RH = 45 to 60% | 12 M | Moderately fit, young and healthy | Decrease in FEV$_1$ equivalent for all protocols. | McKittrick and Adams (1995) |
| 0.35 | 686 | 1 h CE cycle ergometry (mean $\dot{V}_E$ = 60 L/min) | Tdb = 21 to 25 °C RH = 45 to 60% | 14 M | Moderately fit, young, healthy adults, 18 to 34 years old | Significant decreases in FVC and FEV$_1$ with O$_3$ exposure compared to FA exposure; FVC and FEV$_1$ decreases with O$_3$ exposure were attenuated significantly with indomethacin compared to no drug and placebo; SR$_{aw}$ increases were not affected by indomethacin. | Schelegle et al. (1987) |
| 0.37 0.50 0.75 | 726 980 1,470 | 2 h IE cycle ergometry ( $\dot{V}_E$ = 2.5 × rest) | | 20 M 8 F | Young, healthy adults, 19 to 29 years old | Decrease in FVC with 0.50 ppm and FEV$_1$ with 0.50 and 0.75 ppm O$_3$ compared to FA; decrease in V$_{25\%VC}$ with 0.37 and 0.75 ppm and V$_{50\%VC}$ with 0.37, 0.50, and 0.75 ppm O$_3$ exposure compared to FA. | Silverman et al. (1976) |
| 0.40 | 784 | 2 h IE treadmill exercise ( $\dot{V}_E$ = 50 to 75 L/min) | Tdb = 22 °C RH = 40% | 8 M | Young, healthy NS, 18 to 27 years old | Decreases in FVC, FEV$_1$, V$_T$, and TLC and increases in SR$_{aw}$ and f with O$_3$ exposure compared with FA.  Atropine pretreatment abolished O$_3$-induced increase in SR$_{aw}$ and attenuated FEV$_1$ and FEF$_{25-75\%}$ response. | Beckett et al. (1985) |
| 0.40 | 784 | 1 h CE treadmill exercise; ( $\dot{V}_E$ = 20 L/min/m^{2} BSA) | NA | 20 M | Young, healthy NS | V$_T$ fell by 25%, and O$_3$ uptake efficiency in the lower respiratory tract fell by 9% during O$_3$ exposure. | Gerrity et al. (1994) |
| 0.40 | 784 | 2 h IE (4 × 15 min heavy treadmill exercise [ $\dot{V}_E$ = 35 L/min/m^{2} BSA]) | NA | 11 M | Young, healthy NS, 18 to 35 years old | No correlation between pulmonary function and inflammatory endpoints measured in BAL fluid obtained 18 h after exposure; increase in percentage of PMNs, total protein, albumin, IgG, and neutrophil elastase; decrease in percentage of macrophages with O$_3$ exposure compared to FA exposure. | Koren et al. (1989a) |

## Table 7-1 (cont'd).  Controlled Exposure of Healthy Human Subjects to Ozone[a]

| Ozone Concentration[b] | | Exposure Duration and Activity | Exposure Conditions | Number and Gender of Subjects | Subject Characteristics | Observed Effect(s) | Reference |
|---|---|---|---|---|---|---|---|
| ppm | $\square$g/m | | | | | | |
| *Healthy Exercising Adult Subjects (cont'd)* | | | | | | | |
| 0.40 | 784 | 2 h IE (4 × 15 min heavy treadmill exercise [ $\dot{V}_E$ = 35 L/min/m² BSA]) | Tdb = 22 $\square$C RH = 40% | 10 M | Young, healthy NS, 18 to 35 years old | PMN, $PGE_2$, and IL-6 were higher in BAL fluid obtained 1 h post-$O_3$ exposure than 18 h; fibronectin and urokinase-type plasminogen activator were higher 18 h post-$O_3$ exposure than 1 h. | Koren et al. (1991) |
| 0.40 | 784 | 2 h IE (4 × 15 min bicycle ergometry [ $\dot{V}_E$ = 30 L/min/m² BSA]) | Tdb = 22 $\square$C RH = 50% | 13 M | NS, 18 to 31 years old | Indomethacin pretreatment and $O_3$ exposure resulted in a significantly smaller decrease in FVC and $FEV_1$ than $O_3$ exposure alone; airway hyperresponsiveness was not significantly affected by indomethacin pretreatment. | Ying et al. (1990) |
| 0.40 | 784 | 1 h CE (treadmill exercise; $\dot{V}_E$ = 20 L/min/m² BSA) | Tdb = 22 $\square$C RH = 40% | 22 M | Young, healthy NS, 18 to 35 years old | Significant decreases in FVC, $FEV_1$, $FEV_1$/FVC, and $FEF_{25-75\%}$. The half-width of an expired aerosol bolus was significantly increased, suggesting an ozone-induced change in small airway function. | Keefe et al. (1991) |
| 0.40 0.60 | 784 1,176 | 2 h IE (4 × 15 min cycle ergometry at 100 W for males and 83 W for females) | Tdb = 71.5 $\square$C RH = 55% | 7 M 3 F | Healthy NS, 23 to 41 years old | Increase in airway responsiveness to methacholine challenge, in mean percentage of neutrophils, and in $PGF_{2\square}$, $TXB_2$, and $PGE_2$ concentrations measured in BAL fluid 3 h after 0.40- and 0.60-ppm $O_3$ exposure compared with FA exposure. | Seltzer et al. (1986) |
| 0.50 | 980 | 2 h IE (4 × 15 min treadmill exercise; $\dot{V}_E$ = 40 L/min) | Tdb = 21 $\square$C RH = 40% | 18 M | Healthy, young adults, 20 to 30 years old | Decrease in VC, $V_T$, and maximal transpulmonary pressure, and increase in $SR_{aw}$ and f with $O_3$ exposure compared to FA exposure; lidocaine inhalation partially reversed the decrease in VC. | Hazucha et al. (1989) |
| 0.75 | 1,470 | 2 h IE (4 × 15 min light [50 W] cycle ergometry) | NA | 13 M | 4 light S, 9 NS, 19 to 30 years old | Decrease in FVC, $FEV_1$, ERV, IC, and $FEF_{50\%}$ after 1 h exposure to 0.75 ppm $O_3$; decrease in $VO_{2max}$, $V_{Tmax}$, $V_{Emax}$, maximal workload, and heart rate following 0.75-ppm $O_3$ exposure compared with FA. | Folinsbee et al. (1977) |

[a]See Appendix A for abbreviations and acronyms.

[b]Grouped by rest and exercise; within groups listed from lowest to highest $O_3$ concentration.

Silverman et al. (1976) and Folinsbee et al. (1975) exposed a group of 20 males and 8 females to 0.37, 0.50, or 0.75 ppm for 2 h while resting or exercising intermittently. The IE protocol used alternated 15 min of rest with 15 min of exercise, sufficient to increase the $\dot{V}_E$ value at rest by a factor of 2.5. The submaximal exercise responses of the subjects were tested postexposure using a three-stage cycle ergometer test, with loads adjusted to 45, 60, and 75% of maximum oxygen uptake ($\dot{V}O_{2max}$) (Folinsbee et al., 1975). Pulmonary function responses were related to the total inhaled dose or the "effective dose" of $O_3$ calculated as the product of $C \times T \times \dot{V}_E$. Neither submaximal exercise oxygen uptake ($\dot{V}O_2$) nor $\dot{V}_E$ were affected significantly by any level of $O_3$ exposure; however, a significant increase in respiratory frequency (f) and a significant decrease in tidal volume ($V_T$) at the 75% $\dot{V}O_{2max}$ workload were observed. The relationship between the effective dose of $O_3$ and the mean percent change in selected measures of lung function was analyzed using linear regression. Forced vital capacity, maximum expiratory flow at 25 and 50% of FVC ($\dot{V}_{max25\%}$ and $\dot{V}_{max5\ \%}$, respectively), and $FEV_1$ were found to have a significant linear correlation with the effective dose. The description of the relationship between $O_3$ pulmonary function decrements and effective dose was apparently improved by the use of a second-order polynomial model in which effective dose was used as the independent variable.

Although the investigations of Silverman et al. (1976) and others (Bates et al., 1972; Hackney et al., 1975; Hazucha et al., 1973) clearly demonstrate the potentiating effects of exercise on $O_3$ responses, the level of exercise used in these studies was low, requiring increases in $\dot{V}_E$ of only 2 to 2.5 times resting, a level of exercise lower than that of a subject walking at 5.5 km/h (DeLucia and Adams, 1977). In order to address this concern, DeLucia and Adams (1977) exposed six healthy nonsmoking male subjects on 12 separate occasions to FA and 0.15 and 0.30 ppm $O_3$ for 1 h, while at rest and while exercising continuously at workloads that required 25, 45, and 65% of the subjects' $\dot{V}O_{2max}$. They observed a significant time-dependent increase in f during the 65% $\dot{V}O_{2max}$, 0.30-ppm $O_3$ exposure, and, immediately following this same exposure, there was a significant decrease in $FEV_1$ and forced expiratory flow at 25 to 75% of FVC ($FEF_{25\ 75\%}$).

These initial studies, which clearly demonstrated the potentiating effects of exercise on human responses to acute $O_3$ exposure, provided the impetus for a series of studies (Adams et al., 1981; Folinsbee et al., 1978; McDonnell et al., 1983; Kulle et al., 1985; Linn et al., 1986) designed to define more precisely $O_3$ exposure-response relationships. These investigations utilized both IE (Folinsbee et al., 1978; McDonnell et al., 1983) and CE (Adams et al., 1981) of varying intensity. Folinsbee et al. (1978) exposed four groups of 10 subjects each to FA, 0.1, 0.3, and 0.5 ppm $O_3$ for 2 h. One group was exposed while at rest, and the other three groups were exposed while performing IE at levels requiring a ventilation of 30, 50, or 70 L/min. These combinations of ventilation and $O_3$ concentration ($C \times T \times \dot{V}_E$) resulted in a range of total inhaled effective dose of 0.00 to 4.41 mg $O_3$. Adams et al. (1981) exposed eight trained male subjects to FA, 0.2, 0.3, and 0.4 ppm $O_3$ while they exercised continuously at two different workloads (35 and 62% of $\dot{V}O_{2max}$) for durations ranging from 30 to 80 min. Each subject completed all 18 protocols with at least 3 days between each. The findings from these two studies confirmed that significant pulmonary responses occurred at 0.3 ppm when subjects exercised at moderately heavy workloads. It was further demonstrated, by multiple regression analysis, that the $O_3$ effective dose was a better predictor of response than $O_3$ concentration, $\dot{V}_E$, or duration of exposure, alone. Multiple regression analysis also revealed that the majority of variance for pulmonary function responses was accounted for by

$O_3$ concentration, followed by $\dot{V}_E$. In the Adams et al. (1981) study, in which both workload and duration of exposure were varied, duration of exposure was observed to be the poorest predictor of response for all parameters analyzed. However, the minor impact of changes in exposure duration could have been an artifact of the limited combinations of ventilation and durations of exposure used by these investigators.

McDonnell et al. (1983) conducted a study with the primary purpose of discerning the lowest concentration of $O_3$ at which group mean decrements in pulmonary function occur in heavily exercising healthy men. In order to determine a concentration-response relationship, six groups of subjects (n = 20 to 29) were exposed to either an FA control or one of five $O_3$ concentrations (0.12, 0.18, 0.24, 0.30, or 0.40 ppm) at a $\dot{V}_E$ of 67 L/min and exposure duration of 2.5 h (15-min rest, 15-min exercise). These investigators observed small significant changes in FVC, $FEV_1$, $FEF_{25\ 75\%}$, and cough at 0.12 ppm $O_3$ and concentration-dependent responses in all variables measured (FVC, $FEV_1$, $FEF_{25\ 75\%}$, specific airway resistance [$SR_{aw}$], f, $V_T$, and subjective symptoms) at $O_3$ concentrations >0.24 ppm.

Kulle et al. (1985) also conducted a similar study on healthy, nonsmoking men performing IE at a $\dot{V}_E$ of 70 L/min for an exposure duration of 2 h, (16-min rest, 14-min exercise). Twenty subjects were exposed to an FA control or one of four $O_3$ concentrations (0.10, 0.15, 0.20, or 0.25 ppm). These investigators observed a significant $C \times T$ interaction at 0.15 ppm $O_3$ for FVC, $FEV_1$, $FEF_{25\ 75\%}$, and in all variables measured (FVC, $FEV_1$, $FEF_{25\ 75\%}$, $SR_{aw}$, f, $V_T$, and subjective symptoms) at $O_3$ concentrations greater than 0.15 ppm.

Linn et al. (1986) exposed 24 healthy, well-conditioned male subjects (18 to 33 years of age) for 2 h to 0.00, 0.08, 0.10, 0.12, 0.14, or 0.16 ppm $O_3$, using an IE protocol (15-min rest, 15-min exercise; $\dot{V}_E$ = 68 L/min) combined with an ambient heat stress (32 □C and 38% relative humidity [RH]). They observed no statistically significant changes in forced expiratory endpoints and symptoms after exposure to $O_3$ concentrations from 0.08 to 0.14 ppm. These authors observed a small (□2.3%) but significant (p < 0.05) reduction in $FEV_1$, which was not associated with symptoms of respiratory discomfort, following the 2-h 0.16-ppm $O_3$ exposure.

More recently, Seal et al. (1993) examined whether gender or race differences exist in responsiveness to $O_3$. The authors exposed 372 white and black, males and females (n > 90 in each gender-race group) once for 2.33 h to 0.0, 0.12, 0.18, 0.24, 0.30, or 0.40 ppm $O_3$ using an IE protocol (15-min rest, 15-min exercise; $\dot{V}_E$ = 25 L/min/$m^2$ body surface area [BSA]). Statistical analysis (nonparametric two-factor analysis of variance) of the percent changes from baseline for $FEV_1$, $SR_{aw}$, and cough responses demonstrated no significant differences in responsiveness to $O_3$ between the gender-race groups studied. Changes in $FEV_1$, $SR_{aw}$, and cough were first noted at 0.12, 0.18, and 0.18 ppm $O_3$, respectively, for the group as a whole. It is difficult to compare the results from this study with other studies that have examined the $O_3$ concentration-response relationship in healthy adult males because the authors did not present a separate analysis of male responses. For further evaluation of the influence of gender and race on $O_3$ responsiveness, see Section 7.2.1.3.

The observation of significant decrements in pulmonary function in heavily exercising healthy subjects at $O_3$ concentrations of 0.2 ppm and lower has been confirmed by numerous investigators (Adams and Schelegle, 1983; Avol et al., 1984; Folinsbee et al., 1984; Gong et al., 1986) who utilized 1-h continuous heavy exercise exposure protocols. Adams and Schelegle (1983) and Folinsbee et al. (1984) observed significant decrements in FVC and $FEV_1$

in well-trained subjects exposed to 0.2 ppm $O_3$ while exercising with a $\dot{V}_E$ of approximately 80 L/min. Avol et al. (1984) observed small but significant decrements in FVC and $FEV_1$ in a group of 50 competitive cyclists (42 males, 8 females) exposed to 0.16 ppm $O_3$ while exercising with a $\dot{V}_E$ of 57 L/min in combination with added heat stress (32 °C). Similarly, Gong et al. (1986) observed modest but significant decrements in FVC and $FEV_1$ in a group of 17 top-caliber endurance cyclists exposed to 0.12 ppm $O_3$ while exercising at approximately 70% of their $\dot{V}O_{2max}$ (mean $\dot{V}_E = 89$ L/min) with an added heat stress (32 °C). In addition to the above studies that used continuous exercise, Schelegle and Adams (1986) observed significant reductions in FVC and $FEV_1$ and increased symptoms of respiratory discomfort following exposure to 0.18 but not 0.12 ppm $O_3$ in a group of competitive endurance athletes exposed while performing a competitive simulation consisting of a 30-min warm-up followed by a 30-min competitive bout (mean $\dot{V}_E$ over entire protocol = 87 L/min).

The studies reviewed above demonstrate that in healthy young adults performing moderate to severe IE and CE of 1 to 3 h duration, an $O_3$ concentration of 0.12 to 0.18 ppm is required to elicit statistically significant decrements in pulmonary function and subjective respiratory symptoms.

Retrospective analysis by Hazucha (1987) confirmed the previously reported (Adams et al., 1981; Folinsbee et al., 1978) dominant role that $O_3$ concentration plays in determining $O_3$-induced responses. Hazucha (1987) analyzed data from studies that utilized IE protocols of 2 h in duration. While controlling for ventilation, this investigator found that the data best fit a model that was a quadratic function of $O_3$ concentration. Based on this analysis, Hazucha (1987) also concluded that an $O_3$ concentration below which no pulmonary function response would be elicited could not be defined.
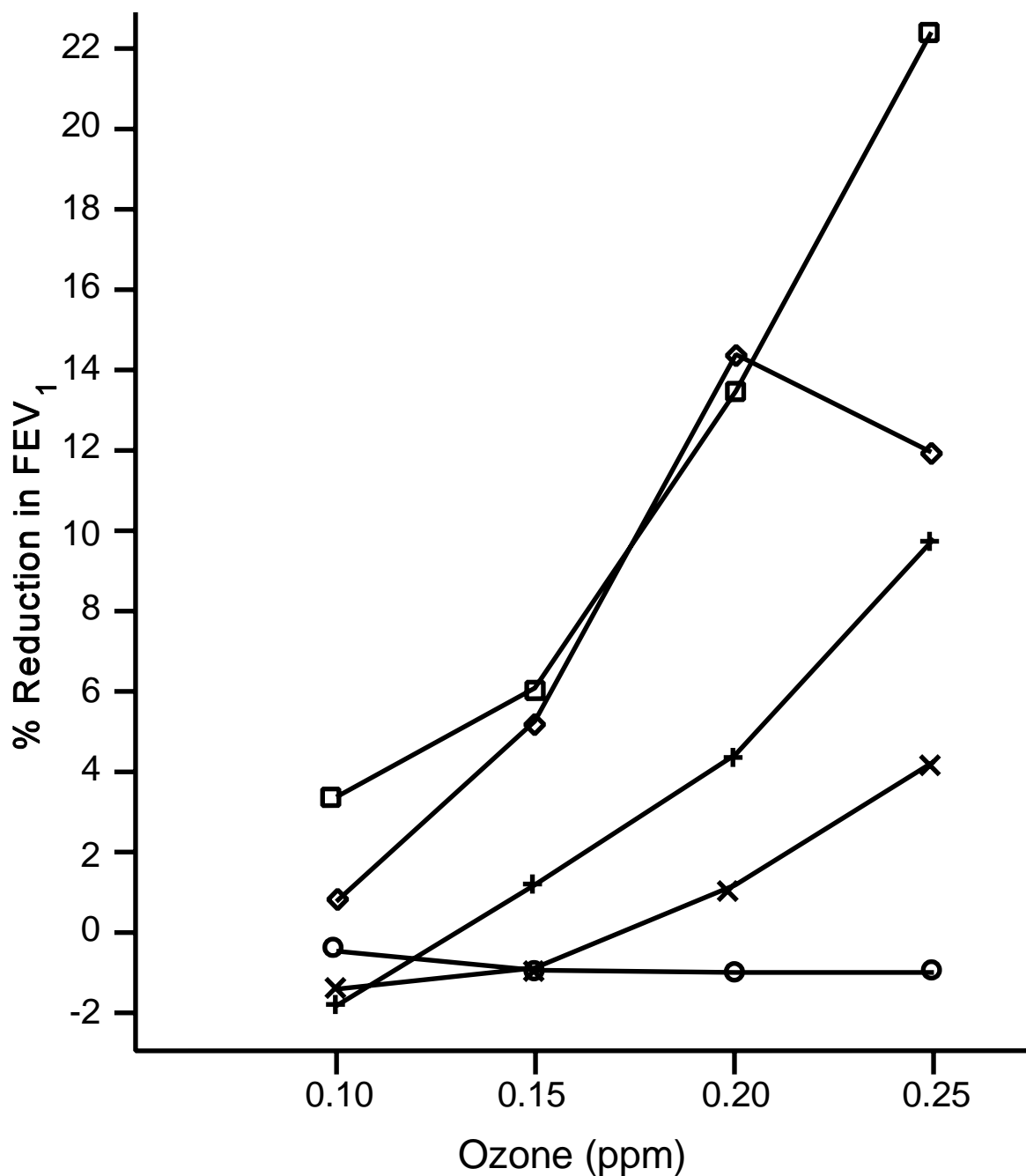
The studies reviewed in this subsection used different patterns (i.e., CE or IE) of exercise during their exposure protocols. An important question to ask is to what extent are the results of these studies comparable when total inhaled doses are the same but exercise pattern differs. A recent study by McKittrick and Adams (1995) addresses this question. These investigators exposed 12 aerobically trained men to 0.30 ppm $O_3$ (three protocols) and FA (three protocols) on six occasions. These protocols consisted of a 1 h CE ($O_3$ and FA) and two 2-h IE ($2 \times O_3$ and $2 \times$ FA) protocols delivered in random sequence separated by a minimum of 3 days. Lung function $FEV_1$ decrements of 17.6, 17.0, and 17.9% were obtained for the 1-h CE and the two 2-h IE, 0.3-ppm $O_3$ protocols, respectively. These values were significantly different from the FA values, but were not significantly different from each other. The $O_3$ CE protocols resulted in greater postexposure values for subjective symptoms than obtained with either of the $O_3$ IE protocols. However, the overall symptom severity during the last minute of exercise for the two IE protocols was not significantly different from the CE postexposure value. McKittrick and Adams (1995) concluded that when the total inhaled dose of $O_3$ is equivalent at a given $O_3$ concentration, there is no difference between pulmonary function responses induced by CE and IE protocols of 2-h or less duration, although subjective symptoms are reduced slightly during the last rest period of IE.

***Intersubject Variability, Individual Sensitivity, and the Association Between Responses***

Bates et al. (1972) noted that variation in sensitivity and response was evident for various symptoms and pulmonary functions assessed following $O_3$ exposure. This observation of large intersubject variability in response to $O_3$ also has been reported by numerous other investigators (Adams et al., 1981; Folinsbee et al., 1978; McDonnell et al., 1983; Kulle et al., 1985) and is illustrated by data from Kulle et al. (1985) plotted in Figure 7-1. The description of the factors that contribute to intersubject variability is important for the understanding of individual responses, mechanisms of response, and health risks associated with acute exposures. The effect of this large intersubject variability on the ability to predict individual responsiveness to $O_3$ was recently demonstrated by McDonnell et al. (1993). These investigators analyzed the data of 290 white male subjects (18 to 32 years of age) who inhaled either 0.00, 0.12, 0.18, 0.24, 0.30, or 0.40 ppm $O_3$ for 2 h while performing an IE protocol ($\dot{V}_E$ = 35 L/min/m$^2$ BSA) to identify personal characteristics (i.e., age, height, baseline pulmonary functions, presence of allergies, and past smoking history) that might predict individual differences in $FEV_1$ response. Of the personal characteristics studied, only age contributed significantly to intersubject responsiveness (younger subjects were more responsive), accounting for 4% of the observed variance. Interestingly, $O_3$ concentration accounted for only 31% of the variance, clearly demonstrating the importance of as yet undefined individual characteristics that determine responsiveness to $O_3$.

McDonnell et al. (1985b) examined the reproducibility of individual responses to $O_3$ exposure in healthy human subjects exposed twice, with from 21 to 385 days separating exposures (mean = 88 days). This investigation was conducted in order to determine whether the observed intersubject variability is due primarily to real differences in $O_3$ responsiveness among subjects, or whether it can be accounted for by other sources of variability. The authors examined FVC, $FEV_1$, $FEF_{25-75\%}$, $SR_{aw}$, cough, shortness of breath (SB), pain on deep inspiration (PDI), $V_T$, and f responses induced by $O_3$ exposure to concentrations ranging from 0.12 to 0.40 ppm. Reproducibility was assessed using the intraclass correlation coefficient (R), which incorporates into a single measure all the information contained in the correlation coefficient, slope, and intercept obtained in linear regression analysis. Similar to the more routinely used correlation coefficient, R is equal to one when two identical measurements occur in the same subject; and the "worst" possible coefficient is equal to $1/(n \square 1)$, which approaches zero for a large n. The ranking of most to least reproducible for the responses studied was FVC (R = 0.92), $FEV_1$ (R = 0.91), $FEF_{25-75\%}$ (R = 0.83), cough (R = 0.77), SB (R = 0.60), $SR_{aw}$ (R = 0.54), PDI (R = 0.37), f (R = $\square$0.20), and $V_T$ (R = $\square$0.03). The value of R was significantly different from zero for FVC, $FEV_1$, $FEF_{25-75\%}$, cough, SB, and $SR_{aw}$. McDonnell et al. (1985b) concluded that the reported large intersubject variability in magnitude of response was due to large differences in the intrinsic responsiveness of individual subjects to $O_3$ exposure. However, the factors that contribute to this large intersubject variability remain undefined.

The examination of intersubject variability is complicated by a poor association between the various $O_3$ responses. In their study investigating $O_3$ exposure-response relationships, McDonnell et al. (1983) observed very low correlation between changes in $SR_{aw}$ and FVC (r = $\square$0.16) for 135 subjects exposed to $O_3$ concentrations ranging from 0.12 to 0.40 ppm for 2.5 h.

**Figure 7-1.** *Individual concentration-response curves for five separate subjects exposed to 0.10, 0.15, 0.20, and 0.25 ppm ozone ($O_3$) for 2 h with moderate intermittent exercise. Illustrates the wide variability in responsiveness to $O_3$ from individual to individual.*

Source: Kulle et al. (1985).

### *Mechanisms of Acute Pulmonary Responses*

The pulmonary responses observed during and following acute exposure to $O_3$ at concentrations between 0.1 and 0.5 ppm in normal healthy human subjects include decreases in TLC, IC, FVC, $FEV_1$, $FEF_{25 75\%}$, and $V_T$; and increases in $SR_{aw}$, f, and airway responsiveness. Ozone exposure also has been shown to result in the symptoms of cough, PDI, SB, throat irritation, and wheezing. When viewed as a whole, changes in these specific parameters can be categorized into four general responses: alterations in (1) lung volumes, (2) airway caliber, (3) bronchomotor responsiveness, and (4) symptoms. The absence of consistent associations among the various responses from individual to individual suggests that the functional responses observed are the result of multiple interactions within the respiratory tract. These interactions may be the result of $O_3$ action on the biochemical, anatomical, and physiological systems of the respiratory tract. In turn, these factors determine $O_3$ dose distribution and the resulting cellular and reflex responses.

Bates et al. (1972) observed that the most significant decrement in pulmonary function was the reduction in the transpulmonary pressure at maximal inspiratory volume without a concomitant decrease in static compliance. This would suggest an inhibition of maximal inspiratory effort after $O_3$ exposure that may result in reductions in IC. These authors speculated that this inhibition is an early result of stimulation of rapidly adapting pulmonary stretch receptors, or "irritant receptors", located in the major bronchi. Since 1972, when this hypothesis was first published, numerous studies have examined the underlying mechanisms leading to the functional responses observed in human subjects. These mechanistic studies have used both animal models and human subjects. This discussion of mechanisms will focus on studies that used human subjects but also will cover those animal studies that have direct relevance to $O_3$-induced functional responses.

The acute inhalation of ambient concentrations of $O_3$ by healthy human subjects has been shown to result in a concentration-dependent increase in $R_{aw}$ (Folinsbee et al., 1978; McDonnell et al., 1983; Kulle et al., 1985; Seal et al., 1993). This $O_3$-induced increase in $R_{aw}$ has been shown to be poorly correlated with changes in forced expiratory endpoints (McDonnell et al., 1983). Ozone-induced increases in $R_{aw}$ have a rapid onset (Beckett et al., 1985) compared with the gradual development of decrements in forced expiratory endpoints (Kulle et al., 1985). Ozone-induced increases in $R_{aw}$ also appear to be greater in atopic subjects as a group (Kreit et al., 1989; McDonnell et al., 1987), although this does not appear to be the case for $O_3$-induced decrements in FVC and symptoms. Taken together, these observations suggest that different pathways lead to $O_3$-induced decrements in IC and to $O_3$-induced increments in $R_{aw}$.

Increases in $R_{aw}$ induced by $O_3$ have been shown to be blocked by atropine sulfate pretreatment in human subjects (Beckett et al., 1985; Adams, 1986). This inhibition suggests that the release of acetylcholine from parasympathetic postganglionic fibers that innervate airway smooth muscle plays a role in this response. However, the observation that a 2-h, 0.6 ppm $O_3$ inhalation also results in a hyperresponsiveness to methacholine, a cholinergic agent (Holtzman et al., 1979), suggests the possibility that acute $O_3$ exposure also can increase the sensitivity of airway smooth muscle to acetylcholine independent of a reflex mechanism involving cholinergic postganglionic nerves. The role that an increase in airway smooth muscle sensitivity to the endogenous release of acetylcholine might play in $O_3$-induced increases in $R_{aw}$ has not been studied.

Analyses by Colucci (1983) have suggested that the increase in $R_{aw}$ is not as large as would be expected when $O_3$ exposure is combined with moderate to heavy exercise. However, the observation that circulating epinephrine levels increase as a function of the relative workload in exercising human subjects (Galbo, 1983; Warren and Dalton, 1983) suggests that stimulation of airway smooth muscle beta-adrenoreceptors may counteract airway smooth muscle contraction induced by $O_3$ exposure. The observations by Beckett et al. (1985) that the beta-agonists abolish $O_3$-induced bronchoconstriction is consistent with this possibility.

Another question to be addressed with regard to $O_3$-induced increases in $R_{aw}$ is where along the airway (central versus peripheral airways) is the increase in resistance produced? Studies of acutely and subchronically exposed animals have demonstrated tissue damage in the centriacinar region (Castleman et al., 1977; Mellick et al., 1977), as well as increases in peripheral resistance and reactivity (Gertner et al., 1983a,b,c; Beckett et al., 1988). Keefe et al. (1991) examined the possibility of an effect on small airways using an inhaled aerosol bolus dispersion technique in 22 healthy, nonsmoking male subjects exposed to 0.4 ppm $O_3$ for 1 h using a CE protocol ($\dot{V}_E$ = 20 L/min/m$^2$ BSA). The bolus dispersion technique is not dependent on vital capacity maneuvers and compares the profile of a bolus of small (0.5- to 1.0-□m) aerosol particles injected into the inspired airstream (at a fixed lung volume) with the profile of the bolus during expiration. Dispersion of the bolus during expiration can be affected by increases in turbulence within the airway, the development of asymmetries in ventilation due to unequal regional time constants within the lung, and an increase in aerosol deposition in the small airways. Keefe et al. (1991) observed that $O_3$ exposure in their subjects resulted in a significant increase in dispersion of an aerosol bolus (without an increased aerosol deposition) that was not correlated with changes in $SR_{aw}$. These findings suggest that exposure to 0.4 ppm $O_3$ under the conditions of this experiment results in changes in small airway function that are not detectable by more conventional techniques.

Ozone-induced alterations in ventilatory pattern have been observed in exercising dogs (Lee et al., 1979) and humans (Adams et al., 1981; Folinsbee et al., 1978; McDonnell et al., 1983; Kulle et al., 1985). In exercising humans, $O_3$ exposure has been shown to result in a decrease in $V_T$ and an increase in f in the absence of any change in $\dot{V}_E$. A rapid, shallow breathing pattern is consistent with the maintenance of an appropriate ventilation with a reduced VT. Reduction of VT is probably related to the reduction of IC and is anecdotally related to reduction in breathing discomfort caused by PDI.

Lee et al. (1979), who produced a reversible vagotomy by cooling the vagus nerves to 0 □C, abolished the rapid, shallow breathing induced by $O_3$ inhalation in conscious dogs. More recently, Schelegle et al. (1993) have shown in anesthetized dogs exposed to $O_3$ that cooling the cervical vagus nerves to 7 □C did not abolish the observed $O_3$-induced rapid, shallow breathing pattern and bronchoconstriction, but cooling the vagus nerves to 0 □C did abolish both the rapid, shallow breathing and the bronchoconstriction. These findings suggest that $O_3$ stimulates nonmyelinated C fiber afferents arising from the lung, whose conduction is not totally blocked at 7 □C but is blocked totally at 0 □C. This conclusion is consistent with the findings of Coleridge et al. (1993) that bronchial C fibers are the only receptors that are stimulated directly during $O_3$ inhalation in anesthetized dogs. If similar bronchial C fibers were stimulated or sensitized in humans exposed to $O_3$, this could explain the $O_3$-induced rapid, shallow breathing observed during exercise, as well as the subjective symptoms associated with taking a deep inspiration.

Hazucha et al. (1989) exposed 11 healthy normal volunteers to FA and 0.5 ppm $O_3$ for 2 h while they were performing moderate IE. Ozone exposure induced a significant decrement in FVC, which was associated with a marked fall in IC without an increase in residual volume. Spraying of the upper airway with lidocaine aerosol in these subjects was immediately followed by return of FVC toward control values. Hazucha et al. (1989) concluded that $O_3$ inhalation stimulates lidocaine-sensitive tracheal and laryngeal airway receptors, which leads to an involuntary inhibition of full inspiration, a reduction in FVC, and a concomitant decrease in maximal expiratory flow rates in humans.

The airway afferents blocked by lidocaine in the Hazucha et al. (1989) investigation remain undefined. However, it seems likely that the lung afferents involved are the same ones that result in $O_3$-induced rapid, shallow breathing in dogs (i.e., bronchial C fibers). When stimulated with exogenous chemicals in animal experiments, bronchial C fibers induce a reflex apnea (Coleridge and Coleridge, 1986). In dogs, this reflex apnea involves the inhibition of inspiratory neurons, expiratory neurons, and □- and □-motoneurons in the intercostal nerves (Koepchen et al., 1977; Schmidt and Wellhoner, 1970). Such a reflex response in humans would explain the reflex inhibition of maximal inspiration consequent to acute $O_3$ exposure.

Data consistent with an $O_3$-induced stimulation of bronchial C fibers in human subjects recently has been published by Hazbun et al. (1993). These investigators observed a significant increase in substance P, the neurotransmitter released from the afferent endings of bronchial C fiber during excitation, in segmental airway washings of seven (2 female/5 male) healthy, nonsmoking subjects after a 1 h CE ($\dot{V}_E$ = 30 L/min/m$^2$ BSA) exposure to 0.25 ppm $O_3$. Substance P was not elevated in bronchoalveolar lavage (BAL) fluid after air exposure. In addition, the segmental airway substance P levels were significantly correlated ($r^2$ = 0.89; $p < 0.05$) with an elevated airway concentration of 8-epi-prostaglandin $F_{2□}$, a marker of oxidative free radical reactions. These results are consistent with (1) an increased release of substance P secondary to an increased discharge of bronchial C fibers induced by $O_3$ inhalation, and (2) an $O_3$-induced inhibition of neutral endopeptidase, the enzyme that degrades substance P within the airways.

Lung C fibers have been shown to be stimulated by prostaglandin $E_2$ and other lung autacoids (Coleridge et al., 1978, 1976). Interestingly, Schelegle et al. (1987), Eschenbacher et al. (1989), and Ying et al. (1990) have shown that pretreatment with the cyclooxygenase inhibitor indomethacin reduces and, in some cases, totally abolishes $O_3$-induced pulmonary function decrements in human subjects. Schelegle et al. (1987) examined whether $O_3$-induced pulmonary function decrements could be inhibited by the prostaglandin synthetase inhibitor indomethacin in healthy human subjects. Fourteen college-age males completed six 1-h exposure protocols consisting of no drug, placebo, and indomethacin pretreatments, with FA and $O_3$ (0.35 ppm) exposure within each pretreatment. Pretreatments were delivered weekly in random order in a double-blind fashion. Exposures consisted of 1 h exercise on a cycle ergometer with work loads set to elicit a mean $\dot{V}_E$ of 60 L/min. Statistical analysis revealed significant effects for FVC and $FEV_1$ across pretreatment, with no drug versus indomethacin and placebo versus indomethacin comparisons being significant. These findings suggest that cyclooxygenase products of arachidonic acid, which are reduced by indomethacin inhibition of cyclooxygenase, play a role in the development of pulmonary function decrements. These and similar findings by Eschenbacher et al. (1989) and Ying et al. (1990) suggest that the release of some cyclooxygenase product consequent to $O_3$ inhalation plays a role in $O_3$-induced pulmonary function decrements. This idea is supported by the findings of Koren et al. (1991),

who obtained a positive correlation between $O_3$-induced pulmonary function decrements and the level of prostaglandin $E_2$ ($PGE_2$) in BAL fluid collected within 1 h after the end of exposure in human subjects who varied greatly in $O_3$ responsiveness.

The release of cyclooxygenase products of arachidonic acid from injured airway epithelium can thus be viewed as a link in a cascade of events, which begins with the initial reaction of $O_3$ with the tissues and ends with the observed pulmonary function responses. The apparent components of this chain of events include factors that influence (1) $O_3$ delivery to the tissue (e.g., the inhaled concentration, breathing pattern, and airway geometry); (2) $O_3$ reactions with components in airway surface liquid and epithelial cell membranes; (3) local tissue responses, including injury and inflammation; and (4) stimulation of neural afferents (bronchial C fibers) and the resulting reflex responses. It still is not understood how each event in this cascade contributes to the pulmonary responses induced by acute $O_3$ inhalation.

The influence that individual responsiveness has on this cascade of events has not been determined; however, recent data suggest that individual $O_3$ responsiveness may feed back and influence the distribution of $O_3$ dose within the lung. Gerrity et al. (1994) tested the hypothesis that $O_3$-induced rapid, shallow breathing helps to limit the dose of $O_3$ reaching the lower respiratory tract. They found that the degree of $O_3$-induced rapid, shallow breathing (25% decrease in $V_T$) was significantly correlated with a decrease in $O_3$ uptake efficiency of the lower respiratory tract. This observation may explain the recent data of Schelegle et al. (1991) and Aris et al. (1993a) that suggest individual responsiveness to $O_3$ as measured by $FEV_1$ decrements may be negatively correlated with the number of neutrophils (PMNs) present in BAL samples. However, the interrelationship among the responsiveness to $O_3$, the distribution of dose within the airway, and resulting airway inflammation is still poorly understood.

### 7.2.1.2 Subjects with Preexisting Disease
*Introduction*

Ten studies (König et al., 1980; Linn et al., 1982a; Koenig et al., 1985; Linn et al., 1978, 1983a; Solic et al., 1982; Kehrl et al., 1985; Superko et al., 1984; Silverman, 1979; Kulle et al., 1984) examining the pulmonary responses to acute $O_3$ exposures of less than 3 h in patients with preexisting disease were discussed in the 1986 criteria document (U.S. Environmental Protection Agency, 1986). This section examines the effects of $O_3$ exposure on pulmonary function in subjects with preexisting disease by reviewing $O_3$ exposure studies that utilized subjects with (1) chronic obstructive pulmonary disease (COPD), (2) asthma, (3) allergic rhinitis, and (4) ischemic heart disease. Because of their important health implications, all of the available studies are reviewed and summarized in Table 7-2. Unless otherwise stated, the term "significant" is used to denote statistical significance at $p < 0.05$.

*Subjects with Chronic Obstructive Pulmonary Disease*

In five of the studies cited above, the $O_3$-induced pulmonary function responses of patients with mild to moderate COPD were examined (König et al., 1980; Linn et al., 1982a, 1983a; Solic et al., 1982; Kehrl et al., 1985). No significant changes in pulmonary function or symptoms were reported in any of the studies of the effects of $O_3$ in patients with COPD. Four of these studies (Linn et al., 1982a, 1983a; Solic et al., 1982; Kehrl et al., 1985) examined the

effects of $O_3$ concentrations between 0.1 and 0.3 ppm $O_3$ in 66 mild to moderate COPD patients using mild IE exposure protocols of 1 to 2 h duration. The total

## Table 7-2. Ozone Exposure in Subjects with Preexisting Disease[a]

| Ozone Concentration[b] ppm | $\mu g/m$ | Exposure Duration and Activity | Exposure Condition | Number and Gender of Subjects | Subject Characteristics | Observed Effect(s) | Reference |
|---|---|---|---|---|---|---|---|
| *Subjects with Chronic Obstructive Pulmonary Disease* | | | | | | | |
| 0.12 | 236 | 1 h IE (2 × 15 min light bicycle ergometry) | Tdb = 25 °C RH = 50% | 18 M, 7 F | 8 smokers, 14 ex-smokers, 3 nonsmokers; $FEV_1/FVC = 32$ to 66% | No significant changes in pulmonary function measurements; small significant decrease in arterial $O_2$ saturation. | Linn et al. (1982a) |
| 0.18 0.25 | 353 490 | 1 h IE (2 × 15 min light bicycle ergometry) | Tdb = 25 °C RH = 50% | 15 M, 13 F | 15 smokers, 11 ex-smokers, 2 nonsmokers; $FEV_1/FVC = 36$ to 75% | No significant changes in pulmonary function measurements; no significant change in arterial $O_2$ saturation. | Linn et al. (1983a) |
| 0.20 | 392 | 2 h IE (4 × 7.5 min light treadmill running) | Tdb = 22 °C RH = 40% | 13 M | 8 smokers, 4 ex-smokers, 1 nonsmoker; productive cough; $FEV_1/FVC = 46$ to 70% | No significant changes in pulmonary function measurements; small significant decrease in arterial $O_2$ saturation. | Solic et al. (1982) |
| 0.30 | 588 | 2 h IE (4 × 7.5 min light treadmill running) | Tdb = 22 °C RH = 40% | 13 M | 9 smokers, 4 nonsmokers; $FEV_1/FVC = 37$ to 65% | No significant changes in pulmonary function measurements or arterial $O_2$ saturation. | Kehrl et al. (1985) |
| 0.41 | 804 | 3 h daily (1 × 15 min light bicycle ergometry during each exposure) for 5 days | Tdb = 22 °C RH = 50% | 17 M, 3 F | All smokers; productive cough; $FEV_1/FVC = 56$ to 82% and/or $FEV_3/FVC = 75$ to 93% | Decrease in FVC and $FEV_3$ with 0.41 ppm $O_3$ compared with FA exposure. | Kulle et al. (1984) |
| *Subjects with Heart Disease* | | | | | | | |
| 0.20 0.30 | 392 588 | 40 min CE treadmill walking | NA | 6 M | Coronary heart disease with angina pectoris threshold | No significant changes in pulmonary function measurements, exercise ventilatory pattern, oxygen uptake, or cardiovascular parameters. | Superko et al. (1984) |

# Table 7-2 (cont'd).  Ozone Exposure in Subjects with Preexisting Disease[a]

| Ozone Concentration[b] ppm | [μ]g/m^{3} | Exposure Duration and Activity | Exposure Conditions | Number and Gender of Subjects | Subject Characteristics | Observed Effect(s) | Reference |
|---|---|---|---|---|---|---|---|
| **Subjects with Allergic Rhinitis** | | | | | | | |
| 0.18 | 353 | 2 h IE (4 × 15 min) | NA | 26 M | History of allergic rhinitis | Increased respiratory symptoms, $SR_{aw}$, and reactivity to histamine with $O_3$ exposure and decreased FVC, $FEV_1$, and $FEF_{25-75\%}$ with $O_3$ exposure compared to FA. | McDonnell et al. (1987) |
| 0.50 | 980 | 4 h rest | Tdb = 20 to 24 [°]C RH = 40 to 48% | 6 M, 6 F | History of seasonal allergic rhinitis; acute response to nasal challenge with antigen | Increase in upper and lower respiratory symptom scores, cell influx, epithelial cells with $O_3$ exposure compared to FA; no effect on acute allergic response to nasal antigen challenge between $O_3$ and FA exposure. | Bascom et al. (1990) |
| **Adult Subjects with Asthma** | | | | | | | |
| 0.10 0.25 0.40 | 196 490 784 | 1 h light IE (2 × 15 min on treadmill, $\dot{V}_E$ = 27 L/min) | Tdb = 21[°] C RH = 40% | 12 M, 9 F, 19 to 40 years old | Stable mild asthmatics with $FEV_1 > 70\%$ and methacholine responsiveness | No significant differences in $FEV_1$ or FVC were observed for 0.10 and 0.25 ppm $O_3$-FA exposures or postexposure exercise challenge; 12 subjects exposed to 0.40 ppm $O_3$ showed significant reduction in $FEV_1$. | Weymer et al. (1994) |
| 0.12 | 236 | 1 h rest | NA | 7 M, 8 F | Never smoked, mild stable asthmatics with exercise-induced asthma | Exposure to 0.12 ppm $O_3$ did not affect pulmonary function. Preexposure to 0.12 ppm $O_3$ at rest did not affect the magnitude or time course of exercise-induced bronchoconstriction. | Fernandes et al. (1994) |
| 0.12 | 236 | 0.75 h IE $\dot{V}_E$ = 30 L/min (15 min rest, 15 min exercise, 15 min rest) followed by 15 min exercise inhaling 0.10 ppm $SO_2$ | Tdb = 22[°] C RH = 75% | 8 M, 5 F, 12 to 18 years old | Asthmatics classified on basis of positive clinical history and methacholine challenge. Asymptomatic at time of study. | Filtered air followed by $SO_2$ and $O_3$ alone did not cause significant changes in pulmonary function.  Ozone followed by $SO_2$ resulted in significant decrease in $FEV_1$ (8%) and $\dot{V}_{max50\%}$ (15%) and a significant increase in $R_T$ (19%). | Koenig et al. (1990) |

## Table 7-2 (cont'd).  Ozone Exposure in Subjects with Preexisting Disease[a]

| Ozone Concentration[b] | | Exposure Duration and Activity | Exposure Conditions | Number and Gender of Subjects | Subject Characteristics | Observed Effect(s) | Reference |
|---|---|---|---|---|---|---|---|
| ppm | $\mu$g/m^{3} | | | | | | |
| *Adult Subjects with Asthma (cont'd)* | | | | | | | |
| 0.12 0.24 | 236 472 | 1.5 h IE, $\dot{V}_E$ = 25 L/min | Tdb = 22 C RH = 65% | 4 M, 4 F (nonasthmatics); 18 to 35 years old; 5 M, 5 F (asthmatics); 18 to 41 years old | Physician-diagnosed asthma confirmed with methacholine challenge test. All nonsmokers and asymptomatic at time of study. Nine were atopic. | No significant changes in pulmonary and nasal function measurements in either asthmatics or nonasthmatics. Significant increase in nasal lavage white cell count and epithelial cell following $O_3$ exposure in asthmatics only. | McBride et al. (1994) |
| 0.12 | 236 | 6.5 h/day IE (6 × 50 min) (2 days of exposure), $\dot{V}_E$ = 28 L/min (asthmatic), $\dot{V}_E$ = 31 L/min (healthy) | NA | 8 M, 7 F (nonasthmatics); 22 to 41 years old; 13 M, 17 F (asthmatics); 18 to 50 years old | Asthmatics classified on basis of positive clinical history, previous physician diagnosis, and low $PD_{20}$. Mild to severe asthmatics. | Significant increase in bronchial reactivity to methacholine in both asthmatics and nonasthmatics.  $FEV_1$ decreased 8.6% in asthmatics and 1.7% in nonasthmatics, with difference not being significant. | Linn et al. (1994) |
| 0.12 | 236 | 1 h rest | NA | 4 M, 3 F, 21 to 64 years old | Mild, stable asthma | Increase in bronchial responsiveness to allergen; no change in baseline airway function. | Molfino et al. (1991) |
| 0.20 | 392 | 2 h IE (4 × 15 min at 2× rest $\dot{V}_E$ cycle ergometry) | Tdb = 31 C RH = 35% | 20 M, 2 F, 19 to 59 years old | Physician diagnosed asthma; 6 smokers, 9 ex-smokers, 7 nonsmokers | No significant changes in pulmonary function measurements; significant blood biochemical changes. | Linn et al. (1978) |
| 0.25 | 490 | 2 h rest | NA | 5 M, 12 F, 20 to 71 years old | Nonsmoking asthmatics selected from a clinical practice | No significant changes in pulmonary function measurements. | Silverman (1979) |

## Table 7-2 (cont'd). Ozone Exposure in Subjects with Preexisting Disease[a]

| Ozone Concentration[b] | | Exposure Duration and Activity | Exposure Conditions | Number and Gender of Subjects | Subject Characteristics | Observed Effect(s) | Reference |
|---|---|---|---|---|---|---|---|
| ppm | $\square$g/m | | | | | [3] | |
| **Adult Subjects with Asthma (cont'd)** | | | | | | | |
| 0.40 | 784 | 2 h IE (4 × 15 min cycle ergometry) | Tdb = 22 $\square$C RH = 50% | 4 M, 5 F (normals), 19 to 31 years old; 4 M, 5 F (asthmatics), 18 to 34 years old | Asthmatics as diagnosed by a physician; history of chest tightness and wheezing | Decrease in FVC and IC with $O_3$ in asthmatics; increase in airway responsiveness to methacholine in asthmatics with $O_3$ and FA; asthmatic subjects had significantly greater decreases in $FEV_1$ and $FEF_{25-75\%}$ with $O_3$ exposure than did normal subjects. | Kreit et al. (1989) Eschenbacher et al. (1989) |
| **Adolescent Subjects with Asthma** | | | | | | | |
| 0.12 | 235 | 1 h rest | Tdb = 22 $\square$C RH $\square$75% | 4 M, 6 F (normals), 13 to 18 years old; 4 M, 6 F (asthmatics), 11 to 18 years old | Asthmatics had a history of atopic extrinsic asthma and exercise-induced bronchospasm | Decrease in FRC with $O_3$ exposure in asthmatics; no consistent significant changes in pulmonary functional parameters in either group or between groups. | Koenig et al. (1985) |
| 0.12 | 235 | 1 h IE (2 × 15 min treadmill walking at mean $\dot{V}_E$ = 32.5 L/min) | Tdb = 22 $\square$C RH $\square$75% | 5 M, 8 F (normals), 12 to 17 years old; 9 M, 3 F (asthmatics), 12 to 17 years old | Asthmatics selected from a clinical practice and had exercise-induced bronchospasm | Decrease in maximal flow at 50% of FVC in asthmatics with $O_3$ exposure compared to FA; no significant changes with combined $O_3$-$NO_2$ exposure. | Koenig et al. (1988) |
| 0.12 0.18 | 235 353 | 40 min IE (1 × 10 min treadmill walking at mean $\dot{V}_E$ = 32.5 L/min) | NA | 4 M, 9 F (normals), 14 to 19 years old; 8 M, 8 F (asthmatics), 12 to 19 years old | Asthmatics had allergic asthma, positive responses to methacholine, and exercise-induced bronchospasm | Decrease in $FEV_1$ and increase in $R_T$ in normals and asthmatics with 0.12 and 0.18 ppm $O_3$ exposure compared to FA; no consistent differences between normals and asthmatics. | Koenig et al. (1987) |

[a]See Appendix A for abbreviations and acronyms.
[b]Grouped by rest and exercise; within groups listed from lowest to highest $O_3$ concentration.

exercise time in all four of these studies was 30 min, with intensity being variable (exercise $\dot{V}_E$ approximately 14 to 28 L/min).  Linn et al. (1982a) observed a small but significant reduction in arterial oxygen saturation in 25 mild to moderate COPD patients at the end of the 0.12 ppm $O_3$ exposure for 1 h (absolute mean difference = 1.3%, $p < 0.05$).  Similarly, Solic et al. (1982) observed a small reduction in arterial oxygen saturation in 13 mild to moderate COPD patients at the end of a 0.2-ppm $O_3$ exposure for 2 h (absolute mean difference = 0.48%, $p < 0.008$).  In contrast, Kehrl et al. (1985) did not find a significant effect on arterial oxygen saturation in 13 mild to moderate COPD patients after exposure to 0.3 ppm $O_3$ using the same IE exposure protocol used by Solic et al. (1982).  Similarly, Linn et al. (1983a) found no significant effect on arterial oxygen  saturation in 28 mild to moderate COPD patients exposed to 0.18 and 0.25 ppm $O_3$ for 1 h.  The combined observations of these studies indicate that persons with COPD are not responsive to $O_3$ concentrations of 0.3 ppm and lower in combination with mild exercise.  However, this conclusion should be viewed within the context of the low total inhaled dose of $O_3$ involved in the above studies, in that studies in healthy subjects using similar total inhaled doses also have not shown significant pulmonary function effects.  Interpretation of these studies also is complicated by the wide range of the pulmonary function impairment of the patients studied ($FEV_1/FVC$ from 0.3 to 0.7), their variable smoking history, and the fact that these patients are older ($\square$60 years of age).  The inconsistency of the observed small decreases in arterial oxygen saturation makes the interpretation of the clinical significance of this data difficult and uncertain.

Despite similar limitations, Kulle et al. (1984) observed small ($<4\%$), statistically significant decreases in FVC and $FEV_3$ in 20 smokers (age range 31 to 51 years) diagnosed with mild chronic bronchitis exposed to 0.4 ppm $O_3$ for 3 h using an IE protocol (one 15-min exercise period beginning 1 h prior to end of exposure, $\dot{V}_E$ approximately 29 to 38 L/min). In addition, Kulle et al. (1984) observed that repeated daily exposure over a 5-day period led to an attenuation of these forced expiratory endpoints, and that this attenuation did not last longer than 4 days.  The pulmonary responses induced by $O_3$ exposure in this study were associated only with mild symptoms.

### Subjects with Asthma

Three studies examining the pulmonary responses to acute $O_3$ exposures in adult (Linn et al., 1978; Silverman, 1979) and adolescent (Koenig et al., 1985) asthmatics were discussed in the earlier criteria document (U.S. Environmental Protection Agency, 1986). Significant decrements in group mean pulmonary function were not observed for adult asthmatics exposed for 2 h at rest (Silverman, 1979) or with light IE (Linn et al., 1978) to $O_3$ concentrations of 0.25 ppm or less.  However, it should be noted that, although group mean pulmonary function responses were not significantly affected in these studies, there were responsive asthmatic subjects who had obvious decrements in pulmonary function.

Koenig and co-workers (Koenig et al., 1985, 1987, 1988) conducted a series of studies examining the pulmonary responses of adolescent asthmatics and nonasthmatics (11 to 19 years of age) exposed to low levels of $O_3$.  Koenig et al. (1985) found no significant changes in pulmonary function or symptoms in 10 adolescent normal and asthmatic subjects (four male, six female) who inhaled 0.12 ppm $O_3$ for 1 h at rest.  The asthmatic subjects in this study were characterized as having histories of atopic (Type I, immunoglobulin E [IgE]-mediated) asthma and exercise-induced bronchospasm.  Subsequently, in two separate studies of similar groups of adolescent asthmatics and nonasthmatics, Koenig et al. (1987, 1988)

observed no significant changes in pulmonary function or symptoms following exposure to 0.12 and 0.18 ppm $O_3$ with moderate IE up to 1 h, although a small significant decrease in flow at 50% of FVC was observed in the adolescent asthmatics exposed to 0.12 ppm $O_3$.

Kreit et al. (1989) and Eschenbacher et al. (1989) have demonstrated that exposure to 0.4 ppm $O_3$ with heavy IE (exercise $\dot{V}_E$ = 30 L/min/m$^2$ BSA) for 2 h elicits a significant decrease in FVC, $FEV_1$, $FEV_1$/FVC, and $FEF_{25\,75\%}$ in both normal and asthmatic subjects. In these studies, $O_3$ exposure caused significantly greater decrements in $FEV_1$, $FEV_1$/FVC, and $FEF_{25\,75\%}$ in asthmatic subjects. In contrast, Kreit et al. (1989) and Eschenbacher et al. (1989) found no significant difference between asthmatic and normal subjects in FVC and subjective symptoms. In addition, the effect of $O_3$ exposure on bronchial responsiveness as measured by the concentration of methacholine needed to increase $SR_{aw}$ 100% ($PC_{1\ SRaw}$) was also studied. The asthmatic subjects had a significant decrease in $PC_{1\ SRaw}$ following FA and $O_3$ exposure. In comparison, the normal subjects had a significant decrease in $PC_{1\ SRaw}$ following $O_3$ exposure, with the percent decrease in mean $PC_{1\ SRaw}$ after $O_3$ exposure being similar in normal and asthmatic subjects, although the asthmatic patients' baseline $PC_{1\ SRaw}$ was significantly lower than that of the normal subjects. The findings of this study indicate that if the total inhaled dose is increased sufficiently by either increasing $\dot{V}_E$ during exposure or $O_3$ concentration, mild to moderate asthmatics will respond with a greater obstructive response than will normal subjects.

Linn et al. (1994) have reported responses of healthy (n = 15) and asthmatic (n = 30) subjects to 0.12 ppm $O_3$ and 100 □g/m$^3$ of respirable sulfuric acid ($H_2SO_4$) aerosol (MMAD = 0.5 □m; geometric standard deviation [□$_g$] = 2), alone and in combination using the EPA prolonged-exposure protocol (see Section 7.2.2). These investigators observed a significant $O_3$-induced reduction in $FEV_1$ that was statistically significant and an increase in airway responsiveness to methacholine for all subjects combined. The asthmatic subjects demonstrated a statistically significant decrease in $FEV_1$ as a function of exposure duration regardless of pollutant exposure. In addition, there was a greater reduction in $FEV_1$ following $O_3$ alone in the asthmatics as compared to the nonasthmatics (□8.6% versus □1.7%), although this difference was not statistically significant. Despite the lack of a significant difference between asthmatics' and nonasthmatics' group mean $FEV_1$ responses with $O_3$ exposure, the responses observed in the asthmatics may be considered more important because their average $FEV_1$ was already significantly depressed by the underlying illness.

The findings of the above studies comparing the pulmonary function responses following $O_3$ exposure in asthmatic and nonasthmatic subjects suggest that asthmatics are at least as sensitive, if not more sensitive, to the acute effects of $O_3$ inhalation. The underlying mechanism that would explain a possible increased responsiveness of asthmatic subjects to $O_3$ is undefined. One possible mechanism could be that asthmatic subjects have an exaggerated airway inflammatory response to acute $O_3$ exposure. A study conducted by McBride et al. (1994) would support this hypothesis. McBride et al. (1994) exposed 10 asymptomatic asthmatic subjects with histories of allergic rhinitis and 8 nonallergic healthy subjects to FA and 0.12 and 0.24 ppm $O_3$ for 90 min using a light IE protocol ($\dot{V}_E$ = approximately 25 L/min). Pulmonary function tests, posterior rhinomanometry, and nasal lavage (NL) were performed before exposure and 10 min and 6 and 24 h after exposure. No significant changes in pulmonary or nasal function were found in either the allergic asthmatic or nonallergic nonasthmatic subjects. The allergic asthmatic subjects had a significant increase in the number of white blood cells in NL fluid 10 min and 24 h following the 0.24-ppm $O_3$ exposure. In

addition, a significant increase in epithelial cells was present 10 min after exposure to 0.24 ppm $O_3$ in the asthmatic subjects. No significant cellular changes were observed in the nonasthmatic subjects. These data indicate that the upper airways of asthmatic individuals are more sensitive to the acute inflammatory effects of $O_3$ than those of nonallergic nonasthmatic subjects.

The above studies compared the effects of $O_3$ inhalation on pulmonary function in asthmatic and normal subjects, but do not address the effect of preexposure to ambient concentrations of $O_3$ on the responsiveness of asthmatic subjects to other respiratory challenges, including other irritant gases, allergens, and exercise. Koenig et al. (1990) reported an increase in the bronchial response to an $SO_2$ challenge in a group of 13 asymptomatic adolescent asthmatic subjects following inhalation of 0.12 ppm $O_3$ for 45 min using a light to moderate IE protocol ($\dot{V}_E$ = approximately 30 L/min).

Molfino et al. (1991) investigated whether resting exposure to 0.12 ppm $O_3$ for 1 h potentiates the airway response to inhaled allergen in seven patients with mild asthma with seasonal symptoms of asthma and positive skin tests for ragweed or grass. This study was conducted over four week-long periods during the winter when ambient allergen levels were low. In each week, there were 3 consecutive study days. On Days 1 and 3, subjects underwent methacholine challenges, whereas, on Day 2, the subjects received one of four combined challenges in a single-blind design: (1) air breathing followed by inhalation of allergen diluent, (2) $O_3$ exposure followed by inhalation of allergen diluent, (3) air breathing followed by inhalation of allergen, and (4) $O_3$ exposure followed by inhalation of allergen. Molfino et al. (1991) observed no significant differences in baseline $FEV_1$ after $O_3$ exposure, but did observe a significant reduction in the provocative concentration of allergen required to reduce $FEV_1$ 15%. This study was limited by its small number of subjects, and the results were confounded by possible ordering effects with the "$O_3$ exposure followed by allergen protocol" being the last protocol for all but one subject. Despite these limitations, the findings suggest that $O_3$ concentrations as low as 0.12 ppm may increase the bronchial responsiveness to allergen in atopic subjects.

In order to examine whether preexposure to $O_3$ results in exacerbation of exercise-induced asthma, two studies were conducted recently (Fernandes et al., 1994; Weymer et al., 1994). Fernandes et al. (1994) preexposed 15 stable mild asthmatics with exercise-induced asthma to 0.12 ppm $O_3$ for 1 h at rest followed by a 6-min exercise challenge test and found no significant effect on either the magnitude or time course of exercise-induced bronchoconstriction. Similarly, Weymer et al. (1994) observed that preexposure to either 0.10 or 0.25 ppm $O_3$ for 60 min while performing light IE did not enhance or produce exercise-induced asthma in 21 otherwise healthy adult subjects with stable mild asthma. Although the results of these studies would suggest that preexposure to $O_3$ neither enhances nor produces exercise-induced asthma in asthmatic subjects, the relatively low total inhaled doses used in the above studies limit the ability to draw any definitive conclusions.

### Subjects with Allergic Rhinitis

McDonnell et al. (1987) exposed 26 adults (18 to 30 years of age) with allergic rhinitis to clean air and 0.18 ppm $O_3$ for 2 h using an IE protocol ($\dot{V}_E$ = 64 L/min at 15-min intervals). The study subjects with allergic rhinitis did not have a history of asthma-like symptoms. Following $O_3$ exposure, the subjects with allergic rhinitis exhibited significant increases in respiratory symptoms, airway reactivity to histamine, and $SR_{aw}$ and significant

decreases in FVC, $FEV_1$, and $FEF_{25-75\%}$ when compared to clean air exposure. When compared to normal subjects without allergic rhinitis similarly exposed to 0.18 ppm $O_3$, the subjects with allergic rhinitis were no more responsive to $O_3$, based on symptoms, forced expiratory parameters, or airway reactivity to histamine aerosols, although subjects with allergic rhinitis did have a small but significantly greater increase in $SR_{aw}$. The data on subjects with allergic rhinitis and asthmatic subjects suggest that both of these groups have a greater rise in $R_{aw}$ to $O_3$ with a relative order of airway responsiveness to $O_3$ being normal < allergic < asthmatic.

Bascom et al. (1990) conducted a study to characterize the upper respiratory response to acute $O_3$ inhalation, nasal challenge with antigen, and the combination of the two. Bascom et al. (1990) exposed 12 resting asymptomatic subjects with histories of allergic rhinitis in a randomized, crossover design on each of 2 days, separated by 2 weeks, to clean air or 0.5 ppm $O_3$ for 4 h. Following exposure, subjects underwent nasal challenge with four doses of antigen (1, 10, 100, and 1,000 protein nitrogen units of ragweed or grass). Upper and lower airway symptoms were rated and NL was performed before and after clean air and 0.5 ppm $O_3$ exposure, and following each antigen challenge. Exposure to $O_3$ caused significant increases in upper and lower airway symptoms, a mixed inflammatory cell influx with a sevenfold increase in NL PMNs, a 20-fold increase in eosinophils and a 10-fold increase in mononuclear cells as well as an apparent sloughing of epithelial cells. There was a significant increase in NL albumin concentration following $O_3$ exposure. When expressed as a change from the postexposure values, there was no significant difference between $O_3$ and clean air exposure in antigen-induced upper and lower airway symptoms, cells, albumin and mediators (histamine and TAME-esterase activity). These results suggest that acute exposure to $O_3$ does not alter the acute response to nasal challenge with antigen.

### Subjects with Ischemic Heart Disease

One study has been conducted examining the cardiopulmonary effects of acute $O_3$ inhalation in patients with ischemic heart disease. Superko et al. (1984) exposed six middle-aged males with angina-symptom-limited exercise tolerance for 40 min to FA and to 0.2 and 0.3 $O_3$ while they were exercising continuously according to a protocol simulating their angina-symptom-limited exercise training prescription (mean $\dot{V}_E$ = 35 L/min). No significant pulmonary function impairment or evidence of cardiovascular strain induced by $O_3$ inhalation was observed. The low workloads were dictated by the patients' angina-symptom-limited exercise tolerance, and these low workloads acted to "protect" them from $O_3$-induced effects by limiting the total inhaled dose.

### 7.2.1.3 Influence of Gender, Age, Ethnic, and Environmental Factors
### Gender Differences

As was noted in the previous $O_3$ criteria document (U.S. Environmental Protection Agency, 1986), the pulmonary function responses to $O_3$ of only a small number of female subjects have been evaluated under controlled laboratory conditions. Although the database on females has expanded (see Table 7-3), there are still fewer data than for males. Most studies involving mixed groups of male and female subjects include too few female subjects to allow for meaningful comparisons between the responses of the sexes, or fail to consider the question at all. There are, however, a few studies that utilize only female subjects. Several studies

cited in the 1986 $O_3$ criteria document suggested that females might be more responsive to $O_3$ than males (Horvath et al., 1979; Gliner et al., 1983; Gibbons and Adams,

## Table 7-3. Gender Differences in Pulmonary Function Responses to Ozone[a]

| Ozone Concentration[b] | | Exposure Duration and Activity | Exposure Conditions[c] | Number and Gender of Subjects | Subject Characteristics | Observed Effect(s) | Reference |
|---|---|---|---|---|---|---|---|
| ppm | $\mu$g/m$^3$ | | | | | | |
| 0.12 | 235 | 2.33 h | Mean T = 22 °C | 30 to 33 F and | Healthy NS, 18 to 35 years | Decrements in $FEV_1$, | Seal et al. (1993) |
| 0.18 | 353 | $\dot{V}_E$ = 25 L/min/m$^2$ | Mean RH = 4% | 30 to 33 M in | old, blacks and whites | increases in $SR_{aw}$ and cough, | |
| 0.24 | 470 | BSA | treadmill | each | | correlated with | |
| 0.30 | 588 | (one | | concentration | | $O_3$ concentration. There were | |
| 0.40 | 784 | exposure/subject) | | group; total of | | no significant differences | |
| | | | | 372 individuals | | between the responses of | |
| | | | | participated | | males and females. | |
| 0.18 | 353 | 1 h (mouthpiece) | T = 21 to 25 °C | 14 F | Mean FVC = 5.11 $\pm$ 0.53 | Significant concentration- | Messineo and Adams |
| | | CE | RH = 45 to 60% | | L, | response effect on FVC and | (1990) |
| | | $\dot{V}_E$ $\cong$ 47 L/min | cycle | | NS, 20 to 24 years old | $FEV_1$; lung size had no effect | |
| | | | | | | on percentage decrements in | |
| 0.30 | 588 | | | 14 F | Mean FVC = 3.74 $\pm$ 0.30 | FVC or $FEV_1$. | |
| | | | | | L, | | |
| | | | | | NS, 19 to 23 years old | | |
| 0.20 | 392 | 1 h (mouthpiece) | T $\cong$ 22 °C | 9 M | NS, 55 to 74 years old | No changes in spirometry in | Reisenauer et al. (1988) |
| 0.30 | 588 | IE (20 min exercise) | RH $\cong$ 75% | | | men or women. Women had | |
| | | $\dot{V}_E$ $\cong$ 28 L/min for | treadmill | 10 F | NS, 56 to 74 years old | significant 13% increase in $R_T$ | |
| | | men | | | | following exposure, which | |
| | | $\dot{V}_E$ $\cong$ 23 L/min for | | | | was sustained at 20 min | |
| | | women | | | | postexposure. | |
| 0.30 | 588 | 1 h (mouthpiece) | T = 21 to 25 °C | 20 M | NS, 18 to 30 years old | Significant decrements in | Adams et al. (1987) |
| | | CE | RH = 45 to 60% | | | FVC, $FEV_1$, and $FEF_{25-75\%}$ | |
| | | $\dot{V}_E$ $\cong$ 70 L/min for | cycle | 20 F | NS, 19 to 25 years old | following $O_3$ exposure. | |
| | | men | | | | No significant differences | |
| | | $\dot{V}_E$ $\cong$ 50 L/min for | | | | between men and women for | |
| | | women | | | | spirometry or $SR_{aw}$. | |

| Ozone Concentration[b] | | Exposure Duration and Activity | Exposure Conditions[c] | Number and Gender of Subjects | Subject Characteristics | Observed Effect(s) | Reference |
|---|---|---|---|---|---|---|---|
| ppm | $\mu$g/m$^3$ | | | | | | |
| 0.45 | 882 | 2 h IE $\dot{V}_E \approx$ 27.9 L/min for men $\dot{V}_E \approx$ 25.4 L/min for women | T = 24 °C RH = 58% cycle | 8 M  8 F | Healthy NS, 51 to 69 years old  Healthy NS, 56 to 76 years old | Range of responses in FEV$_1$: 0 to $-$12% (mean = $-$5.6%). No significant difference in responses of men and women. Tendency for women to have greater effects. | Drechsler-Parks et al. (1987a,b) |
| 0.45 | 882 | 2 h IE Mean $\dot{V}_E$ = 28.5 L/min for men Mean $\dot{V}_E$ = 26.1 L/min for women | Mean T = 23.1 °C Mean RH = 46.1% cycle/treadmill | 10 M  6 F | Healthy NS, 60 to 89 years old  Healthy NS, 64 to 71 years old | Mean decrement in FEV$_1$ = 5.7%. Decrements in FVC and FEV$_1$ were the only pulmonary functions significantly altered by O$_3$ exposure. No significant differences between responses of men and women. | Bedi et al. (1989) |
| 0.48 | 941 | 2 h IE $\dot{V}_E \approx$ 25 L/min | T = 21 °C WBGT cycle | 10 F | Healthy NS, 19 to 36 years old | Mean decrement in FEV$_1$ = 22.4%. Significant decrements in all spirometry measurements. Results not significantly different from a similar study on males (Drechsler-Parks et al., 1984). | Horvath et al. (1986) |

[a]See Appendix A for abbreviations and acronyms.
[b]Listed from lowest to highest O$_3$ concentration.
[c]WBGT = 0.7 T$_{wet\ bulb}$ + 0.3 T$_{dry\ bulb\ or\ globe}$.

1984; Lauritzen and Adams, 1985). DeLucia et al. (1983), on the other hand, did not find significant differences in the responses of young men and young women to $O_3$ exposure.
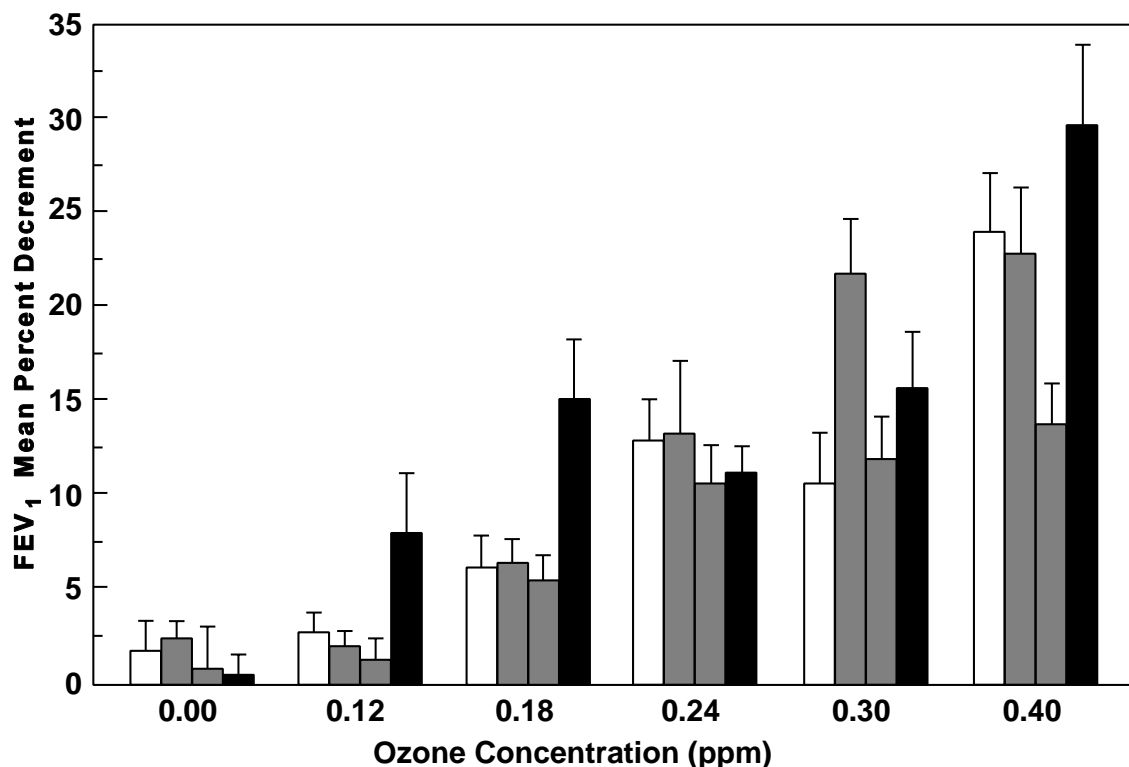
Messineo and Adams (1990) hypothesized that differences previously observed between the responses of males and females exposed to $O_3$ were related to differences in lung size between the sexes. They addressed this issue by selecting two groups of 14 women each. One group had a mean FVC of 5.11 L, and the other group had a mean FVC of 3.74 L. All subjects were 19 to 24 years of age and were healthy nonsmokers who had not lived in a high-air-pollution area for at least 6 mo. The subjects completed three 1-h CE ($\dot{V}_E$ = 47 L/min) exposures: (1) FA, (2) 0.18 ppm $O_3$, and (3) 0.30 ppm $O_3$. The mouthpiece exposures were presented in random order, at least 4 days apart, and all were performed when the subject was in the follicular phase of her menstrual cycle. Two subjects in the small-lung group and one in the large-lung group were unable to complete the 0.30 ppm $O_3$ exposure. Both groups had similar $O_3$-induced percentage decrements (9 to 10% following exposure to 0.18 ppm $O_3$ and 23 and 26% following exposure to 0.30 ppm $O_3$ for the small- and large-lung groups, respectively) in all measures of lung function, regardless of lung size, leading to the conclusion that lung size, per se, is not systematically related to percentage decrements in $FEV_1$ consequent to $O_3$ exposure.

Horvath et al. (1986) exposed 10 healthy, young, nonsmoking females, 19 to 36 years of age (mean age 23.6 years) to 0.48 ppm $O_3$ or FA for 2 h while they exercised intermittently at a target ventilation of 25 L/min. The subjects engaged in three 20-min cycle ergometer exercise periods alternated with four 15-min rest periods. The exposures were a minimum of 1 week apart. The responses of these subjects were compared with those of a group of 10 young males who earlier had completed the same protocol (Drechsler-Parks et al., 1984). There were no statistically significant differences in the responses based on gender. The female subjects had decrements of 18.8, 22.4, and 30.8% in FVC, $FEV_1$, and $FEF_{25\,75\%}$, respectively, compared to 19.8, 25.0, and 31.9% for the male subjects. On an individual basis, 4 of the 10 males and 3 of the 10 females had decrements of 30% or more in $FEV_1$ following the exposure to 0.48 ppm $O_3$. One male subject did not respond to the $O_3$ exposure. It was noted, however, that the female subjects inhaled an absolute dose of $O_3$ about 22% less than the male subjects due to a slightly lower exercise $\dot{V}_E$ and the inherently lower resting $\dot{V}_E$ of females compared to males. However, when $O_3$ dose was related to BSA or to FVC, the females inhaled slightly higher relative doses of $O_3$ than the males.

Adams et al. (1987) compared the responses of 20 young men (18 to 30 years of age) and 20 young women (19 to 35 years of age) exposed to 0.3 ppm $O_3$ via mouthpiece. All subjects were healthy nonsmokers with clinically normal pulmonary function. None had a history of significant allergies, and none had resided in a high-air-pollution area for at least 3 mo. The subjects completed 1-h CE exposures (mean $\dot{V}_E$ $\Box$ 70 L/min for males and 50 L/min for females) to FA and 0.3 ppm $O_3$. The exposures were given in random order and were separated by a minimum of 5 days. Ozone exposure induced significant decrements in FVC, $FEV_1$, and $FEF_{25\,75\%}$ compared to FA exposure. Three females and four males were unable to complete the $O_3$ exposure. Females experienced mean decrements of 14.2, 20.3, and 24.5% in FVC, $FEV_1$, and $FEF_{25\,75\%}$, respectively, compared to mean decrements of 15.8% in FVC, 23.8% in $FEV_1$, and 35.7% in $FEF_{25\,75\%}$ for males. There were no statistically significant differences between the spirometry or $SR_{aw}$ responses related to gender. Because the female subjects inhaled a substantially smaller absolute dose of $O_3$ due to the considerably lower exercise $\dot{V}_E$, yet had similar decrements in pulmonary function compared to men, the

authors concluded that females are more responsive to $O_3$ than males.  In this study, the female subjects inhaled a lower relative dose of $O_3$ compared to males, when expressed on the basis of BSA, but a similar relative dose when expressed on the basis of FVC.

Seal et al. (1993) reported on 372 healthy black and white men and women between 18 and 35 years of age who each were assigned to complete one 2.33-h exposure to FA, 0.12, 0.18, 0.24, 0.30, or 0.40 ppm $O_3$.  Subjects exercised intermittently on a motor-driven treadmill at a work load inducing a $\dot{V}_E$ of about 23 L/min/m$^2$ BSA for women and about 24.5 L/min/m$^2$ BSA for men.  Although female subjects inhaled about 22% less total dose of $O_3$ than males in each exposure-concentration group, there were no significant differences in the changes in $FEV_1$ (see Figure 7-2), $SR_{aw}$, or cough ratings between males and females among either blacks or whites.  Women also inhaled a lower absolute dose of $O_3$ than men.



**Figure 7-2.**  **Mean percent change (± standard error of the mean) in post-minus prevalues of forced expiratory volume in 1 s (FEV₁) for each gender-race group.  Open bars = white women; cross-hatched bars = black women; hatched bars = white men; solid bars = black men.**

Source:  Seal et al. (1993).

Drechsler-Parks et al. (1987a,b) compared the responses of eight men and eight women between 51 and 76 years of age to FA and 0.45 ppm $O_3$. The subjects were all healthy nonsmokers who were long-term residents of a relatively low pollution area. The subjects participated in 2-h IE (20 min rest/20 min exercise at $\dot{V}_E = 25$ L/min) exposures that were presented in random order and were separated by at least 1 week. Except for $FEV_3$, there were no statistically significant differences between the responses of the men and women subjects, although women had slightly larger mean decrements in FVC and $FEV_1$ than men. Individual decrements in FVC and $FEV_1$ ranged from 0 to about 12% for both male and female subjects. Based on $FEV_1$, two females and three males had no response to the $O_3$ exposure. Male subjects inhaled a somewhat larger absolute effective dose of $O_3$ due to higher exercise and resting $\dot{V}_E$. When $\dot{V}_E$ was normalized to BSA, females inhaled a larger dose of $O_3$ than males. When $\dot{V}_E$ was normalized to FVC, the relative inhaled doses of $O_3$ were similar.

Reisenauer et al. (1988) reported on the pulmonary function responses of 9 men and 10 women between 55 and 74 years of age who were exposed to 0.0, 0.2, and 0.3 ppm $O_3$. The three exposures were presented in random order and at the same time of day for each subject. The subjects were exposed via mouthpiece for 1 h, during which seven men exercised for 10 min and rested for 50 min, and the other two men and all of the women alternated two 20-min rest periods and two 10-min exercise periods. Ventilation rates were about 28 L/min for men and 23 L/min for women, although, when $\dot{V}_E$ was normalized to BSA, the relative $\dot{V}_E$ for males and females was similar. All data were pooled, regardless of the total exercise time. There were no significant changes in any parameter of pulmonary function in the males. Females had no significant changes in any spirometric parameter, but, following the 0.3-ppm $O_3$ exposure, did have a small (13%) increase in total respiratory resistance ($R_T$), which remained at this level 20 min postexposure.

Bedi et al. (1989) reported on the responses of 10 men and 6 women (60 to 89 years of age) exposed for 2 h to FA or 0.45 ppm $O_3$ for 3 consecutive days. Only the first $O_3$ day results will be discussed in this section; the issue of repeated exposures is addressed in Section 7.2.1.4. Exposures were conducted at the same time of day, on consecutive days, with the FA exposure always conducted first. The subjects alternated 20-min exercise periods (mean $\dot{V}_E = 28.5$ L/min for men and 26.1 L/min for women) and 20-min rest periods throughout the 2-h chamber exposures. When $\dot{V}_E$ was normalized to BSA, women inhaled slightly higher relative doses of $O_3$; but when normalized to FVC, women inhaled a slightly lower relative dose of $O_3$ than men. There were no statistically significant group mean differences between the responses of men and women subjects. The mean decrements in FVC and $FEV_1$ following the $O_3$ exposure for the 16 subjects were 2.8 and 5.7%, respectively. In an exploratory analysis, the subjects were divided into two groups based on whether their decrement in $FEV_1$ following the first $O_3$ exposure compared to the FA exposure was □5% or <5%. There were eight subjects in each group, with the sensitive group consisting of two females and six males. The mean post-$O_3$ exposure decrement in $FEV_1$ was 320 mL for the sensitive group, versus 21 mL for the nonresponsive group. Similar patterns of response were evident in FVC and $FEV_3$. There were no significant changes in any flow parameter, maximum voluntary ventilation (MVV), expiratory reserve volume, or functional residual capacity.

The question as to whether there is a difference in sensitivity to $O_3$ between men and women remains unresolved. Different conclusions depend on whether $\dot{V}_E$ is normalized to body or lung size in calculating the inhaled doses of $O_3$. The subgroups studied by Bedi et al. (1989) included six males and two females, suggesting that older males may be more sensitive

to $O_3$ than older females.  However, Reisenauer et al. (1988) found a significant increase in $R_T$ only in women.  Horvath et al. (1986), Adams et al. (1987), and Drechsler-Parks et al. (1987a,b) suggested that because their female subjects had similar pulmonary function responses to their male subjects, even though the females inhaled less $O_3$, females were more sensitive than males.  Messineo and Adams (1990) suggested that some factor other than absolute lung size accounted for observed differences between males and females; their two groups of females with widely different lung sizes experienced similar decrements in pulmonary function following equivalent exposures.  Although the currently available literature suggests that females may be somewhat more sensitive to $O_3$ than males, the question is not settled.  Further, comparative studies have included only small subject groups, except for Seal et al. (1993), and often only group mean data are presented, with little information about individual responses.

### Hormonal Influences

Seal et al. (1995) compared the pulmonary function responses of 48 white and 55 black women (18 to 35 years of age) whose menstrual phase was known at the time of a single 2.3-h exposure to 0.18, 0.24, 0.30, or 0.40 ppm $O_3$.  Subjects performed intermittent treadmill exercise ($\dot{V}_E$ = 20 L/min/m$^2$ BSA) during the first 2 h of exposure.  There were no significant effects for $SR_{aw}$ or cough that could be related to menstrual cycle.  There was a race × menstrual phase interaction for $FEV_1$.  However, when the groups of black and white women were analyzed separately, there was no significant primary effect for menstrual cycle phase.  The significance of the observed interaction between race and menstrual cycle phase is unknown.

Weinmann et al. (1995) compared the pulmonary function responses of six healthy, nonsmoking women to a 130-min exposure to 0.35 ppm $O_3$, 4 to 8 days after the onset of menses and 4 to 8 days after ovulation.  Subjects performed intermittent exercise at a workload that induced a $\dot{V}_E$ of 10 × FVC.  Ovulation was confirmed by a blood progesterone test.  Spirometry was performed pre- and 25-min post-$O_3$ exposure.  Although resting $\dot{V}_E$ was the same during both exposures, exercise load had to be reduced 30% during the luteal phase in order to match the ventilatory response to exercise during the follicular phase.  There were no significant effects related to phase of the menstrual cycle.  The authors concluded that menstrual phase does not need to be considered in experimental design.  One problem with the study is that the postexposure measurements were made 25 min after the conclusion of the exposure.  Typically, pulmonary function decrements begin to reverse once exposure ends; thus, any pulmonary function changes that did occur could be expected to be reduced at 25-min post-$O_3$ exposure, compared to immediately after exposure.

Acute $O_3$ exposure has been shown to cause short-term airway inflammation (see Section 7.2.4) induced by PGs, among other inflammatory substances.  It also has been demonstrated that progesterone inhibits PG production in the uterine endometrium, which fluctuates as the progesterone concentration varies throughout the menstrual cycle.  Fox et al. (1993) investigated the hypothesis that $O_3$ exposure during the follicular phase, when progesterone concentration is lowest, might result in greater pulmonary function responses due to reduced anti-inflammatory influences of progesterone.  Nine nonsmoking women completed 1-h mouthpiece exposures to FA and 0.3 ppm $O_3$ while exercising continuously ($\dot{V}_E$ about 50 L/min) during both the follicular and mid-luteal phases of two to four ovulatory menstrual cycles.  There were no differences in any pulmonary function responses to FA related to

menstrual phase, nor was there a difference in the mean FVC decrements following the follicular or mid-luteal phase $O_3$ exposures. The $O_3$-induced decrements in $FEV_1$ and $FEF_{25\,75\%}$ were significantly larger during the follicular phase (17.3 and 23.1%, respectively) than during the mid-luteal phase (13.4 and 15.3%, respectively). The authors speculated that the difference between the $FEV_1$ and $FEF_{25\,75\%}$ responses to the two $O_3$ exposures could be due to differences in circulating progesterone and the effect of progesterone on prostaglandin activity.

Available data (see Table 7-4) do not permit a conclusion regarding the influence of the menstrual cycle on responses to $O_3$ exposure. Two of the three studies available, Fox et al. (1993) and Weinmann et al. (1995), were performed with small groups of subjects and resulted in opposite conclusions. Seal et al. (1995) compared race (black versus white) and menstrual phase, obtaining a significant interaction between race and phase, but post-hoc analysis failed to establish a basis for the interaction, leaving the implications of the study unclear.

### *Age Differences*

It has been hypothesized that age may be a factor in responsiveness to $O_3$. Although children make up a large proportion of the population, few controlled laboratory studies of the pulmonary function effects of any air pollutant have been reported on subjects under age 18. Field and epidemiological studies (see Section 7.4) attempting to relate ambient air pollutant exposure to pulmonary function in children have suggested that children may be more responsive to ambient air pollution than young adults.

The previous $O_3$ criteria document (U.S. Environmental Protection Agency, 1986) included only one laboratory exposure study in which children were the subjects. McDonnell et al. (1985a) evaluated the pulmonary function responses of 23 boys between 8 and 11 years of age to 0.00 and 0.12 ppm $O_3$ in random order. The boys alternated 15-min rest and exercise periods ($\dot{V}_E = 35$ L/min/m$^2$ BSA) for the first 120 min of the 150-min exposure. Forced expiratory spirometry and respiratory symptoms were measured before exposure and at 125 min of exposure, whereas $R_{aw}$ was measured before exposure began and after 145 min of exposure. The group mean decrement in $FEV_1$ following the $O_3$ exposure was 3.4%, compared to 4.3% for a group of young adult males who earlier had completed the same protocol (McDonnell et al., 1983). It should be noted that the absolute $\dot{V}_E$ for the children (39.4 L/min) and adults (65.0 L/min) was similar when normalized for BSA (about 35 L/min/m$^2$ BSA). Assuming that adjusting ventilation for differences in BSA is an appropriate normalizing technique, these children appeared to experience $O_3$-induced pulmonary effects similar to adults. The children reported no symptoms, but the adults reported a small, but statistically significant, increase in cough following $O_3$ exposure.

Although controlled laboratory studies of the effects of exposure to air pollutants are rarely performed with children as subjects, a few, more recent studies are discussed below (see Table 7-5). Avol et al. (1987) have reported on the pulmonary function responses of 33 healthy boys and 33 healthy girls having a mean age of 9.4 years. The children completed exposures to purified air and outdoor ambient air that was drawn into an environmental chamber. Ambient temperature averaged about 33 □C. Exposures were 1 h in duration, were separated by a minimum of 2 weeks, and were conducted from June through September, beginning in the early afternoon when ambient air pollutant concentrations generally peak. The subjects performed continuous exercise throughout the

## Table 7-4. Hormonal Influences on Pulmonary Function Responses to Ozone[a]

| Ozone Concentration[b] | | Exposure Duration and Activity | Exposure Conditions | Number and Gender of Subjects | Subject Characteristics | Observed Effect(s) | References |
|---|---|---|---|---|---|---|---|
| ppm | □g/m³ | | | | | | |
| 0.12 0.24 0.30 0.40 | 235 470 588 784 | 2.3 h IE $\dot{V}_E =$ 20 L/min/m² BSA | NA | 48 WF, 55 BF | Healthy NS, 18 to 35 years old | Significant menstrual cycle phase × race interaction for $FEV_1$. No significant menstrual cycle phase effect when blacks and whites were analyzed separately. No significant menstrual phase effects for $SR_{aw}$ or cough score. | Seal et al. (1995) |
| 0.30 | 588 | 1 h CE $\dot{V}_E \square$ 50 L/min | NA | 9 F | Healthy NS, regular menstrual cycles, 20 to 34 years old | $FEV_1$ decreased 13.1% during the mid-luteal phase and 18.1% during the follicular phase. Decrement in $FEF_{25-75\%}$ was significantly larger during the follicular phase than the mid-luteal phase. Changes in FVC were similar in both phases. | Fox et al. (1993) |
| 0.35 | 686 | 130 min | NA | 9 F | Healthy NS, regular menstrual cycles, 18 to 35 years old | Changes in FVC, $FEV_1$, $FEF_{25-75\%}$, $\dot{V}_{max50\%}$, and $V_{max25\%}$ were similar during both the follicular and luteal phases. | Weinmann et al. (1995) |

[a]See Appendix A for abbreviations and acronyms.
[b]Listed from lowest to highest $O_3$ concentration.

# Table 7-5. Age Differences in Pulmonary Function Responses to Ozone[a]

| Ozone Concentration[b] | | Exposure Duration and Activity | Exposure Conditions | Number and Gender of Subjects | Subject Characteristics | Observed Effect(s) | Reference |
|---|---|---|---|---|---|---|---|
| ppm | μg/m³ | | | | | | |
| 0.113[c] + other ambient pollutants | 221 | 1 h CE $\dot{V}_E \approx 22$ L/min | T = 32.7 °C RH ≈ 43% cycle | 33 M, 33 F | NS for both groups, mean age = 9.4 years old | No differences in responses of boys and girls. Similar decrements (<5% on average) following both purified air and ambient air (O₃ at 0.11 ppm) exposures. | Avol et al. (1987) |
| 0.12 | 235 | 1 h (mouthpiece) IE $\dot{V}_E$ = 4 to 5 × resting | T = 22 °C RH = 75% treadmill | 5 M, 7 F | Healthy NS, 12 to 17 years old | No significant changes in any pulmonary function in healthy subjects. | Koenig et al. (1988) |
| 0.12 | 235 | 40 min (mouthpiece) IE | NA treadmill | 3 M, 7 F | Healthy NS, 14 to 19 years old | No significant change in FEV₁; increased R_T with exposure to 0.18 ppm O₃. Some subjects responded to 5 to 10 mg/mL methacholine after 0.18-ppm O₃ exposure, whereas none responded to 25 mg/mL methacholine at baseline bronchochallenge. | Koenig et al. (1987) |
| 0.18 | 353 | 10 min exercise at $\dot{V}_E$ = 32.6 L/min; 40 min (mouthpiece) IE 10 min exercise at $\dot{V}_E$ = 41.3 L/min | | 4 M, 6 F | | | |
| 0.18 0.24 0.30 0.40 | 353 470 588 784 | 2.3 h IE $\dot{V}_E$ = 20 L/min/m² BSA | NA | 48 WF, 55 BF | Healthy NS, 18 to 35 years old, black and white | Older women had smaller changes in FEV₁ than younger women. No age- related differences in SR_aw or cough score. | Seal et al. (1993) |
| 0.20 0.30 | 392 588 | 1 h (mouthpiece) IE (20 min) $\dot{V}_E \approx 28$ L/min for men $\dot{V}_E \approx 23$ L/min for women | T ≈ 22 °C RH ≈ 75% treadmill | 9 M, 10 F | Healthy NS, 55 to 74 years old | No change in any spirometry measure. Women had 13% increase in R_T after 0.30-ppm exposure. | Reisenauer et al. (1988) |

| Ozone Concentration[b] | | Exposure Duration and Activity | Exposure Conditions | Number and Gender of Subjects | Subject Characteristics | Observed Effect(s)[c] | Reference |
|---|---|---|---|---|---|---|---|
| ppm | $\mu$g/m | | | | | | |
| 0.45 | 882 | 2 h<br>IE<br>$\dot{V}_E \cong$ 26 L/min | T $\cong$ 23 $^\circ$C<br>RH = 53%<br>cycle | 8 M<br>8 F | Healthy NS,<br>51 to 76 years old | Mean decrement in FEV$_1$ = 5.6 $\pm$ 13%; range of decrements = 0 to 12%. | Drechsler-Parks et al. (1987a,b) |
| 0.45 | 882 | 2 h<br>IE<br>Mean $\dot{V}_E$ =<br>28.5 L/min for men<br>Mean $\dot{V}_E$ =<br>26.1 L/min for women | T = 23 $^\circ$C<br>RH = 46%<br>cycle/treadmill | 10 M<br>6 F | Healthy NS,<br>60 to 89 years old | Mean decrement in FEV$_1$ = 5.7%; eight subjects had a 5% or greater difference between their response to O$_3$ and FA, and the other eight had less than a 5% difference between their responses to FA and 0.45 ppm O$_3$. | Bedi et al. (1989) |
| 0.45 | 882 | 2 h<br>IE<br>$\dot{V}_E \cong$ 26 L/min | T $\cong$ 24 $^\circ$C<br>RH = 63%<br>cycle | 8 M<br><br>8 F | Healthy NS,<br>51 to 69 years old<br><br>Healthy NS,<br>56 to 76 years old | 13 subjects had decrements in FEV$_1$ on three separate exposures to 0.45 ppm within 5% of their mean response to the three exposures. The other three subjects were not reproducible. Symptom reports did not correlate well with pulmonary function changes. | Bedi et al. (1988) |
| 0.45 | 882 | 1 h<br>CE<br>$\dot{V}_E \cong$ 26 L/min<br>2 h<br>IE<br>$\dot{V}_E \cong$ 26 L/min | T $\cong$ 23 $^\circ$C<br>RH = 58%<br>cycle/treadmill | 7 M<br>5 F | Healthy NS,<br>60 to 79 years old<br>(all in 60s<br>except one<br>79 years old) | Comparison of 1-h CE protocol and 2-h IE protocol indicated no difference between the changes in pulmonary function following the two protocols. | Drechsler-Parks et al. (1990) |

[a]See Appendix A for abbreviations and acronyms.
[b]Listed from lowest to highest O$_3$ concentration.
[c]Ozone concentration is the mean of a range of ambient concentrations.

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hour of exposure. Boys and girls exercised at similar $\dot{V}_E$, 22 to 23 L/min. It should be noted that the ambient exposure included the full range of air pollutants present in the outdoor air mix on the days of the exposures, except for small fractions of $O_3$ and particles lost in the inlet duct. Concentrations of $O_3$, nitrogen dioxide ($NO_2$), total suspended particulate (TSP), particulate nitrate, particulate sulfate, particulate sodium, and particulate ammonium were measured throughout the exposures. The $O_3$ concentration during the ambient air exposures averaged 0.113 ppm, whereas it averaged 0.003 ppm during the purified air exposures. The children consistently had similar declines in pulmonary function with time, following both FA and ambient air exposures. Typical mean decrements in FVC and $FEV_1$ were 50 mL or less. The investigators also have published similar studies on adolescents and adults (Avol et al., 1984, 1985a). The responses of the adolescents and adults to both exposures were not substantially different from those of the children whose results are reported here. The authors further noted that the children seemed to have difficulty performing consistent, reproducible pulmonary function tests, a factor that could have impacted on these results.

Several studies comparing the pulmonary function responses of healthy and asthmatic adolescents to $O_3$ exposure have appeared in the literature. The responses of the asthmatics are presented in Section 7.2.1.2; only data on normal adolescent subjects will be discussed in this section.

Koenig et al. (1987) reported on 20 adolescents, 14 to 19 years of age, who were exposed for 40 min to air or 0.12 or 0.18 ppm $O_3$ via a mouthpiece system. Ten subjects were exposed to each $O_3$ concentration, but not all subjects were exposed to both concentrations. None of the healthy subjects had a history of asthma or allergies, and all had pulmonary function within the predicted range, based on age, sex, and height. There was a 5- to 7-min break in exposure for pulmonary function test performance following 30 min of resting exposure, followed by a 10-min exercise period ($\dot{V}_E$ = 32.6 $\pm$ 6.4 L/min for the 0.12-ppm $O_3$ exposure and 41.3 $\pm$ 9.3 L/min for the 0.18-ppm $O_3$ exposure). Changes in $FEV_1$ were not significant following any exposure. After exposure to 0.18 ppm $O_3$, $R_T$ was increased 15%.

Koenig et al. (1988) also have reported on the pulmonary function responses of another group of 12 healthy adolescents (12 to 17 years of age) to 1-h exposures to air and 0.12 ppm $O_3$. The subjects were exposed by mouthpiece to air and 0.12 ppm $O_3$ while alternating 15-min periods of exercise ($\dot{V}_E$ = 32.8 $\pm$ 6.0 L/min) with 15-min periods of rest ($\dot{V}_E$ = 8.8 $\pm$ 1.2 L/min). Tests of pulmonary function included forced expiratory spirometry and $R_T$. Healthy subjects had no significant alterations in any parameter of pulmonary function consequent to exposure to air or 0.12 ppm $O_3$.

Although few data are available on the responses of healthy adolescents exposed to $O_3$, the limited existing data do not identify adolescents as being either more or less responsive than young adults.

At the time the 1986 $O_3$ criteria document was released, no studies specifically evaluating the pulmonary function responses of older adults had been reported. Several studies (Folinsbee et al., 1985; Adams et al., 1981) that included a few middle-aged individuals among the subjects were suggestive that there might be a decrease in $O_3$ responsiveness with advancing age. Several reports have since appeared, collectively suggesting that, collectively, healthy older adults (i.e., over 50 years of age) generally are minimally responsive to $O_3$, although some individuals remain responsive to $O_3$.

Drechsler-Parks et al. (1987a) reported on eight men and eight women between 51 and 76 years of age who were exposed for 2 h to FA or 0.45 ppm $O_3$. The subjects were

healthy nonsmokers with normal baseline pulmonary function. The chamber exposures involved alternating 20-min rest and exercise periods ($\dot{V}_E$ averaged $27.9 \pm 0.29$ L/min for men and $25.4 \pm 0.80$ L/min for women). Exposures were presented in random order at least 1 week apart. The only significant difference related to sex was in $FEV_3$, in which women had larger decrements than men. There were no significant decrements in any other parameter of pulmonary function related to $O_3$ exposure, except when the data of all 16 subjects were pooled, significant mean decrements of $5.3 \pm 1.3\%$ in FVC, and $5.6 \pm 1.3\%$ in $FEV_1$ were observed. The range of individual decrements in $FEV_1$ was from 0 to 12%. Two women and three men had no response following the $O_3$ exposure. The subjects reported more symptoms following the $O_3$ exposure than the FA exposure. Seven subjects reported cough, nine reported sore throat, and six reported chest tightness. The authors compared their results on older adults to the results from a group of young adults who had completed the same protocol. All of the older subjects inhaled slightly higher doses of $O_3$ than the younger subjects ($10.23 \times 10^4$ L for older men versus $10.12 \times 10^4$ L for younger men and $8.48 \times 10^4$ L for older women versus $7.94 \times 10^4$ L for younger women). However, older men had a mean decrement in $FEV_1$ of 4.2% versus 23.7% for younger men, whereas older women had a mean decrement in $FEV_1$ of 7.0% versus 14.7% for younger women. The decrements of the older subjects also were compared to published values for the young adults, with the older subjects studied consistently showing smaller changes in pulmonary functions than the young adults. These comparisons indicated that these older adults were less responsive to $O_3$ exposure than typical young adults, in terms of pulmonary function changes and symptom reports.

Reisenauer et al. (1988) reported on the pulmonary function responses of 19 healthy adults between 55 and 74 years of age. All were nonsmokers with baseline pulmonary function within the predicted normal range. None had a history of asthma, atopy, or cardiovascular disease, and none responded to a baseline methacholine bronchochallenge. Subjects were exposed by mouthpiece to 0.0, 0.20, or 0.30 ppm $O_3$ for 1 h. Seven men rested for 50 min and exercised for 10 min, whereas the other two men and all women alternated two 20-min rest periods with two 10-min exercise periods; $\dot{V}_E$ was approximately 28 L/min for men and 23 L/min for women. The three exposures were presented in random order at the same time of day for each individual, but the separation between exposures is not stated. The only significant change in pulmonary function was a 13% increase in $R_T$ with exposure to 0.30 ppm $O_3$ in women only, which was sustained for at least 20 min postexposure. The authors concluded, based on the increase in $R_T$ in the women, that older adults were at increased risk for pulmonary function changes with near-ambient $O_3$ exposure. However, $R_T$ is a highly variable parameter, and no other changes were significant. Given the large number of variables tested, this isolated result possibly is related to the large number of statistical tests performed. In contrast, the results of Koenig et al. (1987) from 10 healthy adolescents exposed to 0.18 ppm $O_3$ using a similar protocol, reported a mean decrement in $FEV_1$ of 2% and an increase of 10.5% in $R_T$ at 2 to 3 min postexposure. At 7 to 8 min postexposure, the increase in $R_T$ was 15.3%. Comparison of these results to those of Reisenauer et al. (1988) at 0.20 ppm $O_3$ supports the contention that younger individuals are more responsive to $O_3$ than older individuals, in that no changes in spirometry were noted in the older adults exposed to 0.30 ppm $O_3$, although older women showed increased $R_T$ with 0.30 ppm $O_3$ exposure, whereas the adolescents had a mean decrement of 1% in $FEV_1$ and a mean increase of 16% in $R_T$ with exposure to 0.18 ppm $O_3$.

Bedi et al. (1988) reported that older men and women 51 to 76 years of age who completed three exposures to 0.45 ppm $O_3$ did not respond equivalently to each of three exposures. The subjects were healthy nonsmokers with baseline pulmonary function within predicted normal limits. The subjects alternated 20-min exercise ($\dot{V}_E$ was approximately 26 L/min) and 20-min rest periods throughout the 2-h chamber exposures. There was a minimum of 1 week between exposures, but separations ranged from 1 to 4 weeks between exposures 1 and 2, and between 1 and 7 weeks between exposures 2 and 3. Analysis of variance indicated no difference between the group mean responses to the three exposures. The data were then subjected to a correlation analysis, which led to the conclusion that the responses within an individual subject were not reproducible. McDonnell et al. (1985b), on the other hand, found good reproducibility of pulmonary function responses after exposure to various concentrations of $O_3$ between 0.12 and 0.40 ppm in young adult males between 18 and 30 years of age.

Seal et al. (1993) compared the pulmonary function responses of 48 white and 55 black women (18 to 35 years) who each completed a 2.3-h exposure to 0.18, 0.24, 0.30, or 0.40 ppm $O_3$. The subjects participated in only one exposure each while exercising intermittently ($\dot{V}_E = 20$ L/min/m$^2$ BSA) during the first 2 h of the exposure. Older subjects within the age range tested had smaller decrements in $FEV_1$ than younger subjects.

One simple method to estimate the $O_3$ exposure dose is to calculate the product of $O_3$ concentration (parts per million), $\dot{V}_E$ (liters per minute), and exposure duration (minutes). Research on young adults (Folinsbee et al., 1978; Adams et al., 1981) has demonstrated that the order of relative importance of the three factors is $O_3$ concentration, $\dot{V}_E$, and exposure duration. Drechsler-Parks et al. (1990) investigated the relative role of the three components of effective dose in 12 healthy, nonsmoking adults between 61 and 79 years of age. The subjects were exposed to both FA and 0.45 ppm $O_3$, once while they performed a 1-h continuous exercise protocol and once while they performed a 2-h IE protocol in which they alternated 20-min exercise periods and 20-min rest periods. Mean $\dot{V}_E$ ranged from 25.2 to 27.3 L/min among the four exposures. Exposures were separated by at least 1 week. Regardless of protocol, $O_3$ exposure induced significant decrements in $FEV_{.5}$, $FEV_1$ (7.7 and 10.6% for the 1- and 2-h exposures, respectively), $FEV_3$, and peak expiratory flow rate (PEFR) compared to FA exposure. There were significant decrements in $FEF_{25-75\%}$ (0.37, 0.46, 0.49, and 0.47 L/s, respectively), $FEF_{5\%}$, $FEF_{25\%}$, and MVV following all four exposures. The only significant difference between the responses to the 1- and 2-h $O_3$ protocols was in $FEV_{.5}$. The total number of symptoms reported was 10 for the 1-h FA exposure, 6 for the 1-h $O_3$ exposure, and 12 for both the 2-h FA and 2-h $O_3$ exposures. It appears that resting ventilation during the 2-h protocol had a smaller effect compared to exercise ventilation. This supports earlier reports that the $O_3$ concentration is the most significant factor among the three factors that contribute to effective dose (Adams et al., 1981; Folinsbee et al., 1978; Hackney et al., 1975).

Available data, although on a limited number of subjects, consistently indicate that responsiveness to $O_3$ is decreased in persons over 50 years of age compared to younger adults. Although there are few data available on adults in their thirties and forties, the statistical modeling study of McDonnell et al. (1993) on subjects from 18 to 32 years of age suggests that responsiveness to $O_3$ is already diminishing by age 30, and that the most responsive individuals are likely to be less than 25 years of age. The results of Bedi et al. (1988) suggest that older adults may be less reproducible in their responses to $O_3$ than younger adult males (McDonnell

et al., 1985b); however, this finding is based on only 16 subjects and should be confirmed before being considered conclusive.

### Ethnic and Racial Factors

Young white males have been the most frequently studied population in published reports on pulmonary function responses to $O_3$. There is concern, however, that responses to $O_3$ may be influenced by ethnic differences based on the observation that blacks have smaller lungs than whites for a given standing or sitting height (Rossiter and Weill, 1974; McDonnell and Seal, 1991). Thus, an equivalent inhaled volume of $O_3$ could result in a larger $O_3$ dose per unit of lung tissue in blacks compared to whites, potentially inducing greater effects in blacks than whites exposed to $O_3$ under the same conditions. Seal et al. (1993) evaluated the pulmonary function responses of 372 individuals, black, white, male, and female (n $>$ 90 per group), between 18 and 35 years of age who were exposed to 0.00, 0.12, 0.18, 0.24, 0.30, or 0.40 ppm $O_3$. Each subject was assigned randomly to an exposure group and participated in only one experimental session. The protocol involved a 2.33-h exposure to the assigned condition. During the first 2 h of exposure, the subjects alternated 15-min rest periods and 15-min exercise periods ($\dot{V}_E$ = 25 L/min/m$^2$ BSA). Spirometric and plethysmographic measurements were made at 5 and 20 min following the final exercise period. The initial nonparametric analysis of the percentage changes in $FEV_1$ indicated that $FEV_1$ responses increased with increasing $O_3$ concentration, and a group effect occurred that was independent of $O_3$ concentration. There was an $O_3$ effect, but no group effect or group $\times O_3$ interaction for $SR_{aw}$, indicating an increase in $SR_{aw}$ with increasing $O_3$ concentration. Both group and $O_3$ effects were significant for cough, but the interaction was not significant. A post hoc analysis, using a different statistical method on the absolute changes in $FEV_1$, indicated that the black males experienced significant decrements in $FEV_1$ following exposure to 0.12 ppm $O_3$, whereas black women and white men and women did not have significant decrements in $FEV_1$ at $O_3$ concentrations below 0.18 ppm. These results are not easily explained because there was no gender difference among whites and no racial difference among women. Furthermore, the black men had significantly greater decrements in $FEV_1$ at only some of the $O_3$ concentrations studied (see Figure 7-2). Although the results can be considered suggestive of an ethnic difference, more subjects must be studied before the issue of ethnic difference in $O_3$ responsiveness can be more definitive. It should be noted that, although this study included a large number of subjects, each subject participated in only one experiment. Thus, the range of individual responsiveness could have been different between groups.

### Environmental Factors

A number of environmental factors, such as ambient temperature and humidity, season of the year, route of inhalation, and smoking history have been hypothesized to potentially impact on responses to $O_3$ exposure in additive or synergistic ways. None of these potentially interacting agents has been addressed adequately in the extant $O_3$ literature. Although $O_3$ concentrations in Los Angeles, for example, generally are highest on hot, dry days, most research on responses to $O_3$ exposure has been conducted under temperature and humidity conditions not substantially different from those typical of indoor environments. The few studies that included temperature and humidity as experimental factors have produced equivocal results (see Chapter 10, Section 10.2.9 in the 1986 $O_3$ criteria document). No new

reports of temperature or humidity effects have appeared since the 1986 $O_3$ criteria document (U.S. Environmental Protection Agency, 1986).

Earlier studies discussed in the 1986 $O_3$ criteria document have suggested that cigarette smokers are less responsive to $O_3$ than nonsmokers. Since then, the question as to whether reactivity to $O_3$ returns with cessation of cigarette smoking has been addressed by Emmons and Foster (1991). Thirty-four individuals with no history of asthma or obvious respiratory disease who enrolled in a smoking cessation program were assigned randomly to an $O_3$ group (n = 18) or an FA group (n = 16). The subjects ranged from 24 to 58 years of age and had a group mean smoking history of 33.9 $\pm$ 13 pack-years. Most of the subjects had baseline pulmonary functions somewhat below predicted values, based on age, height, and sex. Subjects completed 2-h exposures to 0.42 ppm $O_3$ or FA, as assigned, prior to beginning the smoking cessation program. The subjects rested during the exposures, except for 5 min of exercise at 150 kg ⊡ m/min (no $\dot{V}_E$ given) at the beginning of the last 30 min of exposure. Nine subjects in the $O_3$ group and six in the FA group completed the 6-mo smoking cessation program and repeated their assigned exposures at the end of the program. Prior to beginning the smoking cessation program, both the FA and $O_3$ groups had pre- to postexposure changes in FVC, $FEV_1$, and $FEF_{25\,75\%}$ within the variability of repeated tests. The $O_3$ group had a significant mean change in $FEF_{25\,75\%}$ of ⊡22.5%, comparing post- to preexposure, whereas the FA group had a nonsignificant ⊡12% change. Changes in FVC and $FEV_1$ were not significant in either group. It should be noted that smoking cessation led to a group mean improvement in baseline $FEF_{25\,75\%}$ of 22.9%. The post-$O_3$ exposure values for $FEF_{25\,75\%}$ were similar following the initial and the post-smoking cessation exposures. Thus, the difference in the $FEF_{25\,75\%}$ decrement with $O_3$ exposure post-smoking cessation was largely due to the improvement that ensued from 6 mo of abstinence from smoking. The results of Emmons and Foster (1991) suggest that active smoking blunts responsiveness to $O_3$ and that cessation of smoking for 6 mo leads to improved baseline pulmonary function and possibly the reemergence of $O_3$ responsiveness.

### 7.2.1.4 Repeated Exposures to Ozone

Repeated daily exposure to $O_3$ in the laboratory setting leads to attenuated changes in spirometry and symptom responses that were initially termed "adaptation" (Hackney et al., 1977a). A series of repeated exposure studies, performed in various laboratories, was reviewed in the previous criteria document (U.S. Environmental Protection Agency, 1986). The spirometric responses to repeated $O_3$ exposure typically showed that the response was increased on the second exposure day to concentrations in the range of 0.4 to 0.5 ppm $O_3$ in exposures accompanied by moderate exercise (see Table 7-6). Thus, the response was enhanced on the second consecutive day. Mechanisms for enhanced responses had not been established, although it was hypothesized that persistence of $O_3$-induced damage for greater than 24 h may have contributed to the larger Day 2 response. An enhanced Day 2 response was less obvious or absent in exposures that were repeated at lower concentrations or that caused relatively small group mean $O_3$-induced decrements in spirometry. Two reports (Bedi et al., 1985; Folinsbee et al., 1986) indicated that enhanced spirometric responsiveness was present within 12 h, lasting for at least 24 h and possibly 48 h, but was clearly absent after 72 h. After 3 to 5 days of consecutive daily exposures to $O_3$, responses were markedly diminished or absent. One study (Horvath et al., 1981) suggested that the rapidity of this

decline in response was related to the magnitude of the subjects' initial responses to $O_3$ or their "sensitivity".  Finally, the persistence of the attenuation of spirometric and symptom

## Table 7-6. Changes in Forced Expiratory Lung Volume After Repeated Daily Exposure to Ozone[a]

| Ozone Concentration[b] | | Exposure Duration and Activity[c] | Number and Gender of Subjects | Percent Change in FEV$_1$ on Consecutive Exposure Days | | | | | References |
| ppm | μg/m³ | | | First | Second | Third | Fourth | Fifth | |
|---|---|---|---|---|---|---|---|---|---|
| 0.12 | 235 | 6.6 h, IE (40) | 17 M | −12.79 | −8.73 | −2.54 | −0.6 | 0.2 | Folinsbee et al. (1994) |
| 0.20 | 392 | 2 h, IE (30) | 10 M | +1.4 | +2.7 | −1.6 | — | — | Folinsbee et al. (1980) |
| 0.20 | 392 | 2 h, IE (18 and 30) | 8 M, 13 F | −3.0 | −4.5 | −1.1 | — | — | Gliner et al. (1983) |
| 0.20 | 392 | 2 h, IE (18 and 30) | 9 | −8.7 | −10.1 | −3.2 | — | — | Gliner et al. (1983) |
| 0.20 | 392 | 1 h, CE (60) | 15 M | −5.02 | −7.8 | — | — | — | Brookes et al. (1989) |
| 0.25 | 490 | 1 h, CE (63) | 4 M, 2 F | −20.2 | −34.8 | — | — | — | Folinsbee et al. (1986) |
| | | | 5 M, 2 F | −18.8 | — | −22.3 | — | — | |
| 0.35 | 686 | 2 h, IE (30) | 10 M | −5.3 | −5.0 | −2.2 | — | — | Folinsbee et al. (1980) |
| 0.35 | 686 | 1 h, CE (60) | 8 M | −31.0 | −41.0 | −33.0 | −25.0 | — | Foxcroft and Adams (1986) |
| 0.35 | 686 | 1 h, CE (60) | 10 M | −16.1 | −30.4 | — | — | — | Schonfeld et al. (1989) |
| | | | 10 M | −14.4 | — | −20.6 | — | — | |
| 0.35 | 686 | 1 h, CE (60) | 15 M | −15.9 | −24.6 | — | — | — | Brookes et al. (1989) |
| 0.40 | 784 | 3 h, IE (4-5 × resting) | 13 M | −9.2 | −10.8 | −5.3 | −0.7 | −1.0 | Kulle et al. (1982)[f] |
| 0.40 | 784 | 3 h, IE (4-5 × resting) | 11 F | −8.8 | −12.9 | −4.1 | −3.0 | −1.6 | Kulle et al. (1982)[f] |
| 0.40 | 784 | 2 h, IE (65) | 8 M | −18.0 | −29.9 | −21.1 | −7.0 | −4.4 | Folinsbee et al. (1995) |
| 0.42 | 823 | 2 h, IE (30) | 24 M | −21.1 | −26.4 | −18.0 | −6.3 | −2.3 | Horvath et al. (1981) |
| 0.45 | 882 | 2 h, IE (27) | 1 M, 5 F | −13.3 | — | −22.8 | — | — | Bedi et al. (1985) |
| 0.45 | 882 | 2 h, IE (27) | 10 M, 6 F | −5.8 | −5.6 | −1.9 | — | — | Bedi et al. (1989) |
| 0.47 | 921 | 2 h, IE (3 × resting) | 8 M, 3 F | −11.4 | −22.9 | −11.9 | −4.3 | — | Linn et al. (1982b)[g] |
| 0.50 | 980 | 2 h, IE (30) | 8 M | −8.7 | −16.5 | −3.5 | — | — | Folinsbee et al. (1980) |
| 0.50 | 980 | 2.5 h, IE (2 × resting) | 6 | −2.7 | −4.9 | −2.4 | −0.7 | — | Hackney et al. (1977a) |

[a]See Appendix A for abbreviations and acronyms.
[b]Listed from lowest to highest O$_3$ concentration.
[c]Exposure duration and intensity of IE or CE were variable; $\dot{V}_E$ (number in parentheses) given in liters per minute or as a multiple of resting ventilation.
[d]For a more complete discussion of these studies, see Table 7-7 and U.S. Environmental Protection Agency (1986).
[e]Subjects were especially sensitive on prior exposure to 0.42 ppm O$_3$ as evidenced by a decrease in FEV$_1$ of more than 20%. These nine subjects are a subset of the total group of 21 individuals used in this study.
[f]Bronchial reactivity to a methacholine challenge also was studied.
[g]Seven subjects completed entire experiment.

responses has been studied (Horvath et al., 1981; Linn et al., 1982b; Kulle et al., 1982). These studies indicate that the attenuation of response is relatively short-lived, being partially reversed within 3 to 7 days and typically abolished within 1 to 2 weeks. Repeated exposures separated by 1 week (for up to 6 weeks) apparently do not cause any lessening of the spirometric response (Linn et al., 1982b).

Folinsbee et al. (1995) (also see Devlin et al., 1995) exposed a group of 15 healthy males to 0.4 ppm $O_3$ for 2 h/day on 5 consecutive days. Subjects performed heavy IE ($\dot{V}_E$ = 60 to 70 L/min, 15 min rest/15 min exercise). Decrements in $FEV_1$ averaged 18.0, 29.9, 21.1, 7.0, and 4.4% on the 5 exposure days. Baseline preexposure $FEV_1$ decreased from the first day's preexposure measurement and was depressed by an average of about 5% on the third day. This study illustrates that, with high-concentration and heavy-exercise exposures, spirometry and symptom responses are not completely recovered within 24 h.

Besides the absence of pulmonary function responses after several days of $O_3$ exposure, symptoms of cough and chest discomfort usually associated with $O_3$ exposure generally are absent (Folinsbee et al., 1980, 1994; Linn et al., 1982b; Foxcroft and Adams, 1986). In addition, airway responsiveness to methacholine is increased with an initial $O_3$ exposure (Holtzman et al., 1979; Folinsbee et al., 1988), may be further increased with subsequent exposures (Folinsbee et al., 1994), and shows a tendency for the increased response to diminish with repeated exposure (Kulle et al., 1982; Dimeo et al., 1981). A number of possible explanations for the initially enhanced and then lessened response may be related to changes that are occurring in pulmonary epithelia as a consequence of $O_3$ exposure. Inflammatory responses (Koren et al., 1989a), epithelial damage, and changes in permeability (Kehrl et al., 1987) could be invoked to explain at least a portion of these responses. By blocking spirometric and symptom responses with indomethacin pretreatment, Schonfeld et al. (1989) demonstrated that in the absence of an initial spirometric response such effects were not enhanced by repeated exposure. However, the mechanisms of these responses with regard to repeated exposures in humans remains to be elucidated.

Recent studies of repeated $O_3$ exposures have addressed some other features of the responses (see Table 7-7). A series of reports from the Rancho Los Amigos group in California have examined changes in response to $O_3$ as a result of the season of the year in the South Coast Air Basin of Los Angeles, CA. The purpose of this research (Linn et al., 1988; also Hackney et al., 1989; Avol et al., 1988) was to determine whether responsive subjects (n = 12), identified during an initial screening following a period of low ambient $O_3$ exposure, would remain responsive after regular ambient exposure during the "smog season". Responses of so-called "nonresponsive" subjects (n = 13) also were examined across the year. The subjects were exposed to 0.18 ppm $O_3$ on four occasions, spring, fall, winter, and the following spring. Only 17 subjects (8 responders) participated in the final spring exposures. The marked difference in $FEV_1$ response between responsive and nonresponsive subjects seen initially (□12.4% versus +1%) no longer was present after the summer smog season (fall test) or 3 to 5 mo later (winter test). However, when the reduced subset of subjects was exposed during the following spring, the responsive subjects again had significantly larger changes in $FEV_1$. Seasonal changes in $FEV_1$ response to $O_3$ in the responsive and nonresponsive subjects are shown below.

## Table 7-7. Pulmonary Function Effects with Repeated Exposures to Ozone[a]

| Ozone Concentration[b] | | Exposure Duration and Activity | Exposure Conditions | Number and Gender of Subjects | Subject Characteristics | Observed Effect(s) | Reference |
|---|---|---|---|---|---|---|---|
| ppm | μg/m | | | | | | |
| 0.12 | 235 | 6.6 h<br>50 min exercise/10 min rest, 30 min lunch<br>$V_E$ = 38.8 L/min | 18 °C<br>40% RH<br>five consecutive daily exposures | 17 M | Healthy NS | FEV responses were maximal on first day of exposure (13%), less on second day (9%), absent thereafter. Symptom responses only the first 2 days. Methacholine airway responsiveness was at least doubled on all exposure days, but was highest on the second day of ozone. Airway responsiveness was still higher than air control after 5 days of ozone exposure. Trend to lessened response, but it was not achieved after 5 days. | Folinsbee et al. (1994)<br>(also see Table 7-9) |
| 0.18 | 353 | 2 h<br>IE (heavy)<br>$V_E$ 60 to 70 L/min<br>(35 L/min/m² BSA) | 31 °C<br>35% RH<br>(screen exposures in spring 1986; second exposures in summer/fall 1986 and winter 1987 and spring 1987 for responders and nonresponders only) | 59 adult Los Angeles residents<br>12 responsive<br>13 nonresponsive | Responders:<br>Age = 19 to 40 years;<br>6 atopic,<br>2 asthmatic,<br>4 normal<br><br>Nonresponders:<br>Age = 18 to 39 years,<br>13 normal | Responders had $FEV_1$ = 12.4% after initial screening; nonresponders had no change. Responders had nonsignificant response in late summer or early winter, but were responsive again in early spring (spring 1986, 385 mL; Autumn 1986, 17 mL; winter 1987, +16 mL; spring 1987, 347 mL). Nonresponders did not change with season. Suggests that responders responses may vary with ambient exposure, but nonresponders generally remain nonresponsive. | Linn et al. (1988)<br>(also see Hackney et al., 1989) |
| 0.20/0.20<br>0.35/0.20<br>0.35/0.35 | 392/392<br>686/392<br>686/686 | 1 h<br>CE at 60 L/min | 21 to 25 °C<br>40 to 60% RH<br>(three 2-day sets of exposures) | 15 M | Healthy aerobically trained NS, FVC = 4.24 to 6.98 L | Consecutive days of exposure to 0.20 ppm produced similar responses on each day (5.02, 7.80); 0.35/0.20 ppm pair caused increased response to 0.20 ppm on second day (8.74); 0.35/0.35 ppm caused much increased response on Day 2 (15.9, 24.6). Symptom responses were worse on the second exposure to 0.35 ppm, but not with second exposure to 0.20 ppm. | Brookes et al. (1989) |

## Table 7-7 (cont'd). Pulmonary Function Effects with Repeated Exposures to Ozone[a]

| Ozone Concentration[b] | | Exposure Duration and Activity | Exposure Conditions | Number and Gender of Subjects | Subject Characteristics | Observed Effect(s) | Reference |
|---|---|---|---|---|---|---|---|
| ppm | $\mu$g/m | | | | | | |
| 0.35 | 686 | ≅1 h<br>CE (see paper for details) | 22 to 25 °C<br>35 to 50% RH<br>(1 day FA; 1 day $O_3$; 4 days consecutive exposure to $O_3$) | 8 M | Aerobically trained healthy NS (some were known $O_3$ sensitive), age = 22.4 ± 2.2 years | Largest $FEV_1$ decrease on second of 4 days $O_3$ exposure (≅40% mean decrease). Trend for adaptation not complete in 4 days. $\dot{V}O_{2max}$ decreased with single acute $O_3$ exposure (≅6%) but was not significant after 4 days of $O_3$ exposure (≅4%). Performance time was less after acute $O_3$ (211 s) exposure than after FA (253 s). | Foxcroft and Adams (1986) |
| 0.35 | 686 | 60 min<br>CE<br>$\dot{V}_E$ = 60 L/min | 21 to 25 °C<br>40 to 60% RH<br>(two exposures for each subject separated by 24, 48, 72, or 120 h) | 40 M<br>(4 groups of 10) | NS; nonallergic, non-Los Angeles residents for >6 mo; age ≅ 25 years | No differences between responses to exposures separated by 72 or 120 h. Enhanced $FEV_1$ response at 24 h (≅16.1% vs. ≅30.4%). Possible enhanced response at 48 h (≅14.4% vs. ≅20.6%). Similar trends observed for respiratory pattern and $SR_{aw}$. | Schonfeld et al. (1989) |
| 0.45 | 882 | 2 h<br>IE (3 × 20 min exercise)<br>$\dot{V}_E$ = 26 L/min | 23.3 °C<br>62.5% RH<br>(three exposures with a minimum 1-week interval) | 8 M, 8 F | Healthy NS, 61 years old for M and 65 years old for F (FVC = 4.97 L for M and 3.11 L for F) | Spirometric changes were not reproducible from time to time after ozone exposure (r < 0.50). Repeat exposures to air yielded consistent responses. | Bedi et al. (1988) |
| 0.45 | 882 | 2 h<br>IE (3 × 20 min exercise)<br>$\dot{V}_E$ = 27 L/min | 23.3 °C<br>63% RH<br>Exposed for 3 consecutive days, not exposed for 2 days, then exposed to 0.45 ppm again for 1 day | 10 M, 6 F | Healthy NS, 60 to 89 years old (median age = 65 years; mean FVC = 3.99 L; mean $FEV_1$ = 3.01 L; $FEV_1$/FVC range = 61 to 85%) | Overall increase in symptoms, but no single symptom increased significantly. FVC decreased 111 mL and 104 mL on Days 1 and 2, respectively. $FEV_1$ fell by 171 and 164 mL, and $FEV_3$ fell by 185 and 172 mL. No significant changes on Days 3 and 4 or with FA. $FEV_1$ changes were ≅5.8, ≅5.6, ≅1.9, and ≅1.7% on the four $O_3$ days. | Bedi et al. (1989) |

## Table 7-7 (cont'd). Pulmonary Function Effects with Repeated Exposures to Ozone[a]

| Ozone Concentration[b] | | Exposure Duration and Activity | Exposure Conditions | Number and Gender of Subjects | Subject Characteristics | Observed Effect(s) | Reference |
|---|---|---|---|---|---|---|---|
| ppm | □g/m | | | | | | |
| 0.45 (+ 0.30 PAN) | 882 | 2 h IE (20 min rest, 20 min exercise) $\dot{V}_E$ = 27 L/min | 22 □C 60% RH 5 days consecutive exposure to PAN + O$_3$ | 3 M, 5 F | Healthy NS, Mean age = 24 years | FEV$_1$ decreased □19% with O$_3$ alone, □15% on Day 1 of O$_3$ + PAN, □5% on Day 5 of O$_3$ + PAN, □7% 3 days after 5 days of O$_3$ + PAN, □15% after 5 days of O$_3$ + PAN. Similar to O$_3$ adaptation studies, O$_3$ responses peaked after 2 days, were depressed 3 days later, and responses returned 7 days later. PAN probably had no effect on adaptation to O$_3$. | Drechsler-Parks et al. (1987b) (also see Table 7-13) |

[a]See Appendix A for abbreviations and acronyms.
[b]Listed from lowest to highest O$_3$ concentration.

|              | $\Delta FEV_1$ Spring (mL) | $\Delta FEV_1$ Fall (mL) | $\Delta FEV_1$ Winter (mL) | $\Delta FEV_1$ Spring (mL) |
|--------------|---------------------------|--------------------------|----------------------------|----------------------------|
| Responders   | −385                      | −17                      | +16                        | −347                       |
| Nonresponders| +28                       | +90                      | +34                        | +81                        |

These results suggest a seasonal variability in response that may be attributed to increased ambient $O_3$ exposure during the summer months. It must be noted that the responders included subjects who had a history of complaints from ambient air pollution. Furthermore, this group included a significant proportion of allergic individuals whose seasonal allergies could have contributed to their varying responses. Historically, however, studies with the subjects drawn from the population of Los Angeles have reported reduced responses to $O_3$ exposure in the laboratory compared to nonresidents (Hackney et al., 1976, 1977b).

Brookes et al. (1989) reexamined a hypothesis previously tested by Gliner et al. (1983), that repeated exposure to one concentration can alter response to subsequent exposure to a different $O_3$ concentration. Gliner et al. (1983) previously had shown that the response to 0.40 ppm $O_3$ was not influenced by previously being exposed to 0.20 ppm $O_3$ for 2 h on 3 consecutive days. Brookes et al. (1989) tested whether exposure to 0.20 or 0.35 ppm $O_3$ would change subsequent response to 0.20 or 0.35 ppm $O_3$. They found increased responses to 0.20 ppm for both preexposures ($\Delta FEV1 = -5.02$, $-7.80$, and $-8.74\%$ for 0.20 ppm acutely, 0.20 ppm after 0.20 ppm, and 0.20 ppm after 0.35 ppm, respectively), but this trend was significant only for the higher concentration. Although not statistically significant, the response increase seen on the second exposure day at 0.20 ppm is similar to that seem by Gliner et al. (1983). These observations suggest that, although preexposure to low concentrations of $O_3$ may not influence response to higher concentrations, preexposure to a high concentration of $O_3$ may significantly increase response to a lower concentration on the following day.

Schonfeld et al. (1989) confirmed previous observations of Bedi et al. (1985) and Folinsbee et al. (1986) that the period of enhanced responsiveness to $O_3$ following an initial exposure persists for about 24 to 48 h but is absent by 72 h after the initial exposure. In a series of paired exposures to 0.35 ppm with continuous heavy exercise separated by intervals of 1, 2, 3, or 4 days, they found that the responses to the second exposure were clearly increased at 24 h ($\Delta FEV1 = -16.1$ and $-30.4\%$ for the first and second exposures, respectively) and possibly also at 48 h ($\Delta FEV1 = -14.4$ and $-20.6\%$). Similar trends were observed for other physiological variables such as SRaw and respiratory pattern during exercise. With a 3- or 4-day interval between exposures, the responses to the two exposures were similar.

Foxcroft and Adams (1986) demonstrated that decrements in exercise performance seen after a 1-h exposure to 0.35-ppm (continuous heavy exercise) were less after 4 consecutive days of $O_3$ exposure than they were after a single acute exposure. Maximal aerobic power and performance time on a progressive bicycle exercise test were reduced 6% and 42 s, respectively, from FA control, after a single 0.35-ppm exposure. After 4 consecutive days of 1-h exposures, the maximal aerobic power was reduced only 4% and the performance time by only 14 s; these differences from FA control were not statistically

significant. Despite the change in exercise performance, Foxcroft and Adams (1986) did not show the attenuation of $FEV_1$ response seen in many previous studies (Folinsbee et al., 1980; Linn et al., 1982b). However, these investigators selected known $O_3$-sensitive subjects whose $FEV_1$ decrements exceeded 30% on the first 3 days of exposure. The large magnitude of these responses, the trend for the responses to decrease on the third and fourth day, the decreased symptom responses, and the observations of Horvath et al. (1981) that $O_3$-sensitive subjects adapt slowly, suggest that attenuation of response would have occurred if the exposure series had been continued for another 1 or 2 days. These observations support the contention advanced by Horvath et al. (1981) that the progression of attenuation of response is a function of "$O_3$ sensitivity". Furthermore, these results suggest that exercise responses after $O_3$ exposure may be limited, either voluntarily or involuntarily, more by subjective symptoms than by alterations in gas exchange consequent to changes in ventilatory function.

Bedi et al. (1989) examined the responses of elderly subjects (median age, 65 years) to four exposures to 0.45 ppm $O_3$ for 2 h with mild IE. The first three exposures were on consecutive days, with the fourth exposure following the third by 3 days. Changes in $FEV_1$ on the first two exposure days averaged □5.8 and □5.6%, about half the response expected in a group of healthy young males (□12.7%; Folinsbee et al., 1978). There were no significant changes in $FEV_1$ on the third (□1.9%) and fourth (□1.7%) exposure days. Symptom responses were negligible, although there was an overall increase in symptoms on the first day of $O_3$ exposure compared to air exposure. Despite the high concentration of the exposure, there was no enhancement of the spirometry response on the second day of exposure. Although similar observations have been made in previous studies producing small changes in spirometry (Folinsbee et al., 1980, 1994) with repeated exposures, the responses of older subjects are not sufficiently understood to explain these responses. Bedi et al. (1988) had previously reported that responses to $O_3$ in the older subjects tended to be less reproducible, although this factor alone could not explain these responses.

Drechsler-Parks et al. (1987b) examined the response to repeated exposures to 0.45 ppm $O_3$ plus 0.30 ppm peroxyacetyl nitrate (PAN). Exposures to $O_3$ and $O_3$ plus PAN yielded similar changes in spirometry (□$FEV_1$ = □19 and □15%, respectively). Thus, PAN did not increase responses to $O_3$. Repeated exposure to the PAN plus $O_3$ mixture resulted in similar changes to those seen with $O_3$ exposure alone. Responses in $FEV_1$ exceeded □30% on the second exposure and fell to less than □5% after the fifth day. The attenuation of response persisted 3 days after the repeated exposures, but was absent after 7 days. These observations suggest that PAN does not influence the attenuation of response to repeated $O_3$ exposure. If the PAN responses are considered negligible, this study confirms the observation that the attenuation of $O_3$ responses with chamber exposures lasts no longer than 1 week.

Repeated multihour exposure to low concentrations of $O_3$ has been examined (Horvath et al., 1991; Folinsbee et al., 1994; Linn et al., 1994). Horvath et al. (1991) exposed subjects for 2 consecutive days to 0.08 ppm using the 6.6-h prolonged-exposure protocol (see Section 7.2.2). They observed small pre- to postexposure changes in $FEV_1$ (□2.5%) on the first exposure, but no change on the second day. Linn et al. (1994) observed a 1.7% decrease in $FEV_1$ in healthy subjects after a 6.5-h exposure to 0.12 ppm. A second consecutive exposure yielded even smaller (<1%) responses. With exposure to a mixture of $O_3$ plus 100 □g/m$^3$ of $H_2SO_4$ aerosol, there was a 4.2% decrease in $FEV_1$ on the first exposure day. In a group of asthmatics exposed under similar conditions, the $FEV_1$ response on the first day was □8.6% ($O_3$) and □11.6% ($O_3$ plus acid). After adjustment for the exercise effect

($\Box$4.6%), the responses ($\Box$4 and $\Box$7%) were still greater than those of nonasthmatics. Responses were slightly reduced on the second day of exposure.

Folinsbee et al. (1994) exposed 17 subjects to 0.12 ppm $O_3$ for 6.6 h on 5 consecutive days. Spirometry responses were typified by changes in $FEV_1$ that reached $\Box$13% on the first day and $\Box$9% on the second day of exposure. No significant differences in spirometry responses between FA and subsequent $O_3$ exposures were observed. Symptom responses were also greatest on the first exposure day and were largely absent from the third day on. Methacholine responsiveness was tested using a single dose of methacholine and then by comparing changes in $R_{aw}$ as the ratio of $SR_{aw}$ after methacholine aerosol to that after saline aerosol. The responses to $FEV_1$ and methacholine testing are shown below.

|  | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Clean Air |
|---|---|---|---|---|---|---|
| $\Box$%$FEV_1$ | $\Box$12.79 | $\Box$8.73 | $\Box$2.54 | $\Box$0.6 | +0.2 | +1.1 |
| $SR_{aw}$ Ratio | 3.67 | 4.55 | 3.99 | 3.24 | 3.74 | 2.22 |

Methacholine responsiveness was increased (over the clean air response) throughout the 5 days of $O_3$ exposure, although it reached a peak on the second day, and, in some subjects, there was a trend for responsiveness to decrease after 5 days. These results suggest that repeated exposure to low levels of $O_3$, despite the attenuation of symptoms and pulmonary function changes, is not without hazard. It is likely that some epithelial damage persists that contributes to the enhanced response to methacholine throughout the exposure series. However, it must be noted that, in this study, subjects initially were selected based on their $FEV_1$ response to 0.16 ppm $O_3$ for 4 h. This may in part explain the greater $FEV_1$ responses seen in this study, but there was no correlation between individual $FEV_1$ decrements and changes in methacholine responsiveness. Furthermore, the Horvath et al. (1991) subjects were exposed only to 0.08 ppm, and they were somewhat older than the Folinsbee et al. (1994) subjects; the Linn et al. (1994) subjects, on the other hand, had lower ventilation during exercise and were residents of Los Angeles accustomed to exposure to these levels of $O_3$ (see Chapter 4 for typical $O_3$ concentrations).

Based on studies cited here and in the previous criteria document (U.S. Environmental Protection Agency, 1986), several conclusions can be drawn about repeated 1- to 2-h $O_3$ exposures. Repeated exposures to $O_3$ can cause an enhanced (i.e., greater) response on the second day of exposure. This enhancement appears to be dependent on the interval between the exposures (24 h causes the greatest increase) and is absent with intervals $\Box$3 days. An enhanced response also appears to depend to some extent on the magnitude of the initial response. Small responses to the first $O_3$ exposure are less likely to result in an enhanced response on the second day of $O_3$ exposure. Repeated daily exposure also results in attenuation of spirometric responses, typically after 3 to 5 days of exposure. This attenuated response persists for less than 1 or as long as 2 weeks. In temporal conjunction with the spirometry changes, symptoms induced by $O_3$, such as cough and chest discomfort, also are attenuated with repeated exposure. Ozone-induced changes in airway responsiveness attenuate more slowly than spirometric and symptom responses. Attenuation of the changes in airway responsiveness also persist longer than changes in spirometry, although this has been studied only on a limited basis. In longer-duration, lower-concentration studies that do not cause an

enhanced second-day response, the attenuation of response to $O_3$ appears to proceed more rapidly.

### 7.2.1.5 Effects on Exercise Performance

*Introduction*

An early epidemiological study examining race performances in high school cross-country runners (Wayne et al., 1967) suggested that exercise performance is depressed by inhalation of ambient oxidant air pollutants. Wayne et al. (1967) suggested that the detrimental effects of oxidant air pollutants on race performance may have been related to increased $R_{aw}$ or to the associated discomfort in breathing, thus limiting runners' motivation to perform at high levels. The effects of acute $O_3$ inhalation on exercise performance have been evaluated in numerous controlled human studies. These studies can be divided into two categories: (1) those that examine the effects of acute $O_3$ inhalation on maximal oxygen uptake and (2) those that examine the effects of acute $O_3$ inhalation on the ability to complete strenuous continuous exercise protocols up to 1 h in duration. Five studies (Folinsbee et al., 1977; Horvath et al., 1979; Folinsbee et al., 1984; Adams and Schelegle, 1983; Savin and Adams, 1979) examining the effects of acute $O_3$ exposures on exercise performance were discussed in the 1986 EPA criteria document (U.S. Environmental Protection Agency, 1986). This section summarizes the studies reviewed in that document and reviews more recent studies that examine the effect of acute $O_3$ inhalation on maximal oxygen uptake and endurance performance. Studies are also summarized in Table 7-8.

*Effect on Maximal Oxygen Uptake*

Three studies (Folinsbee et al., 1977; Horvath et al., 1979; Savin and Adams, 1979) examining the effects of acute $O_3$ exposures on $\dot{V}O_{2max}$ were discussed in the 1986 EPA criteria document (U.S. Environmental Protection Agency, 1986). Of these studies, only Folinsbee et al. (1977) observed that $\dot{V}O_{2max}$ was significantly decreased (10.5%) following a 2-h exposure to 0.75 ppm $O_3$ with light IE. Reductions in $\dot{V}O_{2max}$ were accompanied by a 9.5% decrease in maximum attained workload, a 16% decrease in maximum ventilation, and a 6% decrease in maximum heart rate. The 16% decrease in maximum ventilation was associated with a 21% decrease in $V_T$. In addition, the $O_3$ exposure resulted in a 22.3% decrease in $FEV_1$ and subjective symptoms of cough and chest discomfort. In contrast, Horvath et al. (1979) did not observe a change in $\dot{V}O_{2max}$ or other maximum cardiopulmonary endpoints in male and female subjects exposed at rest to 0.75 ppm $O_3$ for 2 h, although FVC was significantly decreased (10%). Similarly, Savin and Adams (1979) observed no effect on maximum attained workload or $\dot{V}O_{2max}$ in nine subjects exposed to 0.3 ppm $O_3$ while performing a progressively incremented exercise test to volitional fatigue lasting 30 min. In addition, Savin and Adams (1979) observed no significant effect on pulmonary function, performance time, maximum heart rate, or anaerobic threshold, although maximum ventilation was significantly reduced 7%.

More recent findings of Foxcroft and Adams (1986) and Gong et al. (1986) support the earlier observations of Folinsbee et al. (1977). Foxcroft and Adams (1986) observed significant ($p < 0.05$) reductions in performance time (16.7%), $\dot{V}O_{2max}$ (6.0%), maximum ventilation (15.0%), and maximum heart rate (5.6%) in eight aerobically trained males during a rapidly incremented $\dot{V}O_{2max}$ test following 50-min exposure to 0.35 ppm $O_3$ with CE (exercise $\dot{V}_E = 60$ L/min). Similarly, Gong et al. (1986) found significant

## Table 7-8. Ozone Effects on Exercise Performance[a]

| ppm | $\mu$g/m[b] | Exposure Duration and Activity | Exposure Conditions | Number and Gender of Subjects | Subject Characteristics | Observed Effect(s) | Reference |
|---|---|---|---|---|---|---|---|
| 0.06-0.07 0.12-0.13 | 120-140 245-260 | CE ($\dot{V}_E$ = 30 to 120 L/min) 16 to 28 min progressive maximum exercise protocol | Tdb = 23 to 24.5 °C RH = 50 to 53% | 12 M, 12 F | Athletic | Reduced maximum performance time and increased respiratory symptoms during $O_3$ exposure. | Linder et al. (1988) |
| 0.12 0.18 0.24 | 235 353 470 | 1 h competitive simulation exposures at mean $\dot{V}_E$ = 87 L/min | Tdb = 23 to 26 °C RH = 45 to 60% | 10 M | Highly trained competitive cyclists | Decrease in exercise time of 7.7 min and 10.1 min for subjects unable to complete the competitive simulation at 0.18 and 0.24 ppm $O_3$, respectively; decrease in FVC and $FEV_1$ for 0.18- and 0.24-ppm $O_3$ exposure compared with FA exposure. | Schelegle and Adams (1986) |
| 0.12 0.20 | 235 392 | 1 h CE $\dot{V}_E$ = 89 L/min | Tdb = 31 °C | 15 M, 2 F | Highly trained competitive cyclists | Decrease in $\dot{V}_{Emax}$, $VO_{2max}$, $V_{Tmax}$, workload, ride time, FVC, and $FEV_1$ with 0.20 ppm $O_3$ exposure, but not significant with 0.12-ppm $O_3$ exposure, as compared to FA exposure. | Gong et al. (1986) |
| 0.20 0.35 | 392 686 | 1 h CE or competitive simulation at mean $\dot{V}_E$ = 77.5 L/min | Tdb = 23 to 26 °C RH = 45 to 60% | 10 M | Well-trained distance runners | $V_T$ decreased and f increased with continuous 50-min $O_3$ exposures; decrease in FVC, $FEV_1$, and $FEF_{25-75\%}$ from FA to 0.20 ppm and FA to 0.35-ppm $O_3$ exposure in all conditions; three subjects unable to complete continuous and competitive protocol at 0.35 ppm $O_3$. | Adams and Schelegle (1983) |
| 0.21 | 412 | 1 h CE at 75% $VO_2$max | Tdb = 19 to 21 °C RH = 60 to 70% | 6 M, 1 F | Well-trained cyclists | Decrease in FVC, $FEV_1$, $FEF_{25-75\%}$, and MVV with 0.21 ppm $O_3$ compared with FA exposure. | Folinsbee et al. (1984) |
| 0.25 | 490 | 1 h CE $\dot{V}_E$ = 63 L/min | Tdb = 20 °C RH = 70% | 19 M, 7 F | Active nonathletes | FVC, $FEV_1$, and MVV all decreased with 0.25-ppm $O_3$ exposure compared with FA. | Folinsbee et al. (1986) |
| 0.25 0.50 0.75 | 490 980 1,470 | 2 h rest | NA | 8 M, 5 F | | FVC decreased with 0.50- and 0.75-ppm O exposure compared with FA; 4% nonsignificant decrease in mean $VO_{2max}$ following 0.75 ppm $O_3$ compared with FA exposure. | Horvath et al. (1979) |
| 0.35 | 686 | 50 min CE $\dot{V}_E$ = 60 L/min | NA | 8 M | Trained nonathletes | $V_T$ decreased, f increased with 50-min $O_3$ exposures; decrease in FVC, $FEV_1$, $FEF_{25-75\%}$, performance time, $VO_{2max}$, $V_{Emax}$, and $HR_{max}$ from FA to 0.35-ppm $O_3$ exposure. | Foxcroft and Adams (1986) |

## Table 7-8 (cont'd).  Ozone Effects on Exercise Performance[a]

| Ozone Concentration[b] | | Exposure Duration and Activity | Exposure Conditions | Number and Gender of Subjects | Subject Characteristics | Observed Effect(s) | Reference |
|---|---|---|---|---|---|---|---|
| ppm | μg/m | | | | | | |
| 0.75 | 1,470 | 2 h IE (4 × 15 min light [50 W] bicycle ergometry) | NA | 13 M | 4 light S, 9 NS | Decrease in FVC, $FEV_1$, ERV, IC, and $FEF_{50\%}$ after 1-h 0.75-ppm $O_3$ exposure; decrease in $VO_{2max}$, $V_{Tmax}$, $V_{Emax}$, maximal workload, and heart rate following 0.75-ppm $O_3$ exposure compared with FA. | Folinsbee et al. (1977) |

[a]See Appendix A for abbreviations and acronyms.
[b]Listed from lowest to highest $O_3$ concentration.

reductions in performance time (29.7%), $\dot{V}O_{2max}$ (16.4%), maximum ventilation (18.5%), and maximum workload (7.8%) in 17 top-caliber endurance cyclists during a rapidly incremented $\dot{V}O_{2max}$ test following 1-h exposure to 0.2 ppm $O_3$ with very heavy CE ($\dot{V}_E$ = 90 L/min) and the addition of ambient heat stress (31 □C). In both studies (Foxcroft and Adams, 1986; Gong et al., 1986), the reductions in maximal exercise endpoints were accompanied by significant decrements in pulmonary function and marked subjective symptoms of respiratory discomfort. More recently, Linder et al. (1988) observed small decrements in performance time during a progressive maximal exercise test at $O_3$ concentrations as low as 0.06 ppm. These small effects were associated with increased respiratory symptoms and small, inconsistent changes in $FEV_1$. Hence, it appears that maximal oxygen uptake is reduced if it is preceded by an $O_3$ exposure entailing a sufficient total inhaled dose of $O_3$ to result in significant pulmonary function decrements or subjective symptoms of respiratory discomfort.

### *Effect on Endurance Exercise Performance*

Two studies (Adams and Schelegle, 1983; Folinsbee et al., 1984) that addressed the effects of acute $O_3$ exposures on the ability of highly trained subjects to complete strenuous continuous exercise protocols were discussed in the 1986 EPA criteria document (U.S. Environmental Protection Agency, 1986).

Adams and Schelegle (1983) exposed 10 well-trained distance runners to FA and 0.20 and 0.35 ppm $O_3$ while the runners exercised on a bicycle ergometer at workloads simulating either a 1-h steady-state "training" bout or a 30-min warm-up followed immediately by a 30-min "competitive bout". The exercise levels in the steady-state training bout were of sufficient magnitude (68% of their $\dot{V}O_{2max}$) to increase mean $\dot{V}_E$ to 80 L/min. The $\dot{V}_E$ averaged over the entire competitive simulation was also 80 L/min, whereas the mean $\dot{V}_E$ during the 30-min competitive bout was 105 L/min. Subjective symptoms increased as a function of $O_3$ concentration for both training and competitive protocols. In the competitive protocol, four runners exposed to 0.20 ppm $O_3$ and nine exposed to 0.35 ppm $O_3$ indicated that they could not have performed maximally. Three subjects were unable to complete both the training and competitive protocols at 0.35 ppm $O_3$, and a fourth failed to complete only the competitive ride.

Folinsbee et al. (1984) exposed six well-trained men and one well-trained woman to 0.21 ppm $O_3$ while they exercised continuously on a bicycle ergometer for 1 h at 75% of their $\dot{V}O_{2max}$ ($\dot{V}_E$ = 81 L/min). Following $O_3$ exposure, FVC and $FEV_1$ were reduced significantly and the subjects reported symptoms of laryngeal and tracheal irritation and chest soreness and tightness when taking deep breaths. Anecdotal reports obtained from the cyclists suggested that their performance would have been limited if they experienced similar symptoms during competition.

Avol et al. (1984) exposed 50 well-conditioned cyclists to 0.00, 0.08, 0.16, 0.24, and 0.32 ppm $O_3$ for 1 h in ambient heat (32 □C) while they exercised continuously ($\dot{V}_E$ = 57 L/min). Reductions in $FEV_1$ and symptoms, initially detected at 0.16 ppm $O_3$, increased in a concentration- dependent manner. Three and 16 cyclists could not complete the 1-h exposure to 0.16 and 0.24 ppm $O_3$, respectively, without a reduction in workload. Similarly, in their study of the effects of $O_3$ exposure on $\dot{V}O_{2max}$, Gong et al. (1986) reported that 6 of 17 highly trained endurance cyclists were not able to complete 1-h exposure to 0.2 ppm $O_3$ with very heavy CE ($\dot{V}_E$ = 90 L/min) and the addition of ambient heat stress (31 □C).

In a study designed to determine the effects of the inhalation of low ambient $O_3$ concentrations on simulated competitive endurance performance, Schelegle and Adams (1986) exposed 10 highly trained endurance athletes to 0.12, 0.18, and 0.24 ppm $O_3$ while they were performing a 1-h "competitive" protocol. The competitive protocol used in this study was similar to that used by Adams and Schelegle (1983) except that the workload during the final 30-min competitive bout was more intense; it was selected based on the maximum workload (approximately 86% of their $\dot{V}O_{2max}$, mean $\dot{V}_E = 120$ L/min) each subject could maintain for 30 min while breathing FA. All subjects completed the FA exposure, whereas one, five, and seven subjects could not complete the 0.12-, 0.18-, and 0.24-ppm $O_3$ exposures, respectively. Following 0.18- and 0.24-ppm $O_3$ exposures, FVC and $FEV_1$ were reduced significantly ($p < 0.05$), and subjective symptoms were elevated significantly ($p < 0.05$). No significant effect of $O_3$ was found for metabolic or ventilatory pattern responses. Similarly, Folinsbee et al. (1986) found that highly trained runners experienced a reduced run time on a treadmill (speed and grade set at approximately 80% of their subjects $\dot{V}O_{2max}$) when exposed to 0.18 ppm $O_3$ compared with FA. These subjects did have significantly elevated symptoms of respiratory discomfort and significantly decreased FVC and $FEV_1$, whereas arterial oxygen saturation at the end of the run was not affected by $O_3$ exposure.

Determining the mechanisms leading to the observed decrements in maximal oxygen uptake and the inability to complete strenuous exercise protocols is problematic. As stated by Astrand and Rodahl (1977) "the capacity for prolonged rhythmic muscular exercise is limited by an interrelated composite of cardiorespiratory, metabolic, environmental, and psychological factors." Many investigators cited above have concluded that the observed reductions in exercise performance appeared to be due to symptoms limiting the ability of their subjects to perform. However, in every case, this is a conclusion achieved by exclusion and not by the demonstration of a causal relationship. Other factors could also contribute to $O_3$-induced decrements in exercise performance. One possibility is that stimulation of neural receptors in the airways may result in an inhibition of alpha-motor nerve activity to respiratory muscles during inspiration (Koepchen et al., 1977; Schmidt and Wellhoner, 1970), resulting in the observed decrease in $V_T$ and, at the same time, increasing the subject's sensation of respiratory effort. This mechanism would not be directly related to symptoms of discomfort but, because of the common role of airway neural afferents, may be difficult to discern from the effects of symptoms of respiratory discomfort. Indeed, a reflex inhibition of the ability to inspire would be consistent with the reduced $V_T$ following $O_3$ exposure in subjects performing maximal exercise and would be consistent with the development of a physiologically induced ventilatory limitation to maximal oxygen uptake.

## 7.2.2  Pulmonary Function Effects of Prolonged (Multihour) Ozone Exposures

Since 1988, a series of studies has described the responses of subjects exposed to relatively low (0.08 to 0.16 ppm) $O_3$ concentrations for durations of 4 to 8 h (see Table 7-9). These studies have demonstrated statistically significant changes in spirometry, $R_{aw}$, symptoms, and airway responsiveness during and after exposures. As in studies conducted at higher concentrations of $O_3$ for shorter periods of time, there is broad variability in response.

The only related study cited in the previous criteria document (U.S. Environmental Protection Agency, 1986) was that of Kerr et al. (1975), who exposed

## Table 7-9. Pulmonary Function Effects After Prolonged Exposures to Ozone[a]

| Ozone Concentration[b] | | Exposure Duration and Activity | Exposure Conditions | Number and Gender of Subjects | Subject Characteristics | Observed Effect(s) | Reference |
|---|---|---|---|---|---|---|---|
| ppm | $\mu$g/m³ | | | | | | |
| 0.08<br>0.10<br>0.12 | 157<br>196<br>235 | 6.6 h<br>IE (6 × 50 min)<br>$\dot{V}_E \approx 39$ L/min | 18 °C<br>40% RH | 22 M | Healthy NS, 18 to 33 years old | FVC and $FEV_1$ decreased throughout the exposure; $FEV_1$ decrease at end exposure was 7.0, 7.0, and 12.3%, respectively. $FEV_1$ change >15% occurred in 3, 5, and 9 subjects at 0.08, 0.10, and 0.12 ppm, respectively. Methacholine responsiveness increased by 56, 89, and 121%, respectively. | Horstman et al. (1990) |
| | | See Horstman et al. (1990) and Folinsbee et al. (1988) | | | | A lognormal model was fitted to $FEV_1$ data. Model parameters indicate $O_3$ concentration had greater effect than $\dot{V}_E$ or duration (estimated exponent for $[O_3] \approx 4/3$). | Larsen et al. (1991) |
| 0.08<br>0.10 | 157<br>196 | 6.6 h<br>IE (6 × 50 min)<br>$\dot{V}_E$ = 40 L/min | 18 °C<br>40% RH | 38 M | Healthy NS, mean age 25 years old | $FEV_1$, decreased 8.4% at 0.08 ppm and 11.4% at 0.10 ppm. Symptoms of cough, PDI, and SB increased with $O_3$ exposure. | McDonnell et al. (1991) |
| 0.08 | 157 | 6.6 h<br>IE (6 × 50 min)<br>$\dot{V}_E$ = 35 to 38 L/min<br>(1 day of air, 2 days of $O_3$) | 25 °C<br>48% RH | 5 F, 6 M | Healthy NS, 30 to 45 years old | FVC decreased 2.1%, $FEV_1$ decreased 2.2% on first day of $O_3$ exposure; no change on second $O_3$ day. | Horvath et al. (1991) |
| 0.12 | 235 | 6.6 h<br>IE (6 × 50 min)<br>$\dot{V}_E$ = 42.6 L/min | 18 °C<br>40% RH<br>(1 exposure to clean air; 1 exposure to $O_3$) | 10 M | Healthy NS, 18 to 33 years old | $FEV_1$ decreased by 13% after 6.6 h. FVC dropped 8.3%. Cough and PDI increased with $O_3$ exposure. Airway responsiveness to methacholine doubled after $O_3$ exposure. | Folinsbee et al. (1988) |
| (a) 0.12<br>(b) Varied from 0.0 to 0.24 (increased by 0.06 ppm/h then decreased by 0.06 ppm/h) | 235 | 8 h<br>IE (8 × 30 min)<br>$\dot{V}_E$ = 40 L/min | 22 °C<br>40% RH<br><3 $\mu$g/m³ TSP | 23 M | Healthy NS, 20 to 35 years old | (a) $FEV_1$ decreased 5% by 6 h and remained at this level through 8 h.<br>(b) $FEV_1$ change mirrored $O_3$ concentration change with a lag time of $\approx$2 h. Max decrease of 10.2% after 6 h. $FEV_1$ change was reduced in last 2 h of exposure. | Hazucha et al. (1992) |

# Table 7-9 (cont'd). Pulmonary Function Effects After Prolonged Exposures to Ozone[a]

| Ozone Concentration[b] | | Exposure Duration and Activity | Exposure Conditions | Number and Gender of Subjects | Subject Characteristics | Observed Effect(s) | Reference |
|---|---|---|---|---|---|---|---|
| ppm | μg/m³ | | | | | | |
| 0.12 | 235 | 6.5 h/day IE (6 × 50 min) (2 days of exposure) $\dot{V}_E$ = 28 L/min (asthmatic) $\dot{V}_E$ = 31 L/min (healthy) | 21 °C 50% RH | 15 (8 M, 7 F) | Healthy NS, 22 to 41 years old | Bronchial reactivity to methacholine increased with $O_3$ exposure in healthy subjects. $FEV_1$ decreased 2% (pre- to postexposure) in healthy subjects and 7.8% in asthmatics. Responses were generally less on the second day. Two healthy subjects and four asthmatics had $FEV_1$ decreases >10%. | Linn et al. (1994) |
| | | | | 30 (13 M, 17 F) | Asthmatic NS, 18 to 50 years old | | |
| 0.12 | 235 | 6.6 h IE (6 × 50 min) $\dot{V}_E$ = 38.8 L/min | 18 °C 40% RH (5 consecutive days of exposure to $O_3$, 1 day exposure to CA) | 17 M | Healthy NS, mean age 25 ± 4 years old | $FEV_1$ decreased by 12.8, 8.7, 2.5, and 0.6 and increased by 0.2 on Days 1 to 5 of $O_3$ exposure, respectively. Methacholine airway responsiveness increased by >100% on all exposure days. Symptoms increased on the first $O_3$ day, but were absent on the last 3 exposure days. | Folinsbee et al. (1994) |
| 0.16 | 314 | 4 h IE (4 × 50 min) $\dot{V}_E$ ≈ 38.9 L/min | 18 °C 40% RH (one exposure to $O_3$, no control exposure) | 15 M | Healthy NS, mean age 25 ± 4 years old | FVC decreased 9.5% and $FEV_1$ decreased 16.6%. $FEV_1$/FVC ratio decreased from 0.79 to 0.73. | |

[a]See Appendix A for abbreviations and acronyms.
[b]Listed from lowest to highest $O_3$ concentration.

subjects for 6 h to 0.5 ppm $O_3$, with only two brief 15-min periods of moderate exercise ($\dot{V}_E$ = 44 L/min) during the exposure. Small changes in spirometry were observed. Because of the minimal extent of exercise and the high $O_3$ concentration, these results cannot be compared to the more recent studies.

The first prolonged $O_3$ exposure study involving low concentrations and a substantial amount of "moderate exercise"[1] was reported by Folinsbee et al. (1988). The basic protocol used by these investigators has been used in a number of subsequent investigations and therefore merits describing in some detail. The exposures lasted 6 h and 35 min ($\Box$6.6 h). Except for a 35-min lunch break (during which $O_3$ exposure continued at rest) after 3 h, the subjects exercised at a moderate level (with a ventilation of about 40 L/min) for 50 min of each hour. Pulmonary function tests were conducted during the 10-min rest period and at the beginning and end of exposure. The exposure was intended to simulate a day of heavy outdoor work or play. For convenience, this protocol is referred to as the EPA prolonged-exposure protocol.

In this study (Folinsbee et al., 1988), a group of 10 subjects was exposed to clean air and 0.12 ppm $O_3$ for 6.6 h. Forced vital capacity and $FEV_1$ decreased in a roughly linear fashion throughout the exposure and had fallen by 8.3 and 13%, respectively, by the end of the exposure. Symptoms of cough and chest discomfort were increased, and airway responsiveness to methacholine was approximately doubled after $O_3$ exposure. There was a wide range of response, three subjects had $FEV_1$ decrements of 25% or greater, and the three least sensitive subjects had less than 5% change in $FEV_1$.
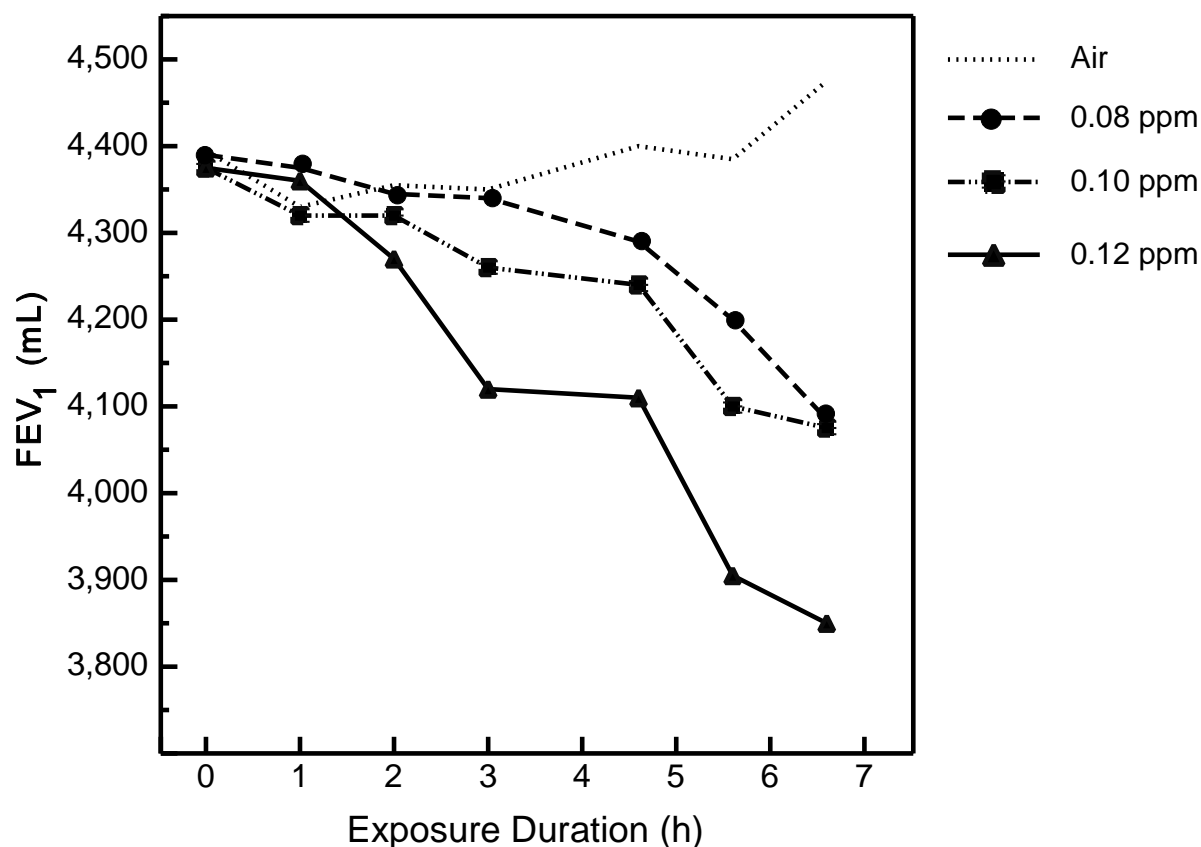
In order to extend these initial observations, Horstman et al. (1990) used the same protocol to expose a group (n = 22) of subjects to clean air and three different $O_3$ concentrations (0.08, 0.10, and 0.12 ppm). At 0.12 ppm $O_3$, responses were similar to those observed in the previous study, with the exception that the symptom responses were smaller in the new group of subjects. A similar (but of smaller magnitude) pattern of response in spirometry, $R_{aw}$, and airway responsiveness was seen at the two lower concentrations. The mean $FEV_1$ responses during the four exposures are shown in Figure 7-3. The responses were dependent on concentration and exposure duration (ventilation was not varied) and averaged 7, 8, and 13% at the three $O_3$ concentrations. Larsen et al. (1991) used these data (Horstman et al., 1990) to develop a "dose-response" relationship for percent change in $FEV_1$ as a function of $O_3$ concentration and exposure duration. The lognormal multiple linear regression model suggested that $FEV_1$ responses were approximately linear with duration of exposure but that $O_3$ concentration plays a slightly more important role. The exponent of approximately 4/3 suggests that doubling $O_3$ concentration would be similar to increasing exposure duration by about 2″ times.

A series of additional exposures were conducted at 0.08 and 0.10 ppm $O_3$ to study changes in cells and inflammatory mediators from BAL (see Section 7.2.4), but pulmonary function was measured as well. McDonnell et al. (1991) reported an 8.4% decrease in $FEV_1$ at 0.08 ppm and an 11.4% decrease at 0.10 ppm. These responses were slightly larger than those seen in the previous Horstman et al. (1990) study. The duration-$FEV_1$ response data were fit to a three-parameter logistic model, which significantly improved the amount of

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[1]The "moderate" exercise descriptor is based on previously published EPA guidelines for representative types of exercise (see Table 10-3, U.S. Environmental Protection Agency, 1986). Note, however, that exercise continued at this level (40 L/min) for 6 to 8 h should be considered as "heavy" or "strenuous work or play".
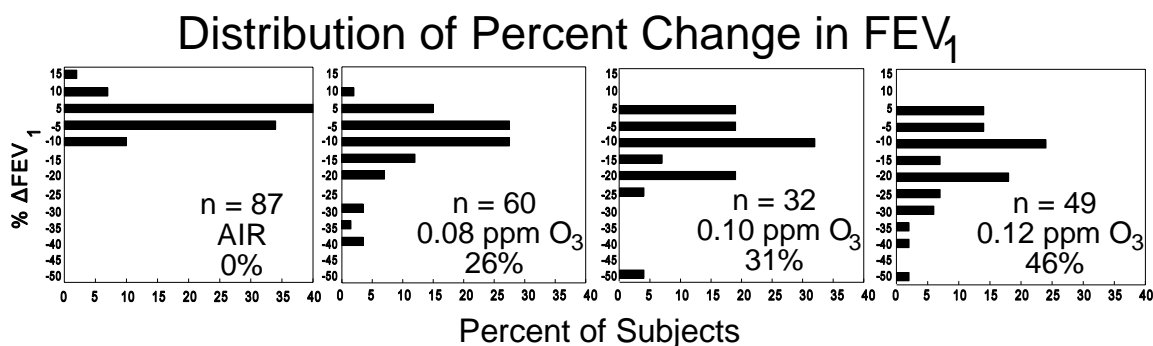
**Figure 7-3.** *The forced expiratory volume in 1 s (FEV₁) is shown in relation to exposure duration at different ozone concentrations. A 35-min resting exposure period was interposed between the end of the third hour and the beginning of the fourth hour. There were six 50-min exercise periods (minute ventilation ⬜39 L/min) during the exposure; these measurements were made 5 min after the end of each exercise. The total exposure duration was 6.6 h. The standard error of the mean (not shown) for these FEV₁ averages ranged from 120 to 160 mL.*

Source: Horstman et al. (1990).

variance explained by the model compared to a linear model; this is consistent with exploratory analyses in the Folinsbee et al. (1988) report. The reasonably good fit to the logistic model suggests that the $O_3$-pulmonary function response relationship may have a sigmoid shape. The primary importance of this observation is that it suggests that there is a response plateau. That is, for a given $O_3$ concentration and exercise ventilation level (i.e., dose rate), and after a certain length of exposure, the $FEV_1$ response tends not to increase further (i.e., plateau) with increasing duration of exposure.

In the fourth study in this series (Folinsbee et al., 1994), 17 subjects were exposed to 0.12 ppm $O_3$ for 6.6 h on 5 consecutive days. Subjects who were not responsive to $O_3$ were not selected to participate in this study. Responses in $FEV_1$ on the first of these exposures averaged □12.8%. Again, symptom responses were modest with a significant increase in lower respiratory symptoms on the first exposure day. A significant increase in airway responsiveness to methacholine also was shown. The response to the repeated exposures is discussed in Section 7.2.1.4. In addition, 15 subjects were exposed to 0.16 ppm for 4 h using the same hourly exposure protocol as described above. In these subjects, FVC decreased 9.5%, and $FEV_1$ declined 16.6%.

Folinsbee et al. (1991) took the $FEV_1$ response data from all four studies conducted at the EPA Health Effects Research Laboratory, using the same prolonged-exposure protocol, and examined the distribution of responses among the subjects at the three concentrations. This response distribution is illustrated graphically in Figure 7-4, which illustrates that $FEV_1$ decrements as large as 30 to 50% have been observed with prolonged exposure to $O_3$ concentrations □0.12 ppm. This response distribution allows one to determine the number or percentage of subjects with responses in excess of a certain level. The proportion of subjects with an $FEV_1$ decrease in excess of 10% is shown in Figure 7-4. With air exposure, no one exceeded this response level; however, 46% of the subjects exposed to 0.12 ppm $O_3$ had a >10% drop in $FEV_1$ after 6.6 h.

## Distribution of Percent Change in FEV₁



**Figure 7-4.**  *The distribution of response for 87 subjects exposed to clean air and at least one of 0.08, 0.10, or 0.12 ppm ozone ($O_3$) is shown here. The $O_3$ exposures lasted 6.6 h, during which time the subjects exercised for 50 min of each hour with a 35-min rest period at the end of the third hour. Decreases in forced expiratory volume in 1 s ($FEV_1$) are expressed as percent change from baseline. For example, the bar labeled "□10" indicates the percent of subjects with a decrease in $FEV_1$ of >5% but □10%, and the bar labeled "5" indicates improvement in $FEV_1$ of >0% but □5%. Each panel of the figure indicates the percentage of subjects at each $O_3$ concentration with a decrease of $FEV_1$ in excess of 10%.*

This response distribution also illustrates the wide range of response to $O_3$ under these exposure conditions and reinforces the observation by others (McDonnell et al., 1983; Horvath et al., 1981) of a substantial range of individual response to $O_3$.
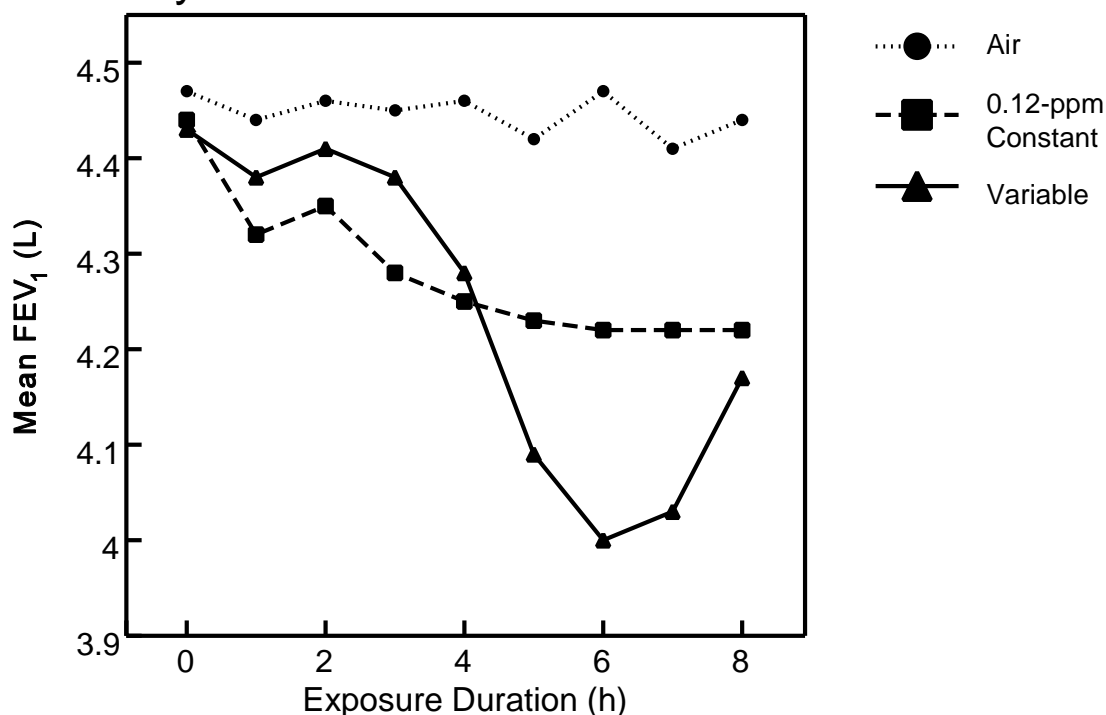
Horvath et al. (1991) examined the responses of healthy men and women (ages 30 to 45) to 0.08 ppm $O_3$ for 6.6 h using the EPA prolonged-exposure protocol. When compared with the clean air exposure, $FEV_1$ decreased about 5% with $O_3$ exposure. However, the variability of this response among this small heterogeneous group of subjects was enough to preclude statistical significance of this observation. No significant changes were observed with a second exposure on the next day. On the first day of $O_3$ exposure, 7 of the 11 subjects reported chest tightness. The authors point out that the range of variability in response in their study was similar to that reported by Folinsbee et al. (1988) and Horstman et al. (1990), although fewer subjects experienced large negative changes in $FEV_1$. One possible explanation for the differences between the findings of Horvath et al. (1991) and Horstman et al. (1990) may be that the subjects in Horvath's study were significantly older, which may result in reduced responses to $O_3$, as Drechsler-Parks et al. (1987a) have shown (see Section 7.2.1.3). The ventilation during exercise (37 to 39 L/min) was similar to that reported by Horstman et al. (1990). An additional $FEV_1$ measurement was made in this study at the end of the lunch period (i.e., after 40 min of rest). At this time, the small decrements in $FEV_1$ seen after the third exercise were reversed, and the $FEV_1$ was similar to the response in FA at the same time point. Although spirometry was not measured at this time in the other prolonged-exposure studies (Folinsbee et al., 1988; Horstman et al., 1990), it was noted that the decline in $FEV_1$ was attenuated between the third and fourth postexercise measurement. These observations suggest that the subjects' lung function may indeed have improved during the lunch rest period.

Linn et al. (1994) have reported responses of 45 healthy and asthmatic subjects to 0.12 ppm $O_3$ using the EPA prolonged-exposure protocol. In healthy subjects, they observed a small (1.7%) decrease in $FEV_1$, which was statistically significant, and an increase in airway responsiveness to methacholine. The functional responses in asthmatics (e.g., a 7.8% decrease in $FEV_1$) were greater than those of the healthy subjects. They observed smaller responses on a second consecutive day of exposure, as did Horvath et al. (1991) and Folinsbee et al. (1994). The ventilation averaged 31 and 28 L/min in the healthy and asthmatic subjects, respectively. The $FEV_1$ responses observed in this study, although statistically significant, are much lower than those observed by EPA investigators (Folinsbee et al., 1988; Horstman et al., 1990; Folinsbee et al., 1994). The smaller responses may be due to previous ambient exposures, lower ventilations, or a larger proportion of $O_3$-insensitive subjects in Los Angeles. Only 1 of 15 healthy subjects experienced an $FEV_1$ decrement in excess of 10%, whereas 9 of 30 asthmatics had $FEV_1$ decrements in excess of 10%. Asthmatic responses ranged from 12% to 35%.

To further explore the factors that determine responsiveness to $O_3$, Hazucha et al. (1992) designed a protocol to examine the effect of varying, rather than constant, $O_3$ concentrations. In this study, subjects were exposed to a constant level of 0.12 ppm $O_3$ for 8 h and to an $O_3$ level that increased linearly from 0 to 0.24 ppm for the first 4 h and then decreased linearly from 0.24 to 0 over the second 4 h of the 8 h exposure (triangular concentration profile). Subjects performed moderate exercise for the first 30 min of each hour. The overall exposure dose for these two exposures, calculated as the $C \times T \times \dot{V}_E$, was almost identical (difference < 1%). With exposure to the constant 0.12 ppm $O_3$, the $FEV_1$ declined

approximately 5% by the fifth hour of exposure and remained at that level for the remainder of the exposure. These responses are illustrated in Figure 7-5. This observation clearly indicates a response plateau, suggested in other studies (Horstman et al., 1990), with an exposure regimen that produces relatively small changes in lung function.

## Steady Versus Variable Ozone Concentration



**Figure 7-5.** *The forced expiratory volume in 1 s (FEV$_1$) is shown in relation to exposure duration (hours) under three exposure conditions. Subjects exercised (minute ventilation ☐40 L/min) for 30 min during each hour; FEV$_1$ was measured at the end of the intervening rest period. Standard error of the mean for these FEV$_1$ averages (not shown) ranged from 120 to 150 mL.*

Source: Hazucha et al. (1992).

With the triangular O$_3$ concentration profile, the FEV$_1$ decreased almost twice as much after 6 h of exposure. The initial response over the first 3 h was minimal, and then there was a substantial decrease in FEV$_1$, corresponding to the higher average O$_3$ concentration, that reached a nadir after 6 h. Despite continued exposure to a lower O$_3$ concentration (<0.12 ppm), the FEV$_1$ began to improve and was reduced by only 5.9% at the end of the 8-h exposure. (However, note that the average O$_3$ concentration in the eighth hour was 0.03 ppm). This study illustrates two important points. First, a response plateau occurs. It is intuitively obvious that there must be a limit to the acute decrease that can occur in FEV$_1$. However, from this study, it is also clear that the response plateau must be dependent on the O$_3$ concentration because much larger decreases in FEV$_1$ occur with exposure to O$_3$ concentrations higher than 0.12 ppm. Second, the response to O$_3$ exposure is dependent on the dose rate (some function of C and $\dot{V}_E$) and the cumulative dose (some function of dose rate and T), at least when the O$_3$ concentration is varied. This study also affirms the observation (Folinsbee et al., 1978; Adams et al., 1981; Hazucha, 1987; Larsen et al., 1991) that
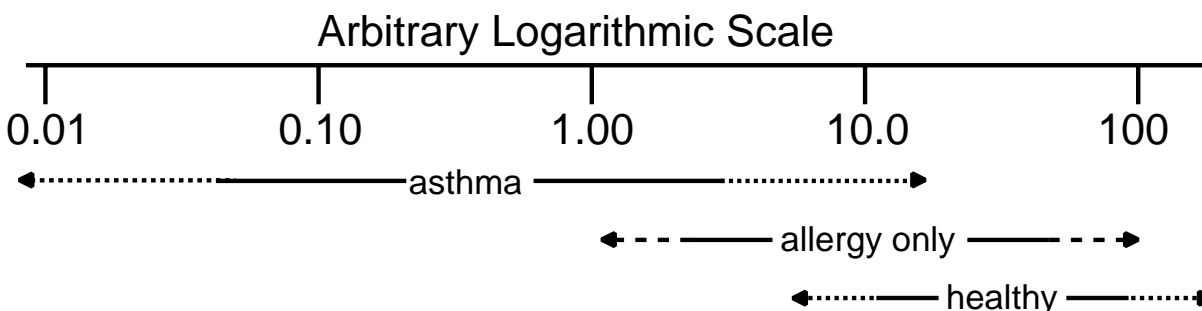
$O_3$ concentration is a more important factor in determining $O_3$ responses than is either exposure duration or the volume of air breathed during the exposure.

## 7.2.3 Increased Airway Responsiveness

Increased airway responsiveness indicates that the airways are predisposed to bronchoconstriction induced by a variety of stimuli (e.g., specific allergens, $SO_2$, cold air, etc.). Airway responsiveness is usually measured by having the individual forcefully exhale into a spirometer designed to measure expiratory flow rates (e.g., $FEV_1$) or, less commonly, by measuring $R_{aw}$ in a body plethysmograph. In order to determine the level of airway responsiveness, airway function is measured before and immediately after the inhalation of small amounts of an aerosolized bronchoconstrictor drug (e.g., methacholine or histamine). The dose of the bronchoconstrictor drug is increased in a step-wise fashion until a predetermined degree of airway response (e.g., a 20% drop in $FEV_1$ or a 100% increase in $R_{aw}$) has occurred. The dose of the bronchoconstrictor drug that produced the aforementioned response is often referred to as the "$PD_2$" (i.e., the provocative dose that produced a 20% drop in $FEV_1$) or the "$PD_1$" (i.e., the provocative dose that produced a 100% increase in $R_{aw}$).

A high level of bronchial responsiveness is a hallmark of asthma. However, varying degrees of increased airway responsiveness may occur in other lung disease (e.g., chronic bronchitis or viral respiratory infections) or in healthy asymptomatic individuals. The range of nonspecific bronchial responsiveness, as expressed by the $PD_2$ for example, is at least 1,000-fold from the most sensitive asthmatics to the least sensitive healthy subjects (see Figure 7-6). The average $PD_2$ for healthy subjects is 10 to 100 times that of mild to moderate asthmatics (Chatham et al., 1982; Cockcroft et al., 1977). Atopic or allergic individuals without asthma (intermediate in responsiveness between healthy subjects and mild asthmatics) typically have a lower $PD_2$ than healthy individuals (Townley et al., 1975; Cockcroft et al., 1977). Increasing severity of asthma, as indicated by increasing symptoms or medication usage, is associated with decreasing $PD_2$. Mild asthmatics may have a $PD_2$ that is 10 times higher than that of moderate or severe asthmatics (Cockcroft et al., 1977). A low $PD_2$ in nonasthmatics also is associated with increased symptoms and a reduced baseline $FEV_1$ (Kennedy et al., 1990). The average changes in airway responsiveness induced by $O_3$ range from 150 to 500%. This means that, in a healthy subject exposed to $O_3$, a $PD_2$ of 20 units would decrease to a $PD_2$ between 13 and 4 units. Therefore, with a pronounced $O_3$-induced change in airway responsiveness, a healthy subject could move from the normal range into the upper half of the mild asthmatic range of airway responsiveness.

Increases in airway responsiveness are an important consequence of exposure to $O_3$. Results of studies reporting changes in airway responsiveness following $O_3$ exposure are summarized in Table 7-10. These studies vary with regard to exposure regimens, type and dose of bronchoconstrictive agent, and subject population. Increased airway responsiveness associated with $O_3$ exposure was first reported by Golden et al. (1978), who studied histamine-responsiveness in eight healthy men after exposure to 0.6 ppm $O_3$ for 2 h at rest and found that the histamine-induced $\Delta R_{aw}$ for the group was 300% greater 5 min after $O_3$ exposure than at baseline. Two of their subjects, however, had an increased response to histamine 1 week or greater after exposure, raising the possibility that high $O_3$ levels can result in more persistent increases in airway responsiveness. Later, Holtzman et al. (1979) found in 16 nonasthmatic subjects that a 10-breath methacholine or histamine challenge

## Arbitrary Logarithmic Scale

| 0.01 | 0.10 | 1.00 | 10.0 | 100 |

◄·················——————— asthma ————— ······················►

◄ - - ———— allergy only ———— - - ►

◄········——— healthy ———·······►

**Figure 7-6.   Airway function can be measured before and immediately after the inhalation of an aerosolized bronchoconstrictor drug like methacholine.  The provocative dose that produces a 20% drop in forced expiratory volume in 1 s has been used to express the range of nonspecific bronchial responsiveness.**

increased SRaw almost twice as much after $O_3$ as after air exposure, but this effect resolved after 24 h.  Atopic subjects showed similar increases in responsiveness to histamine after $O_3$ exposure.  The authors concluded that the increased nonspecific bronchial responsiveness after $O_3$ exposure was not related to atopy.  König et al. (1980) found increased responsiveness to inhaled acetylcholine after a 1-h exposure to 627 and 1,960 $\mu g/m^3$ (0.32 and 1.00 ppm, respectively).  Folinsbee and Hazucha (1989) found increased airway responsiveness in 18 females 1 and 18 h after a 70-min exposure to 0.35 ppm $O_3$ when compared to air.  Taken together, these studies suggest that $O_3$-induced increases in airway responsiveness usually resolve 18 to 24 h after exposure, but may persist in some individuals for longer periods.

Dimeo et al. (1981) were the first to investigate "adaptation" to the increases in airway responsiveness following $O_3$ exposure.  Over 3 days of a 2 h/day exposure to 0.40 ppm $O_3$, they found progressive attenuation of the increases in airway responsiveness such that, after the third day of $O_3$ exposure, histamine airway responsiveness was no longer different from the sham exposure levels.  Kulle et al. (1982) extended these findings by exposing two groups of healthy volunteers (n = 48) to 0.40 ppm $O_3$ for 3 h/day for 5 days in a row and found that there was a significantly enhanced response to methacholine after the first 3 days of exposure, but this response slowly normalized by the end of the fifth day.  Thus, the attenuation of $O_3$-induced increases in airway responsiveness followed the same time course as attenuation of other pulmonary function changes.

Gong et al. (1986) demonstrated increased airway responsiveness to histamine at 0.2 ppm $O_3$ in 17 vigorously exercising elite cyclists who were exposed for 1 h.  Folinsbee et al. (1988) found an approximate doubling of the mean methacholine responsiveness in a group of healthy volunteers exposed for 6.6 h to 0.12 ppm $O_3$.  However, on an individual basis, no relationship was found between $O_3$-induced changes in airway responsiveness and those in FVC and $FEV_1$, suggesting that changes in airway responsiveness and lung volume occurred by different mechanisms.  Horstman et al. (1990) extended Folinsbee's observations by demonstrating significant decreases in the $PD_1$   in 22 healthy subjects immediately after a

## Table 7-10. Increased Airway Responsiveness Following Ozone Exposures[a]

| Ozone Concentration[b] | | Exposure Duration and Activity | Exposure Conditions | Number and Gender of Subjects[c] | Subject Characteristics | Observed Effect(s) | Reference |
|---|---|---|---|---|---|---|---|
| ppm | μg/m | | | | | | |
| 0.08<br>0.10<br>0.12 | 157<br>196<br>235 | 6.6 h<br>IE at ̇39 L/min | 18 °C<br>40% RH | 22 M | Healthy NS, 18 to 32 years old | 33, 47, and 55% decreases in cumulative dose of methacholine required to produce a 100% increase in $SR_{aw}$ after exposure to $O_3$ at 0.08, 0.10, and 0.12 ppm, respectively. | Horstman et al. (1990) |
| 0.10<br>0.32<br>1.00 | 196<br>627<br>1,960 | 2 h | NA | 14 | Health NS, $24 \pm 2$ years old | Increased airway responsiveness to methacholine immediately after exposure at the two highest concentrations of $O_3$. | König et al. (1980) |
| 0.12<br>0.20 | 235<br>392 | 1 h at $\dot{V}_E$ = 89 L/min followed by 3 to 4 min at ̇150 L/min | 31 °C<br>35% RH | 15 M, 2 F | Elite cyclists, 19 to 30 years old | Greater than 20% increase in histamine responsiveness in one subject at 0.12 ppm $O_3$ and in nine subjects at 0.20 ppm $O_3$. | Gong et al. (1986) |
| 0.12 | 235 | 6.6 h with IE at ̇25 L/min/m² BSA | NA | 10 M | Healthy NS, 18 to 33 years old | Approximate doubling of mean methacholine responsiveness after exposure. On an individual basis, no relationship between $O_3$-induced changes in airway responsiveness and $FEV_1$ or FVC. | Folinsbee et al. (1988) |
| 0.12 ppm $O_3$-100 ppb $SO_2$<br>0.12 ppm $O_3$-0.12 ppm $O_3$<br>Air-100 ppb $SO_2$ | | 45 min in first atmosphere and 15 min in second IE | 75% RH<br>22 °C | 8 M, 5 F | Asthmatic, 12 to 18 years old | Greater declines in $FEV_1$ and $\dot{V}_{max50\%}$ and greater increase in respiratory resistance after $O_3$-$SO_2$ than after $O_3$-$O_3$ or air-$SO_2$. | Koenig et al. (1990) |
| Air-antigen<br>0.12 ppm $O_3$-antigen | | 1 h at rest | NA | 4 M, 3 F | Asthmatic, 21 to 64 years old | Increased bronchoconstrictor response to inhaled ragweed or grass after $O_3$ exposure compared to air. | Molfino et al. (1991) |
| 0.35 | 686 | 70 min with IE at 40 L/min | NA | 18 F | Healthy NS, 19 to 28 years old | $PD_{100}$ decreased from 59 CIU after air exposure to 41 CIU and 45 CIU, 1 and 18 h after $O_3$ exposure, respectively. | Folinsbee and Hazucha (1989) |

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**Table 7-10 (cont'd).  Increased Airway Responsiveness Following Ozone Exposures**[a]

| Ozone Concentration[b] | | Exposure Duration and Activity[a] | Exposure Conditions | Number and Gender of Subjects | Subject Characteristics[c] | Observed Effect(s) | Reference |
|---|---|---|---|---|---|---|---|
| ppm | $\Box$g/m | | | | | | |
| 0.20 | 392 | 2 h with IE at 2 × resting | 22 $\Box$C | 12 M, 7 F | Healthy NS, 21 to 32 years old | 110% increase in $\Box SR_{aw}$ to a 10-breath histamine (1.6%) aerosol challenge after exposure to $O_3$ at 0.40 ppm, but no change at 0.20 ppm.  Progressive adaptation of this effect over 3-day exposure. | Dimeo et al. (1981) |
| 0.40 | 784 | 2 h with IE at 2 × resting | 55% RH | | | | |
| 0.40 | 784 | 2 h/day for 3 days | | | | | |
| 0.40 | 784 | 3 h/day for 5 days in a row | | 13 M, 11 F | Healthy NS, 19 to 46 years old | Enhanced response to methacholine after first 3 days, but this response normalized by Day 5. | Kulle et al. (1982) |
| 0.40 | 784 | 2 h with IE at $\dot{V}_E$ = 53 to 55 L/min | 22 $\Box$C 50% RH | 8 M, 10 F | 9 asthmatics (5 F, 4 M), 9 healthy (5 F, 4 M), 18 to 34 years old | Decreased $PC_{100SR_{aw}}$ from 33 mg/mL to 8.5 mg/mL in healthy subjects after $O_3$.  $PC_{100SR_{aw}}$ fell from 0.52 mg/mL to 0.19 mg/mL in asthmatic subjects after exposure to $O_3$ and from 0.48 mg/mL to 0.27 mg/mL after exposure to air. | Kreit et al. (1989) |
| 0.60 | 1,176 | 2 h at rest | NA | 5 M, 3 F | Healthy NS, 22 to 30 years old | 300% increase in histamine-induced $\Box R_{aw}$ 5 min after $O_3$ exposure; 84 and 50% increases 24 h and 1 week after exposure (p > 0.05), respectively.  Two subjects had an increased response to histamine 1 week after exposure. | Golden et al. (1978) |
| 0.60 | 1,176 | 2 h with IE at 2 × resting | 22 $\Box$C 55% RH | 11 M, 5 F | 9 atopic, 7 nonatopic, NS, 21 to 35 years old | Ten-breath methacholine or histamine challenge increased $SR_{aw}$ $\Box$150% in 16 nonasthmatics after $O_3$.  On average, the atopic subjects had greater responses than the nonatopic subjects.  The increased responsiveness resolved after 24 h.  Atropine premedication blocked the $O_3$-induced increase in airway responsiveness. | Holtzman et al. (1979) |

[a]See Appendix A for abbreviations and acronyms.
[b]Listed from lowest to highest $O_3$ concentration.

6.6-h exposure to concentrations of $O_3$ as low as 0.08 ppm.  Because methacholine challenges were not conducted at later time points in any of these studies, the duration of the increased airway responsiveness after ambient-level $O_3$ exposure could not be determined.

No doubt exists that $O_3$, even at ambient concentrations, produces acute increases in airway responsiveness.  Whether $O_3$ exposure causes protracted increases in airway responsiveness in healthy individuals, induces asthma, or predisposes individuals to asthma is a more difficult question to answer (see Section 7.4.2).  However, the increases in airway responsiveness following $O_3$ exposure, even if short in duration, may have important clinical implications.  Several studies have been conducted specifically to determine the significance of acute increases in airway responsiveness after $O_3$ exposure.  These studies, designed to test the hypothesis that an $O_3$ exposure heightens the response to a subsequent bronchoconstrictor challenge, have exposed asthmatics to $O_3$ or air and, then, to a known bronchoconstrictor agent to compare the pulmonary function changes after $O_3$ to those after air.  Kreit et al. (1989) were first to investigate the change in airway responsiveness that occurs after $O_3$ exposure in individuals with asthma.  They exposed nine mild asthmatics (baseline $PC_{1\ SRaw} < 1.5$ mg/mL) for 2 h to 0.40 ppm $O_3$ with IE and found that the baseline $PC_{1\ SRaw}$ declined from 0.52 to 0.19 mg/mL after $O_3$ as compared to 0.48 to 0.27 mg/mL after air.  Koenig et al. (1990) demonstrated that a 45-min exposure to 0.12 ppm $O_3$ followed by a 15-min exposure to 100 ppb $SO_2$ caused greater changes in $FEV_1$, respiratory resistance, and $\dot{V}_{max5\ \%}$ in 14 adolescent asthmatics than did an air-$SO_2$ exposure combination.

Molfino et al. (1991) examined the effects of a 1-h resting exposure to 0.12 ppm $O_3$ on the response to a ragweed or grass allergen inhalation challenge.  Asthmatic subjects were exposed twice to air and twice to $O_3$, once per week over a period of 4 weeks.  Two allergen challenges were performed, once after air and once after $O_3$ exposure.  The other air and $O_3$ exposures were followed by a placebo challenge.  A ragweed allergen extract was used for six of the seven subjects.  The order of experiments was not randomized (in an effort to avoid unexpectedly severe reactions); six of the seven subjects were exposed to the ozone-allergen condition last and five of the seven were exposed to the air-placebo condition first.  Allergen responsiveness was expressed as the allergen concentration needed to cause a 15% reduction in $FEV_1$ or $PC_{15}$.  The $PC_{15}$ was lower after the $O_3$ exposure than after the air exposure (p = 0.04).  These observations suggest that allergen-specific airway responsiveness is increased after $O_3$ exposure.  Although it is expected that specific bronchial reactivity will be increased by $O_3$ exposure based on the marked increases in nonspecific bronchial responsiveness induced by $O_3$ exposure, such a response would not have been anticipated under these mild exposure conditions where lung function or symptomatic responses have not been observed.  The lack of randomization in this study makes it difficult to assess the validity of conclusions based on the statistical analysis.  These results are provocative but should be considered preliminary until this experiment can be repeated.

Ozone may be a clinically important co-factor in the response to airborne bronchoconstrictor substances in individuals with asthma.  It is plausible that this phenomenon could contribute to increased asthma exacerbations and, even, consequent increased hospital admissions (see Section 7.4.1).  Whether the increased airway responsiveness following $O_3$ exposure produces an accentuated bronchoconstrictor response to inhaled allergens or $SO_2$ in healthy individuals or those with lung diseases other than asthma is unknown.

Several studies have been undertaken to determine the mechanism of $O_3$-induced increases in airway responsiveness (also see Chapter 6).  Early experiments in dogs (Lee et al.,

1977) and humans (Golden et al., 1978) suggested an important role for vagal reflexes because vagal nerve cooling and atropine inhibited the increase in histamine-induced bronchoconstriction caused by $O_3$. Ozone exposure increased bronchomotor responses to cholinergic stimuli (e.g., acetylcholine and methacholine) in dogs (Holtzman et al., 1983) and humans (Seltzer et al., 1986). Subsequent studies, however, revealed that bilateral vagotomy did not inhibit $O_3$-induced hyperresponsiveness to subcutaneous histamine in guinea pigs (Gordon et al., 1984). These data provide strong evidence that $O_3$-induced increased airway responsiveness is mediated, at least in part, by cholinergic receptors on airway smooth muscle cells. Interestingly, Gordon et al. also noted that isometric tension in guinea pig tracheal smooth muscle and lung parenchymal strips in response to histamine and carbachol was not affected by exposure to $O_3$, suggesting that $O_3$ affected the in vivo milieu surrounding the smooth muscle rather than produced direct effects on the smooth muscle itself.

It can be hypothesized that the increased epithelial permeability caused by $O_3$ (see Chapter 6) may allow greater penetration of bronchoconstrictor substances, including methacholine and histamine, and that this would lead to increased airway responsiveness. However, Roum and Murlas (1984) suggested that the increased epithelial permeability after $O_3$ could not totally explain this phenomenon because parenteral cholinergic challenge after $O_3$ more reproducibly caused bronchospasm than did inhalation challenge with methacholine. The increased responsiveness to parenteral compared to inhaled cholinergic challenge may, however, have been due to increased bronchial blood flow after $O_3$ exposure. Therefore, the findings of Roum and Murlas do not exclude increased epithelial permeability as the cause of increased airway responsiveness after $O_3$ exposure.

Holtzman et al. (1983) first pointed out that $O_3$-induced acute inflammation may be important in the induction of the increased airway responsiveness. In mongrel dogs exposed to $O_3$, they found bronchial wall PMN infiltration in those animals that developed increased airway responsiveness to acetylcholine, but not in animals that failed to develop increased airway responsiveness. O'Byrne et al. (1984) later demonstrated that hydroxyurea simultaneously decreased peripheral blood leukocyte counts, decreased PMN influx into bronchial tissue, and prevented increased airway responsiveness in dogs exposed to $O_3$. Both $O_3$-induced increased airway responsiveness and bronchial tissue PMN influx returned 6 weeks after treatment was discontinued when peripheral leukocyte counts had normalized. Seltzer et al. (1986) found a larger percentage of PMNs (30.8% versus 8.0%) in BAL fluid after $O_3$ exposure in their subjects that had a greater than threefold decrease in the provocative concentration, which caused a □8 L × cm $H_2O$/L/s increase in $SR_{aw}$ for methacholine, compared to those subjects that had less than a twofold decrease. These data suggest a possible association between inflammation and increased airway responsiveness after $O_3$ exposure.

An early study in dogs (O'Byrne et al., 1984) suggested that oxygenation products of arachidonic acid that are sensitive to inhibition by the anti-inflammatory drug indomethacin play a role in $O_3$-induced hyperresponsiveness without affecting the influx of PMNs. In the first of several human studies with a PG inhibitor, indomethacin did not attenuate the increase in airway responsiveness in subjects exposed to 0.4 ppm $O_3$ for 2 h (Ying et al., 1990), but did ameliorate the effect of $O_3$ on spirometric endpoints. Kleeberger and Hudak (1992) observed a marked reduction in PMN influx in $O_3$-exposed mice given indomethacin without any change in $O_3$-induced increases in permeability, as indicated by BAL protein. However, Hazucha et al. (1996) found no effect of ibuprofen on PMN levels or protein in the BAL fluid of $O_3$-exposed humans (also see Section 7.2.4.5). Seltzer et al. (1986) and Koren et al. (1989a,b)

found that $O_3$ increases a large number of BAL inflammatory mediators (including $PGE_2$, $PGF_{2\alpha}$, and thromboxane $B_2$ [$TXB_2$]), one or more of which may play a role in the increase in airway responsiveness after $O_3$ exposure.

The role of reactive oxygen metabolites or neuropeptide mediators in the increase in airway responsiveness after $O_3$ has not been investigated. Furthermore, there has been no direct assessment of alterations in nerve afferents, changes in neurotransmitter concentrations, changes in smooth muscle postsynaptic receptors, or modulation of nerve signal transmission by inflammatory mediators as these pertain to the increase in airway responsiveness after $O_3$. In conclusion, although the mechanism of $O_3$-induced increases in airway responsiveness is not completely understood, it appears to be associated with a number of cellular or biochemical changes in the airway (see Section 7.2.4 and Tables 7-11 and 7-12). Because these alterations are part of a complex process, it comes as no surprise that the mechanistic studies on $O_3$-induced increases in airway responsiveness have not pinpointed an isolated derangement.

## 7.2.4 Inflammation and Host Defense
### 7.2.4.1 Introduction

In general, inflammation can be considered as the host response to injury, and the induction of inflammation can be accepted as evidence that injury has occurred. Several outcomes are possible: (1) inflammation can resolve entirely; (2) continued acute inflammation can evolve into a chronic inflammatory state; (3) continued inflammation can alter the structure or function of other pulmonary tissue, leading to diseases such as fibrosis or emphysema; (4) inflammation can alter the body's host defense response to inhaled microorganisms, particularly in potentially vulnerable populations such as the very young and old; and (5) inflammation can alter the lung's response to other agents such as allergens or toxins. It is also possible that the profile of response can be altered in persons with preexisting pulmonary disease (e.g., asthma or COPD) or smokers. At present, it is known that short-term exposure of humans to $O_3$ can cause acute inflammation and that long-term exposure of laboratory animals results in a chronic inflammatory state (see Chapter 6). However, the relationship between repetitive bouts of acute inflammation in humans caused by $O_3$ and the development of chronic respiratory disease is unknown.

The previous $O_3$ criteria document (U.S. Environmental Protection Agency, 1986) contained no studies in which inflammation was measured in humans exposed to $O_3$. Fiberoptic bronchoscopy since has been used to sample cells and fluids lining the respiratory tract of humans for many markers (Reynolds, 1987). Bronchoalveolar lavage primarily samples the alveolar region of the lung; however, the use of small volume lavages (Rennard et al., 1990) or balloon catheters also allows sampling of the airways. Nasal lavage allows sampling of cells and fluid removed from the nasal passages.

In the past 6 years, several studies have analyzed BAL and NL cells and fluid from humans exposed to $O_3$ for markers of inflammation and lung damage (see Tables 7-11 and 7-12). The presence of PMNs in the lung has long been accepted as a hallmark of inflammation and has been taken as the major indicator that $O_3$ causes inflammation in the

## Table 7-11. Bronchoalveolar Lavage Studies of Inflammatory Effects from Controlled Human Exposure to Ozone[a]

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| Ozone Concentration[b] | | Exposure Duration | Activity Level ($\dot{V}_E$) | Number and Gender of Subjects | Observed Effect(s) | Reference |
|---|---|---|---|---|---|---|
| ppm | μg/m$^3$ | | | | | |
| 0.08 0.10 | 157 196 | 6.6 h | IE (40 L/min) six 50-min exercise periods + 10 min rest; 35 min lunch | 18 M, 18 to 35 years old | BAL fluid 18 h after exposure to 0.1 ppm $O_3$ had significant increases in PMNs, protein, PGE$_2$, fibronectin, IL-6, lactate dehydrogenase, and α-1 antitrypsin compared with the same subjects exposed to FA. Similar but smaller increases in all mediators after exposure to 0.08 ppm $O_3$ except for protein and fibronectin. Decreased phagocytosis of yeast by alveolar macrophages was noted at both concentrations. | Devlin et al. (1990, 1991) Koren et al. (1991) |
| 0.20 | 392 | 4 h | IE (50 min at 40 L/min, 10 min rest) | 15 M, 13 F, 21 to 39 years old | Bronchial lavage, bronchial biopsies, and BAL done 18 h after exposure. BAL shows changes similar to other studies. Airway lavage shows increased cells, LDH, IL-8. Biopsies show increased number of PMNs. | Aris et al. (1993a) |
| 0.30 | 588 | 1 h (mouth-piece) | CE (60 L/min) | 5 M | Significantly elevated PMNs in the BAL fluid 1, 6, and 24 h after exposure, with peak increases at 6 h. | Schelegle et al. (1991) |
| 0.40 | 784 | 2 h | IE (70 L/min) at 15-min intervals | 11 M, 18 to 35 years old | BAL fluid 18 h after exposure had significant increases in PMNs, protein, albumin, IgG, PGE$_2$, plasminogen activator, elastase, complement C3a, and fibronectin. | Koren et al. (1989a,b) |
| 0.40 | 784 | 2 h | IE (70 L/min) at 15-min intervals | 11 M, 18 to 35 years old | Macrophages removed 18 h after exposure had changes in the rate of synthesis of 123 different proteins as assayed by computerized densitometry of two-dimensional gel protein profiles. | Devlin and Koren (1990) |
| 0.40 | 784 | 2 h | IE (70 L/min) at 15-min intervals | 11 M, 18 to 35 years old | BAL fluid 18 h after exposure contained increased levels of the coagulation factors, tissue factor, and factor VII. Macrophages in the BAL fluid had elevated tissue factor mRNA. | McGee et al. (1990) |
| 0.40 | 784 | 2 h | IE (70 L/min) at 15-min intervals | 10 M, 18 to 35 years old | BAL fluid 1 h after exposure to 0.4 ppm $O_3$ had significant increases in PMNs, protein, PGE$_2$, TXB$_2$, IL-6, LDH, α-1 antitrypsin, and tissue factor compared with the same subjects exposed to FA. Decreased phagocytosis of yeast by alveolar macrophages. | Koren et al. (1991) |

**Table 7-11 (cont'd).  Bronchoalveolar Lavage Studies of Inflammatory Effects from Controlled Human Exposure to Ozone[a]**

| Ozone Concentration[b] | | Exposure Duration | Activity Level ($\dot{V}_E$) | Number and Gender of Subjects | Observed Effect(s)[3] | Reference |
|---|---|---|---|---|---|---|
| ppm | $\mu$g/m | | | | | |
| 0.40 | 784 | 2 h/day for 5 days, 2 h either 10 or 20 days later | IE (40 L/min) at 15-min intervals | 16 M, 18 to 35 years old | BAL done immediately after fifth day of exposure and again after exposure 10 or 20 days later.  Most markers of inflammation (PMNs, IL-6, IL-8, protein, $\alpha$1-antitrypsin, $PGE_2$, fibronectin) showed complete attenuation; markers of damage (LDH, elastase) did not.  Reversal of attenuation was not complete for some markers, even after 20 days. | Devlin et al. (1995) |
| 0.40 | 784 | 2 h | IE (60 L/min) at 15-min intervals | 10 M | Subjects given 800 mg ibuprofen or placebo 90 min before exposure.  Subjects given ibuprofen had less of a decrease in $FEV_1$ after $O_3$ exposure.  BAL fluid 1 h after exposure contained similar levels of PMNs, protein, fibronectin, LDH, $\alpha$-1 antitrypsin, $LTB_4$, and C3a in both ibuprofen and placebo groups.  However, subjects given ibuprofen had decreased levels of IL-6, $TXB_2$, and $PGE_2$. | Hazucha et al. (1996) |
| 0.40 0.60 | 784 1,176 | 2 h | IE (83 W for women, 100 W for men) at 15-min intervals | 7 M, 3 F, 23 to 41 years old | BAL fluid 3 h after exposure had significant increases in PMNs, $PGE_2$, $TXB_2$, and $PGF_{2\alpha}$ at both $O_3$ concentrations. | Seltzer et al. (1986) |

[a]See Appendix A for abbreviations and acronyms.
[b]Listed from lowest to highest $O_3$ concentration.

**Table 7-12. Additional Studies of Inflammatory and Host Defense Effects
from Controlled Human Exposure to Ozone[a]**

| Ozone Concentration[b] | | Exposure Duration | Activity Level ($\dot{V}_E$) | Number and Gender of Subjects | Observed Effect(s) | Reference |
|---|---|---|---|---|---|---|
| ppm | ☐g/m^{3} | | | | | |
| *Nasal Lavage Studies* | | | | | | |
| 0.12 0.24 | 235 470 | 90 min | IE (20 L/min) at 15-min intervals | 5M, 5F, asthmatic; 4M, 4F, nonasthmatic; 18 to 41 years old | NL done immediately and 24 h after exposure. Increased number of PMNs at both times in asthmatic subjects exposed to 0.24 ppm $O_3$; no change in nonasthmatic subjects. No change in lung or nasal function. | McBride et al. (1994) |
| 0.30 | 588 | 6 h/day for 5 consecutive days | IE (light treadmill) | 24 M (12 $O_3$, 12 air) | Subjects inoculated with type 39 rhinovirus prior to exposure. NL was performed on the morning of Days 1 to 5, 8, 15, and 30. No difference in virus titers in NL fluid of air and $O_3$-exposed subjects at any time tested. No difference in PMNs or interferon gamma in NL fluid, or in blood lymphocyte proliferative response to viral antigen. | Henderson et al. (1988) |
| 0.40 | 784 | 2 h | IE (70 L/min) at 15-min intervals | 11 M, 18 to 35 years old | NL done immediately before, immediately after, and 22 h after exposure. Increased numbers of PMNs at both times after exposure; increased levels of tryptase, a marker of mast cell degranulation, immediately after exposure; increased levels of albumin 22 h after exposure. | Graham and Koren (1990) Koren et al. (1990) |
| 0.50 | 980 | 4 h on 2 consecutive days | Resting | 41 M (21 $O_3$, 20 air-exposed), 18 to 35 years old | NL done immediately before and after each exposure and 22 h after the second exposure. Increased levels of PMNs at all times after the first exposure, with peak values occurring immediately prior to the second exposure. | Graham et al. (1988) |
| 0.50 | 980 | 4 h | Resting | 6 M, 6 F, allergic rhinitics, 31.4 ± 2.0 (SD) years old | NL done immediately after exposure. Increased upper and lower respiratory symptoms and increased levels of PMNs, eosinophils, and albumin in NL fluid. | Bascom et al. (1990) |

**Table 7-12 (cont'd).  Additional Studies of Inflammatory and Host Defense Effects from Controlled Human Exposure to Ozone[a]**

| Ozone Concentration[b] | | Exposure Duration | Activity Level ($\dot{V}_E$) | Number and Gender of Subjects | Observed Effect(s) | Reference |
|---|---|---|---|---|---|---|
| ppm | $\mu$g/m^{3} | | | | | |
| *Clearance Studies* | | | | | | |
| 0.20 0.40 | 392 784 | 2 h | IE (light treadmill) | 7 M, 27.2 $\pm$ 6.0 (SD) years old | Subjects inhaled radiolabeled iron oxide particles immediately before exposure. Concentration-dependent increase in rate of particle clearance 2 h after exposure, although clearance was confined primarily to the peripheral airways at the lower $O_3$ concentration. | Foster et al. (1987) |
| 0.40 | 784 | 1 h | CE (40 L/min) | 15 M or F, 18 to 35 years old | Subjects inhaled radiolabeled iron oxide particles 2 h after exposure. No $O_3$-induced difference in clearance of particles during the next 3 h or the following morning. | Gerrity et al. (1993) |
| 0.40 | 784 | 2 h | IE (70 L/min) at 15-min intervals | 8 M, 20 to 30 years old | Subjects inhaled $^{99m}$Tc-DTPA 75 min after exposure.  Significantly increased clearance of $^{99m}$Tc-DTPA from the lung in $O_3$-exposed subjects.  Subjects had expected changes in FVC and $SR_{aw}$. | Kehrl et al. (1987) |
| 0.50 | 784 | 2.25 h | IE (70 L/min) at 15-min intervals | 16 M, 20 to 30 years old | Similar design and results as earlier study (Kehrl et al., 1987).  For the combined studies the average rate of clearance was 60% faster in $O_3$-exposed subjects. | Kehrl et al. (1989) |
| *In Vitro Studies* | | | | | | |
| 0.25 0.50 | 490 980 | 6 h | Human nasal epithelial cells | | Increased in ICAM-1, IL-6, IL-1, and TNF expression at 0.5 ppm. No increase in IL-8 expression.  No increases at 0.25 ppm. | Beck et al. (1994) |
| 0.25 0.50 1.00 | 490 980 1,960 | 1 h | Airway epithelial cell line | | Concentration-dependent increased secretion of $PGE_2$, $TXB_2$, $PGF_{2\alpha}$, $LTB_4$, and $LTD_4$.  More secretion basolaterally than apically. | McKinnon et al. (1993) |
| 0.25 0.50 1.00 | 490 980 1,960 | 1 h | Airway epithelial cell line and alveolar macrophages | | Increased secretion of IL-6, IL-8, and fibronectin by epithelial cells, even at lowest $O_3$ concentration.  No $O_3$-induced secretion of these compounds by macrophages. | Devlin et al. (1994) |

**Table 7-12 (cont'd).  Additional Studies of Inflammatory and Host Defense Effects
from Controlled Human Exposure to Ozone[a]**

| Ozone Concentration[b] | | Exposure Duration | Activity Level ($\dot{V}_E$) | Number and Gender of Subjects | Observed Effect(s) | Reference |
|---|---|---|---|---|---|---|
| ppm | $\mu$g/m$^3$ | | | | | |
| *In Vitro Studies (cont'd)* | | | | | | |
| 0.30 | 588 | 1 h | Alveolar macrophages | | Concentration-dependent  increases in PGE$_2$ production, and decreases in phagocytosis of sheep erythrocytes. No O$_3$-induced secretion of IL-1, TNF, or IL-6. | Becker et al. (1991) |
| 1.00 | 1,960 | | | | | |

[a]See Appendix A for abbreviations and acronyms.
[b]Listed from lowest to highest O$_3$ concentration.

lungs of humans.  Soluble mediators of inflammation (or its resolution) such as cytokines and arachidonic acid metabolites also have been measured in the BAL fluid of humans exposed to $O_3$.  Cytokines that have been reported most often are interleukin (IL)-6 and IL-8, although IL-1 and tumor necrosis factor (TNF) also have been studied.  Soluble metabolites of arachidonic acid involved in inflammation and host defense (e.g., $PGE_2$ and $PGF_{2\alpha}$, thromboxane, and leukotrienes [LTs] such as $LTB_4$) also have been reported in the BAL fluid of humans exposed to $O_3$.  In addition to their role in inflammation, many of these compounds have bronchoconstrictive properties and may be involved in increased airway hyperreactivity observed following $O_3$ exposure.

Under normal circumstances, the epithelia lining the large and small airways develop tight junctions and restrict the penetration of exogenous particles and macromolecules from the airway lumen into the interstitium and blood, as well as restrict the flow of plasma components into the airway lumen.  However, several studies (see Table 7-12) show that $O_3$ disrupts the integrity of the epithelial cell barrier in human airways, as measured by increased passage of radiolabeled compounds out of the airways, as well as passage of markers of plasma influx such as albumin, immunoglobulin, and other proteins into the airways.  In addition, markers of epithelial cell damage such as lactate dehydrogenase (LDH) activity also have been measured in the BAL fluid of humans exposed to $O_3$.

Inflammatory cells of the lung such as alveolar macrophages (AMs), monocytes, and PMNs also constitute an important component of the pulmonary host defense system.  In their unstimulated state, they present no danger to surrounding pulmonary cells and tissues, but upon activation, they are capable of generating free radicals and enzymes with microbicidal capabilities, but they also have the potential to damage nearby cells.  Animal studies have demonstrated that $O_3$ decreases host defense system function (see Chapter 6, Section 6.2.3).

Other soluble factors that have been studied include those involved with fibrin deposition and degradation (Tissue Factor, Factor VII, and plasminogen activator), potential markers of fibrogenesis (fibronectin, platelet derived growth factor), and components of the complement cascade (C3a).

## 7.2.4.2  Inflammation Assessed by Bronchoalveolar Lavage

Seltzer et al. (1986) were the first to demonstrate that exposure of humans to $O_3$ resulted in inflammation in the lung.  In this study, 10 volunteers were exposed to 0.4 or 0.6 ppm $O_3$ for 2 h while undergoing exercise, and BAL was performed 3 h later.  Bronchoalveolar lavage fluid from subjects exposed to $O_3$ contained 7.8-fold more PMNs compared with BAL fluid from the same subjects exposed to FA.  Additionally, BAL fluid from $O_3$-exposed subjects contained increased levels of $PGE_2$, $PGF_{2\alpha}$, and $TXB_2$ compared to fluid from air-exposed subjects.  Koren et al. (1989a,b) also described inflammatory changes in the lungs of 11 subjects exposed to 0.4 ppm $O_3$ for 2 h while undergoing IE at 70 L/min in a study designed to simulate adults working outdoors or children actively playing.  Bronchoalveolar lavage was performed 18 h after $O_3$ exposure.  Subjects exposed to $O_3$ had an eightfold increase in PMNs in the BAL fluid, confirming the observations of Seltzer et al.  In addition, Koren et al. reported a twofold increase in BAL fluid protein, albumin, and immunoglobulin G (IgG) levels, suggestive of increased epithelial cell permeability as a result of $O_3$ exposure.  There was also a 12-fold increase in IL-6 levels in the BAL fluid.  Interleukin-1 and TNF were not present in detectable levels in the BAL fluid of any subject.  There was, however, a twofold increase in the proinflammatory eicosanoid $PGE_2$, as well as a

twofold increase in the complement component C3a. This study also provided evidence for stimulation of fibrogenic processes in the lung by demonstrating significant increases in two components of the coagulation pathway, Tissue Factor and Factor VII (McGee et al., 1990), as well as urokinase plasminogen activator and fibronectin (Koren et al., 1989a). Taken together, these two studies demonstrate that exposure of humans to moderate levels of $O_3$ results in an inflammatory reaction in the lung, as evidenced by substantial increases in PMNs and proinflammatory compounds. Furthermore, these studies demonstrate that both cells and mediators capable of damaging pulmonary tissue are increased after $O_3$ exposure, as are compounds that play a role in fibrotic and fibrinolytic processes.

Although animal studies have shown that the terminal bronchioles are a major site of $O_3$-induced inflammation, few human studies have confirmed this finding because BAL primarily samples cells and fluid in the terminal bronchioles and alveoli. However, isolated lavage of the mainstream bronchus using balloon catheters or the more traditional BAL using small volumes of saline have the ability to preferentially measure $O_3$-induced changes in the large airways. In one study, isolated airway lavage was performed on 14 subjects 18 h after exposure to 0.2 ppm $O_3$ while undergoing moderate exercise (Aris et al., 1993a). Increases in total lavagable cells, LDH activity, and IL-8 were reported. In contrast, Schelegle et al. (1991), observed no increase in PMNs in the bronchial fluid; however, bronchial biopsies showed increased numbers of PMNs in airway tissue.

The data suggestive of $O_3$-induced changes in epithelial cell permeability described by Koren et al. (1989a, 1991) and Devlin et al. (1991) support earlier work in which epithelial cell permeability, as measured by increased clearance of radiolabled diethylene triamine pentaacetic acid ($^{99m}$Tc-DTPA) from the lungs of humans exposed to $O_3$, was demonstrated (Kehrl et al., 1987). In that study, eight healthy subjects who inhaled $^{99m}$Tc-DTPA just prior to exposure to air or 0.4 ppm $O_3$ for 2 h while undergoing heavy exercise (65 L/min) had increased clearance of the compound. Kehrl et al. (1989) reported similar observations on an additional 16 subjects. For the combined group of 24 subjects exposed for 2 h to 0.4 ppm $O_3$, the average clearance rate was 60% faster than that observed after air exposure, strongly suggesting increased permeability from the airway lumen and alveolar space to the blood and interstitial spaces. The average $O_3$-induced decrement in FVC in these subjects was 10%. These changes in permeability most likely are associated with acute inflammation and potentially could allow better access of inhaled antigens and other substances to the submucosa.

Studies in which human AM and airway epithelial cells were exposed to $O_3$ in vitro suggest that most of the components found in increased levels in the BAL fluid of $O_3$-exposed humans are produced by epithelial cells. Macrophages exposed to 0.3 and 1.0 ppm (but not 0.1 ppm) $O_3$ for 1 h showed small increases in $PGE_2$, but no change in superoxide anion or cytokine production (Becker et al., 1991). In contrast, airway epithelial cells exposed in vitro to 0.1, 0.25, 0.5, and 1.0 ppm $O_3$ for 1 h showed large concentration-dependent increases in $PGE_2$, $TXB_2$, $LTB_4$, $LTC_4$, and $LTD_4$ (McKinnon et al., 1993). These cells also showed increases in IL-6, IL-8, and fibronectin at $O_3$ concentrations as low as 0.1 ppm (Devlin et al., 1994). Interestingly, macrophages removed 18 h later from subjects exposed to 0.4 ppm $O_3$ for 2 h while undergoing intermittent heavy exercise (Koren et al., 1989a) showed changes in the rate of synthesis of 123 different proteins as measured by quantitative computerized densitometry of two-dimensional gel protein profiles. However, AMs exposed to $O_3$ in vitro showed changes only in the rate of synthesis of six proteins, suggesting that most of the

changes seen in the in vivo-exposed AMs were due to actions resulting from mediators released by other cells following $O_3$ exposure, which then altered macrophage function.

Numerous studies have shown that humans exposed to $O_3$ for 5 consecutive days experience decrements in pulmonary function on the first and second days, but the decrements diminish with each succeeding day so that by the fifth day, no such effects are observed (see Section 7.2.1). However, these studies did not address the question of whether repeated exposure to $O_3$ also resulted in attenuation of inflammation or lung damage. Animal studies suggest that although some markers of inflammation may be diminished, underlying damage to lung epithelial cells continues (Tepper et al., 1989). In a recent study (Devlin et al., 1995), humans were exposed to 0.4 ppm $O_3$ for 5 consecutive days (2 h/day while undergoing IE) and then were exposed to $O_3$ a single time either 10 or 20 days later. The results show that numerous indicators of inflammation (e.g., PMN influx, IL-6, IL-8, $PGE_2$, BAL protein, fibronectin, macrophage phagocytosis) show attenuation (i.e., there is a complete disappearance of response, and values are no different from those observed in the same individual after 5 days of exposure to FA). Ten days later, some of these markers regained full susceptibility, but others did not regain susceptibility even after 20 days. In agreement with animal studies, some markers (LDH, elastase) never show attenuation, indicating that tissue damage may continue to occur during repeated exposure.

### 7.2.4.3  Inflammation Induced by Ambient Levels of Ozone

Devlin et al. (1991) reported an inflammatory response in humans exposed to levels of $O_3$ at or below 0.12 ppm. In this study, 10 volunteers were exposed to 0.08 and 0.10 ppm $O_3$ for 6.6 h while undergoing moderate exercise (40 L/min) and underwent BAL 18 h later. An additional eight subjects were exposed to 0.08 ppm $O_3$. Increased numbers of PMNs and levels of IL-6 were found at both $O_3$ concentrations. There also were increases in most of the other compounds reported by Koren et al. (1989a,b), including fibronectin and $PGE_2$. Alveolar macrophage phagocytic capability was also monitored in this study, and it was reported that macrophages removed from humans exposed to both $O_3$ concentrations had decreased ability to phagocytize *Candida albicans* opsonized with complement. Comparison of the magnitude of inflammatory changes observed in this study and by Koren et al. (1989a,b), when normalized for differences in concentration, duration of exposure, and ventilation, suggest that lung inflammation from $O_3$ may occur as a consequence of exposure to ambient levels while exercising. Although the mean changes in IL-6, $PGE_2$, and PMNs reported by Devlin et al. (1991) were small, there was a considerable range of response among the individuals participating in the study. Thus, although some of the study population showed little or no response to $O_3$, others had increases in IL-6 or PMNs that were as large as or larger than those reported by Koren et al. (1989a,b) when subjects were exposed for 2 h to 0.4 ppm $O_3$. Interestingly, those individuals who had the largest increases in inflammatory mediators in this study did not necessarily have the largest decrements in pulmonary function, suggesting separate mechanisms underlying these two responses to $O_3$. These data suggest that, although the population as a whole may have a small inflammatory response to low levels of $O_3$, there may be a significant subpopulation that is very sensitive to these low levels of $O_3$. Furthermore, even a small inflammatory response (if it recurs) in the population as a whole should not be discounted.

### 7.2.4.4  Time Course of Inflammatory Response

The time course of the inflammatory response to $O_3$ in humans has not been explored fully. Studies in which BAL was performed 1 h (Devlin et al., 1990; Koren et al., 1991) or 3 h (Seltzer et al., 1986) after exposure to 0.4 ppm $O_3$ demonstrate that the inflammatory response is quickly initiated, and other data (Koren et al., 1989a,b) indicate that, even 18 h after exposure, inflammatory mediators such as IL-6 and PMNs are still substantially elevated. However, a comparison of these studies shows there are differences in the magnitude of response of some indicators, depending on when BAL is performed after $O_3$ exposure. Ozone-induced increases in PMNs, IL-6, and $PGE_2$ are greater 1 h after $O_3$ exposure, whereas BAL levels of fibronectin and plasminogen activator are greater 18 h after exposure. Still other compounds (protein, Tissue Factor) are equally elevated both 1 and 18 h after $O_3$ exposure. Schelegle et al. (1991) exposed five subjects to FA or 0.3 ppm $O_3$ for 1 h with a ventilation of 60 L/min. Each subject was exposed to $O_3$ on three separate occasions, and BAL was performed 1, 6, or 24 h after exposure. In addition, BAL was separated into two fractions: the first 60 mL wash was designated the "proximal airways" fraction (PA), and the remaining three 60 mL washes were pooled and designated the "distal airways and alveolar surface" fraction (DAAS). The percent of PMNs in the PA sample was statistically elevated at 1, 6, and 24 h after $O_3$ exposure, with a peak response at 6 h. The percent of PMNs in the DAAS sample was elevated at only the 6 and 24 h time points, with equivalent elevations at each time.

### 7.2.4.5 Effect of Anti-Inflammatory Agents on Ozone-Induced Inflammation

Previous studies (Schelegle et al., 1987; Eschenbacher et al., 1989) have shown that indomethacin, an anti-inflammatory agent that inhibits the production of cyclooxygenase products of arachidonic acid metabolism, is capable of blunting the well-documented decrements in pulmonary function observed in humans exposed to $O_3$. In a recent study, 10 healthy male volunteers were given 800 mg ibuprofen, another anti-inflammatory agent that blocks cyclooxygenase metabolism, or a placebo 90 min prior to a 2-h exposure to 0.4 ppm $O_3$. An additional 200 mg was administered following the first hour of exposure. Bronchoalveolar lavage was performed 1 h after the exposure. As expected, subjects given ibuprofen had blunted decrements in lung function following $O_3$ exposure compared to the same subjects given a placebo (Hazucha et al., 1996). Bronchoalveolar lavage fluid from subjects given ibuprofen also had reduced levels of the cyclooxygenase product $PGE_2$ as well as IL-6, but no decreases were observed in PMNs, fibronectin, permeability, LDH activity, or macrophage phagocytic function (Hazucha et al., 1995). These data suggest that although anti-inflammatory agents may blunt $O_3$-induced decrements in $FEV_1$ and increases in $PGE_2$, most inflammatory mediators are elevated in the BAL of these subjects.

### 7.2.4.6 Use of Nasal Lavage To Assess Ozone-Induced Inflammation in the Upper Respiratory Tract

Bronchoalveolar lavage has proven to be a powerful research tool to analyze changes in the lung following exposure of humans to xenobiotics. However, because BAL is expensive, somewhat invasive, and requires specialized personnel and facilities, it usually is done only with small numbers of subjects and in selected medical centers. Therefore, there is increasing interest in the use of NL as a tool in assessing $O_3$-induced inflammation in the upper respiratory tract, which is the primary portal for inspired air, and therefore the first region of the respiratory tract to come in contact with airborne xenobiotics. Nasal lavage is simple and

rapid to perform, is noninvasive, and allows collection of multiple sequential samples from the same person.  Graham et al. (1988) reported increased levels of PMNs in the NL fluid of 21 humans exposed to 0.5 ppm $O_3$ at rest for 4 h on 2 consecutive days, with NL performed immediately before and immediately after each exposure as well as 22 h after the second exposure.  Nasal lavage fluid contained elevated numbers of PMNs at all postexposure times tested, with peak values occurring immediately prior to the second day of exposure.  There were no changes in PMN numbers at any time in 20 subjects exposed to clean air for 2 consecutive days.  Bascom et al. (1990) exposed 12 subjects with allergic rhinitis to 0.5 ppm $O_3$ at rest for 4 h, followed immediately by NL.  They reported a sevenfold increase in PMNs, a 20-fold increase in eosinophils, and a 10-fold increase in mononuclear cells following $O_3$ exposure, as well as a 2.5-fold increase in albumin.  Graham and Koren (1990) compared inflammatory mediators present in both the NL and BAL fluids of humans exposed to $O_3$.  The same 11 subjects who were exposed to 0.4 ppm $O_3$ for 2 h with BAL performed 18 h later, as described earlier (Koren et al., 1989a,b), also underwent NL immediately before, immediately after, and 18 h after each exposure (Graham and Koren, 1990).  There were significant increases in PMNs in the NL fluid taken both immediately after exposure and on the next day.  Increases in NL and BAL PMNs were similar (6.6- and eightfold, respectively), demonstrating a qualitative correlation between changes in the lower airways as assessed by BAL and the upper respiratory tract as assessed by NL.  Furthermore, all individuals who had increased PMNs in BAL fluid also had increased PMNs in NL fluid, although the NL PMN increase could not quantitatively predict the BAL PMN increase.  Albumin, a marker of epithelial cell permeability, was increased 18 h later, but not immediately after exposure.  There were no changes in $PGE_2$, plasminogen activator, $LTC_4$, $LTD_4$, or $LTE_4$ (Graham and Koren, 1990).  However, tryptase, a constituent of mast cells contained in the same granules as histamine, was found in elevated levels immediately after $O_3$ exposure, but not 18 h later (Koren et al., 1990).  McBride et al. (1994) reported that asthmatic subjects are more sensitive to upper airway inflammation at $O_3$ concentrations that do not affect lung function.  Nasal lavage and lung and nasal function were compared in 10 asthmatic and 8 nonasthmatic subjects exposed in a head dome to 0.12 and 0.24 ppm $O_3$ for 90 min during intermittent moderate exercise ($\dot{V}_E = 20$ L/min).  A significant increase in the number of PMNs in NL fluid was detected in the asthmatic subjects both immediately and 24 h after exposure to 0.24 ppm $O_3$.  Total white blood count, a surrogate for PMN influx, was signficantly correlated with IL-8 in the NL fluid.  No significant cellular changes were seen in nonasthmatic subjects, and no changes in lung or nasal function or biochemical mediators were found in either asthmatic or nonasthmatic subjects.  These studies suggest that NL may serve as a sensitive and reliable tool to detect inflammation in the upper airways of humans exposed to xenobiotics.

### 7.2.4.7  Changes in Host Defense Capability Following Ozone Exposure

Concern about the effect of $O_3$ on human host defense capability derives from numerous animal studies demonstrating that acute exposure to as little as 0.08 ppm $O_3$ causes decrements in antibacterial host defenses and little, if any, effect on the course of acute viral infection (see Chapter 6, Section 6.2.3).  A study of experimental rhinovirus infection in susceptible human volunteers failed to show any effect of 5 consecutive days of $O_3$ exposure on the clinical evolution or host response to a viral challenge (Henderson et al., 1988).  In this study, 24 young males were inoculated with type 39 rhinovirus (1,000 TCID-50) administered as nose drops.  Half were then exposed to 0.3 ppm $O_3$ (6 h/day) for 5 consecutive days while

undergoing intermittent light exercise, and half were exposed to clean air under the same regimen. There was no difference in rhinovirus titers in nasal secretions between the $O_3$-exposed and control groups, nor were there any differences in levels of interferon gamma or PMNs in NL fluid or in blood lymphocyte proliferative response to rhinovirus antigen. However, recent findings that rhinovirus can attach to the intracellular adhesion molecule (ICAM) receptor on respiratory tract epithelial cells (Greve et al., 1989) and that $O_3$ can up-regulate the ICAM receptor on nasal epithelial cells (Beck et al., 1994) suggest that more studies are needed to explore more fully the potential interaction between $O_3$ exposure and viral infectivity.

In a single study, human AM host defense capacity was measured in vitro in AMs removed from subjects exposed to 0.08 and 0.10 ppm $O_3$ for 6.6 h while undergoing moderate exercise. Alveolar macrophages from $O_3$-exposed subjects had significant decrements in complement-receptor-(but not antigen-antibody [Fc]-receptor)-mediated phagocytosis of *Candida albicans* (Devlin et al., 1991). These data show that acute in vivo exposure of humans to $O_3$ results in impairment of AM host defense capability, potentially resulting in decreased ability to phagocytose and kill inhaled microorganisms in vivo. Human AMs also have been exposed to $O_3$ in vitro to investigate whether changes in macrophage host defense functions are due to a direct effect of $O_3$ on AMs or secondary effects resulting from lung injury and inflammation. Becker et al. (1991) exposed AMs to 0.1 to 1.0 ppm $O_3$ in vitro for 1 h and showed a concentration-dependent decrease in phagocytosis of antibody-coated sheep erythrocytes; a small increase in $PGE_2$; and production of significantly lower levels of IL-1, IL-6, and TNF on stimulation with lipopolysaccharide when compared with air-exposed cells (Becker et al., 1991). Although the few studies in which animals have been exposed to virus in conjunction with $O_3$ exposure provide some evidence to suggest that $O_3$ impairs the immune system's ability to fight viral infections, there is insufficient human data to know whether $O_3$ exposure affects viral infectivity. However, there is potential cause for concern that $O_3$ may render humans and animals more susceptible to a subsequent bacterial challenge.

There are two studies that have investigated the effect of $O_3$ exposure on mucociliary clearance of inhaled particles, with conflicting results. In one study (Foster et al., 1987), seven male volunteers inhaled radiolabeled ferric oxide ($^{99m}$Tc-$Fe_2O_3$) particles and then were exposed to 0.2 and 0.4 ppm $O_3$ for 2 h while undergoing light IE. The investigators observed a concentration-dependent increase in rate of particle clearance 2 h after exposure, although increased clearance was confined primarily to the peripheral airways in subjects exposed to 0.2 ppm $O_3$. In the second study (Gerrity et al., 1993), 15 male or female subjects were exposed to 0.4 ppm $O_3$ for 1 h while undergoing CE (40 L/min); 2 h after exposure, subjects inhaled $^{99m}$Tc-$Fe_2O_3$ particles, and clearance was measured with a gamma camera for the next 3 h and on the next morning. There was no difference in the clearance rate of particles in air and $O_3$-exposed subjects. The discrepancy between these studies may be explained by differences in exposure protocol, time of particle inhalation, or time of clearance measurement, or by the presence of cough immediately following $O_3$ exposure, which may have accelerated clearance in the first study.

## 7.2.5 Extrapulmonary Effects of Ozone

It is still believed that $O_3$ reacts immediately on contact with respiratory system tissue and is not absorbed or transported to extrapulmonary sites to any significant degree (see Chapter 8). A number of laboratory animal studies presented in Chapter 6, however, suggest

that reaction products formed by the interaction of $O_3$ with respiratory system fluids or tissues may produce effects measured outside the respiratory tract—either in the blood, as changes in circulating blood lymphocytes, erythrocytes, and serum, or as changes in the structure or function of other organs, such as the parathyroid gland, the heart, the liver, and the central nervous system (see Chapter 6, Section 6.3). Very little is known, however, about the mechanisms by which $O_3$ could cause these extrapulmonary effects.

The results from human exposure studies discussed in the previous criteria document (U.S. Environmental Protection Agency, 1986) failed to demonstrate any consistent extrapulmonary effects (see Chapter 10, Section 10.6 of the 1986 document). Early studies on peripheral blood lymphocytes collected from human volunteers did not find any significant genotoxic or functional changes at $O_3$ exposures of 0.4 to 0.6 ppm for up to 4 h/day. Limited data on human subjects available at the time the 1986 criteria document was published also indicated that 0.5 ppm $O_3$ exposure for over 2 h caused transient changes in blood erythrocytes and sera (e.g., erythrocyte fragility and enzyme activities), but the physiological significance of these studies remains questionable. The conclusions drawn from these early studies raise doubt that cellular damage or altered function is occurring to circulating cells at $O_3$ exposures under 0.5 ppm.

Studies published since the publication of the previous criteria document (U.S. Environmental Protection Agency, 1986) on the potential extrapulmonary effects of in vivo $O_3$ exposure of human subjects have not been very definitive. Johnson et al. (1986) exposed 11 male nonsmokers to 0.5 ppm $O_3$ for 4 h on 2 consecutive days. When compared to air controls, $O_3$ exposure did not result in any significant change in the activity of blood plasma $\alpha$-1-proteinase inhibitor. Schelegle et al. (1989) exposed 20 $O_3$-sensitive, healthy young men to 0.20 and 0.35 ppm $O_3$ with heavy exercise ($\dot{V}_E$ = 50 L/min). Plasma concentrations of $PGF_{2\alpha}$ were elevated after 40 and 80 min of exposure to the higher $O_3$ level (0.35 ppm). It is likely, however, that the elevation of this ecosanoid in the blood was due either to increased production or to decreased metabolism of $PGF_{2\alpha}$ in the lung.

The demonstration in the previous section (Section 7.2.4) of an array of inflammatory mediators and immune modulators released at the airway surface provides a possible mechanism for effects to occur elsewhere in the body.

## 7.2.6  Ozone Mixed with Other Pollutants

Although it is well known that polluted air contains a large number of chemical species, the most common approach to evaluating air pollution effects under laboratory conditions has been assessment of responses consequent to exposure to single pollutants. This has been the case for a variety of reasons, not the least of which is the problem inherent in adequately controlling the concentrations of multiple pollutants simultaneously. Further, atmospheric chemistry is very complicated, and it is difficult to adequately assess the exposure mixture as the number of constituent pollutants increases. Observed effects may be related to unknown reaction products, the monitored pollutants being only surrogates. Other problems inherent in mixture studies involve considerations such as whether pollutants are presented simultaneously or in sequential or overlapping patterns. Ideally, the selected pattern should at least approximate one that occurs in the ambient environment. In spite of these difficulties, information from mixture studies is important from the standpoint of attempts to better understand responses of humans to the complex mixture of ambient air.

The previous $O_3$ criteria document (U.S Environmental Protection Agency, 1986) evaluated the limited database of information available on mixtures of $O_3$ with one or more pollutants and concluded that pulmonary function changes were no more than additive and, in most cases, were attributable to $O_3$ alone. Several new studies have since appeared in which human subjects were exposed to mixtures of two or more pollutants or to individual pollutants sequentially (Table 7-13), extending the database for controlled studies. Epidemiological studies also have investigated mixtures of pollutants and have not found evidence suggestive of synergistic effects (see Section 7-4).

### 7.2.6.1 Ozone and Sulfur-Containing Pollutants

Horvath et al. (1987) compared the pulmonary function responses of male subjects (19 to 29 years of age) with normal baseline pulmonary function to four experimental conditions: (1) FA, (2) 0.25 ppm $O_3$, (3) 1,200 to 1,600 $\mu g/m^3$ $H_2SO_4$ aerosol, and (4) 0.25 ppm $O_3$ + 1,200 to 1,600 $\mu g/m^3$ $H_2SO_4$ aerosol. Exposures were completed in random sequence, a minimum of 1 week apart, and were conducted at 35 $°C$ and 83% RH. Subjects alternated 20-min rest and exercise ($\dot{V}_E$ = 30 to 32 L/min) periods throughout the 2-h exposures. The results indicated that neither $O_3$ alone nor $O_3$ mixed with $H_2SO_4$ aerosol had significant effects on any pulmonary function, metabolic, or ventilatory parameter.

Koenig et al. (1990) evaluated sequential $O_3$ (0.12 ppm) and $SO_2$ (0.10 ppm) exposures in 13 allergic, asthmatic adolescents (12 to 18 years of age). Three subjects used no regular medications, the other 10 used one or more of beta-adrenergic agents, theophylline, and antihistamines. All subjects had a $PC_2$ for methacholine of 10 mg/mL or less. Subjects took their morning medication on experiment days if needed, but at least 4 h elapsed between any medication use and the start of the experiment. The subjects participated in three exposures at 22 $°C$ and 75% RH, which were presented in random order and at least 1 week apart. The three exposures were (1) air + $SO_2$, (2) $O_3$ + $O_3$, and (3) $O_3$ + $SO_2$. The mouthpiece exposures were 1 h in duration, during which the subjects breathed one test gas for 45 min, followed by a second gas for the final 15 min. Subjects exercised at a $\dot{V}_E$ of about 30 L/min during the second and fourth 15-min segments of the exposure. Pulmonary functions were measured 2 to 3 and 7 to 8 min postexposure. Changes in $FEV_1$ and $R_T$ were significantly greater following the $O_3$ + $SO_2$ exposure than following the other two exposures. Although the subject group was small, the results indicate that $O_3$ exposure may potentiate responses to $SO_2$ exposure in asthmatic adolescents. It should be noted that the $SO_2$ concentration (0.10 ppm) used in this study is a subthreshold level.

Linn et al. (1994) evaluated the pulmonary function and symptom responses of 15 atopic and normal subjects and 30 asthmatic subjects exposed to FA, 0.12 ppm $O_3$, 100 $\mu g/m^3$ respirable $H_2SO_4$ aerosol (MMAD = 0.5 $\mu m$), and a mixture of the two pollutants. The chamber exposures were 6.5 h in duration, during which the subjects walked on a treadmill ($\dot{V}_E$ $≅$ 29 L/min) for 50 min of each hour. There was a 30-min lunch period following the third hour. Pulmonary function and symptom responses were measured preexposure and during the hourly 10-min breaks, and a methacholine bronchochallenge test was performed following each exposure. Relative to responses to the FA exposure, $H_2SO_4$

# Table 7-13. Ozone Mixed with Other Pollutants[a]

| Concentration[b] | | | Exposure Duration and | Exposure | Number and Gender of | Subject | | |
| ppm | µg/m^{3} | Pollutant | Activity | Conditions | Subjects | Characteristics[c] | Observed Effect(s) | Reference |
|---|---|---|---|---|---|---|---|---|
| *Peroxyacetyl Nitrate* | | | | | | | | |
| 0.485 | 951 | $O_3$ | 2 h | T = 21 °C | 10 F | Healthy NS, | Exposure to the mixture of PAN + $O_3$ | Horvath et al. (1986) |
| 0.27 | 1,337 | PAN | IE | WBGT | | 19 to 36 years old | induced decrements in FVC and $FEV_1$ | |
| | | | $\dot{V}_E$ ≅ 25 L/min | | | | averaging 10% greater than observed | |
| | | | | | | | following exposure to $O_3$ alone. | |
| 0.45 | 882 | $O_3$ | 2 h | T ≅ 22 °C | 3 M, 5 F | Healthy NS, | No differences between | Drechsler-Parks et al. |
| 0.30 | 1,485 | PAN | IE | RH ≅ 60% | | mean age = 24 years | responses to exposure to | (1987b) |
| | | | $\dot{V}_E$ ≅ 27 L/min | | | | $O_3$ alone and $O_3$ + PAN. | |
| 0.45 | 882 | $O_3$ | 2 h | T = 24 °C | 16 M, 16 F | Healthy NS; | No differences between | Drechsler-Parks et al. |
| 0.60 | 1,128 | $NO_2$ | IE | RH = 55 to 58% | | 16 subjects, | responses to $O_3$ alone, $O_3$ + $NO_2$, $O_3$ + | (1989) |
| 0.13 | 644 | PAN | $\dot{V}_E$ ≅ 25 L/min | | | 19 to 26 years old; | PAN, or $O_3$ + $NO_2$ + PAN. | |
| | | | | | | 16 subjects, | | |
| | | | | | | 51 to 76 years old | | |
| *Nitrogen-Containing Pollutants* | | | | | | | | |
| 0.12 | 235 | $O_3$ | 1 h (mouthpiece) | T = 22 °C | 5 M, 7 F | Healthy NS, | No significant changes in any pulmonary | Koenig et al. (1988) |
| 0.30 | 564 | $NO_2$ | IE | RH = 75% | | 12 to 17 years old | function with $O_3$ alone or $O_3$ + $NO_2$. | |
| | | | $\dot{V}_E$ = 4 to 5 times | | | | | |
| | | | resting | | | | | |
| 0.20 | 392 | $O_3$ | 5 h | T = 20 °C | 6 M, 4 F | Healthy NS, | Exposure to $HNO_3$ or $H_2O$ fog followed by | Aris et al. (1991) |
| | 500 | $HNO_3$ | IE (50 min/h exercise) | RH = 5% | | minimum of 10% decrement | $O_3$ induced smaller pulmonary function | |
| | | $H_2O$ | $\dot{V}_E$ ≅ 40 L/min | | | in $FEV_1$ after 3 h exposure | decrements than air followed by $O_3$. | |
| | | | 2 h $HNO_3$ or $H_2O$ fog | | | to 0.20 ppm $O_3$ with 50 min | | |
| | | | or air, followed by 1-h | | | exercise/h | | |
| | | | break, followed by 3 h | | | | | |
| | | | $O_3$ | | | | | |
| 0.30 | 588 | $O_3$ | 2 h CE for 20 min | T = 28 to 29 °C | 6 M | Healthy subjects, | Possible small decrease in $SG_{aw}$ | Kagawa (1986) |
| 0.30 | 564 | $NO_2$ | $\dot{V}$ ≅ 25 L/min | RH = 50 to 60% | | some smokers | | |
| | 200 | $H_2SO_4$ | | | | | | |
| 0.15 | 294 | $O_3$ | 2 h, 60 min total exercise | | 6 M | | Possible small decrease in $SG_{aw}$ | |
| 0.15 | 282 | $NO_2$ | $\dot{V}$ ≅ 25 L/min | | | | | |
| | 200 | $H_2SO_4$ | | | | | | |
| 0.15 | 294 | $O_3$ | 2 h, 60 min total exercise | | 3 M | | Possible small decrease in $FEV_1$ | |
| 0.15 | 282 | $NO_2$ | $\dot{V}$ ≅ 25 L/min | | | | | |
| 0.15 | 393 | $SO_2$ | | | | | | |
| | 200 | $H_2SO_4$ | | | | | | |

## Table 7-13 (cont'd).  Ozone Mixed with Other Pollutant$^a$

| ppm | $\mu$g/m$^3$ | Pollutant | Exposure Duration and Activity | Exposure Conditions | Number and Gender of Subjects | Subject Characteristics [c] | Observed Effect(s) | Reference |
|---|---|---|---|---|---|---|---|---|
| Concentration[b] | | | | | | | | |
| *Nitrogen-Containing Pollutants (cont'd)* | | | | | | | | |
| 0.30 0.60 | 588 1,128 | $O_3$ $NO_2$ | 1 h (mouthpiece) CE $\dot{V}_E \approx 70$ L/min for men $\dot{V}_E \approx 50$ L/min for women | | 20 M, 20 F | Healthy NS, $21.4 \pm 1.5$ (SD) years old for F, $22.7 \pm 3.3$ (SD) years old for M | No differences between responses to $O_3$ and $NO_2 + O_3$ for spirometric parameters.  Increase in $SR_{aw}$ with $NO_2 + O_3$ was significantly less than for $O_3$ alone. | Adams et al. (1987) |
| 0.30 0.60 | 588 1,128 | $O_3$ $NO_2$ | 2-h exposure to $NO_2$ or FA, followed 3 h later by 2-h exposure to $O_3$ IE  $\dot{V}_E = $ 20 L/min/m$^2$ BSA | T = 21 °C RH = 40% | 21 F | Healthy NS, 18 to 34 years old | No significant effect of $NO_2$ exposures on any measured parameter. Sequential exposure of $NO_2$ followed by $O_3$ induced small but significantly larger decrements in $FEV_1$ and $FEF_{25-75\%}$ than FA/$O_3$ sequence.  Subjects had increased airway responsiveness to methacholine after both exposures, with significantly greater responsiveness after the $NO_2$/$O_3$ sequences than after the FA/$O_3$ sequence. | Hazucha et al. (1994) |
| *Sulfur-Containing Pollutants* | | | | | | | | |
| 0.12 0.10 | 235 262 | $O_3$ $SO_2$ | 1 h (mouthpiece) IE $\dot{V}_E \approx 30$ L/min 45-min exposure to air or $O_3$, followed by 15-min exposure to $O_3$ or $SO_2$ | T = 22 °C RH = 75% | 8 M, 5 F | All allergic asthmatics, 12 to 18 years old, medications withheld for at least 4 h before exposures | Prior exposure to $O_3$ potentiated pulmonary function responses to $SO_2$; decrements in $FEV_1$ were $\approx$3, $\approx$2, and $\approx$8% for the air/$O_3$, $O_3$/$O_3$, and $O_3$/$SO_2$ exposures, respectively. | Koenig et al. (1990) |
| 0.08 0.12 0.18 | 157 235 353 100 100 | $O_3$ $O_3$ $O_3$ NaCl $H_2SO_4$ | 3-h exposure to aerosol, followed 24 h later by a 3-h exposure to $O_3$. IE (10 min per half hour) $\dot{V}_E = 4$ times resting (30 to 364 min) | T = 21 °C RH $\approx$ 40% | Nonasthmatic, 16 M, 14 F Asthmatic 10 M, 20 F | NS, 18 to 45 years old NS, 21 to 42 years old | No significant changes in symptoms or lung function with any aerosol/$O_3$ combination in the healthy group.  In asthmatics, $H_2SO_4$ preexposure enhanced the small decrements in FVC that occurred following exposure to 0.18 ppm $O_3$.  Asthmatics had no significant changes on $FEV_1$ with any $O_3$ exposures, but symptoms were greater. | Utell et al. (1994) |
| 0.12 | 235 100 | $O_3$ $H_2SO_4$ | 6.5 h 2 consecutive days 50 min exercise/h $\dot{V}_E = 29$ L/min | T = 21 °C RH = 50% | Nonasthmatic, 8 M, 7 F Asthmatic, 13 M, 17 F | NS, 22 to 41 years old NS, 18 to 50 years old | Exposure to $O_3$ or $O_3 + H_2SO_4$ induced significant decrements in forced expiratory function.  Differences between $O_3$ and $O_3 + H_2SO_4$ were, at best, marginally significant.  $O_3$ is the more important pollutant for inducing respiratory effects.  A few asthmatic and nonasthmatic subjects were more responsive to $O_3 + H_2SO_4$ than to $O_3$ alone. | Linn et al. (1994) |

## Table 7-13 (cont'd). Ozone Mixed with Other Pollutants[a]

| ppm | $\mu$g/m | Pollutant | Exposure Duration and Activity | Exposure Conditions[c] | Number and Gender of Subjects | Subject Characteristics | Observed Effect(s) | Reference |
|---|---|---|---|---|---|---|---|---|
| | Concentration[b] | | | | | | | |

*Sulfur-Containing Pollutants (cont'd)*

| ppm | $\mu$g/m | Pollutant | Exposure Duration and Activity | Exposure Conditions[c] | Number and Gender of Subjects | Subject Characteristics | Observed Effect(s) | Reference |
|---|---|---|---|---|---|---|---|---|
| 0.12 | 235 | $O_3$ | 1.5 h with IE for | $T = 22\ °C$ | Asthmatic | NS, 12 to 19 years old | No significant pulmonary function changes | Koenig et al. (1994) |
| 0.30 | 564 | $NO_2$ | 2 consecutive days; | $RH = 65\%$ | adolescents; | | following any exposure compared to response | |
| | 70 | $H_2SO_4$ | $\dot{V}_E \cong 23.2$ L/min | | 22 completed | | to clean air. Six additional subjects started the | |
| 0.05 | | $HNO_3$ | | | study; | | study, but dropped out due to uncomfortable | |
| | | | | | 15 M, 7 F | | symptoms. | |
| 0.25 | 490 | $O_3$ | 2 h | $T = 35\ °C$ | 9 M | Healthy NS, | No significant effects of exposure to $O_3$ alone | Horvath et al. (1987) |
| | 1,200 to | $H_2SO_4$ | IE | $RH = 83\%$ | | 19 to 29 years old | or combined with $H_2SO_4$ aerosol. | |
| | 1,600 | aerosol | $\dot{V}_E = 30$ to 32 L/min | | | | | |

[a]See Appendix A for abbreviations and acronyms.
[b]Grouped by pollutant mixture.
[c]$WBGT = 0.7\ T_{wet\ bulb} + 0.3\ T_{dry\ bulb\ or\ globe}$.

aerosol exposure alone induced no significant alteration in pulmonary function, symptoms, or bronchial reactivity to methacholine. Exposure to $O_3$ alone ($FEV_1$ decrement of about 100 mL compared to the FA response) or mixed with $H_2SO_4$ aerosol ($FEV_1$ decrement of about 189 mL compared to the FA exposure) induced significant decrements in forced expiratory function and increased bronchial reactivity. Both effects were greater on the first of 2 consecutive days of exposure. Group mean lung function and methacholine reactivity changes were somewhat larger following $O_3 + H_2SO_4$ aerosol compared to exposure to $O_3$ alone, but the differences were, at best, marginally significant and usually nonsignificant, depending on the function tested. However, there were a few individual subjects who showed significantly larger pulmonary function decrements following the exposure to $O_3 + H_2SO_4$ than following exposure to $O_3$ alone. The authors concluded that $O_3$ is more important than $H_2SO_4$ aerosol in inducing pulmonary dysfunction in normal, atopic, and asthmatic adults. There does, however, appear to be a more sensitive subpopulation that responds to $O_3 + H_2SO_4$ aerosol more strongly than the average adult.

Utell et al. (1994) reported on the pulmonary function and symptomology responses of 30 healthy adults (18 to 45 years of age) and 30 allergic asthmatics (21 to 42 years of age) who were exposed for 3 h to sodium chloride (NaCl) aerosol (100 $\mu g/m^3$) or $H_2SO_4$ aerosol (100 $\mu g/m^3$) and, 24 h later, to 0.08, 0.12, or 0.18 ppm $O_3$ for 3 h. The study was an incomplete block design, in that each subject completed chamber exposures to each of two $O_3$ concentrations following each of the aerosols (four of the possible six combinations per subject). Out of the total number of subjects, 20 healthy and 20 asthmatic subjects completed each of the possible exposure combinations. Subjects exercised for 10 min out of each half-hour of exposure ($\dot{V}_E$ = 4 times resting; 30 to 36 L/min). Environmental conditions averaged 21 $\pm$ 1 $°$C and 40 $\pm$ 5% RH. Ozone exposures were separated by at least 2 weeks. Healthy subjects had no significant pulmonary function response (2.1% or less) to $O_3$ exposure, regardless of the $O_3$ concentration or the aerosol preexposure. As a group, asthmatics had mean decrements in FVC of 5% or greater in only a few cases: 7.6% following the NaCl/0.08 ppm $O_3$ combination, 6.3% following the NaCl/0.12 ppm $O_3$ combination, and 6.5% following the $H_2SO_4$/0.18 ppm $O_3$ combination. No combination of aerosol and $O_3$ concentration induced a decrement in $FEV_1$ of 5% or greater. Although the statistical analysis indicates that exposure to $H_2SO_4$ aerosol significantly altered the pattern of response and recovery to $O_3$ exposure on the next day in asthmatics, the group mean data presented in the report show that functionally there is little difference between the responses to the various exposures or in the time course of recovery. The individual responses of the asthmatic subjects are reported to be more variable than those of the healthy subjects. Asthmatic subjects reported more respiratory symptoms than healthy subjects, but there was no dose-response relationship between $O_3$ concentration and symptom intensity for healthy or asthmatic subjects. The variability of the responses of the asthmatic subjects makes interpretation of these results difficult. Some of the asthmatic subjects were reported to experience exercise-induced bronchospasm, and, without FA control exposures, it is impossible to determine what, if any, portion of the asthmatic subjects' response is related to exercise-induced bronchospasm, compared to that related to $O_3$ exposure.

Kagawa (1986) exposed Japanese men to three mixtures: (1) $O_3$ (0.30 ppm) + $NO_2$ (0.30 ppm) + $H_2SO_4$ (200 $\mu g/m^3$), (2) $O_3$ (0.15 ppm) + $NO_2$ (0.15 ppm) + $H_2SO_4$ (200 $\mu g/m^3$), or (3) $O_3$ (0.15 ppm) + $NO_2$ (0.15 ppm) + $SO_2$ (0.15 ppm) + $H_2SO_4$ (200 $\mu g/m^3$). Exposures were 2 h in duration, and subjects exercised for a total of 20 min during exposure 1 and for 60 min during exposures 2 and 3. Some of the subjects were

smokers.  Reported symptoms were attributed to $O_3$ exposure, whereas small decrements in airway conductance ($\square$10%) were observed following exposures to mixtures 1 and 2.  Although the magnitude of the $FEV_1$ decrement is not stated, a possible decrease was observed after exposure 3.  The responses observed with these mixed exposure conditions were no different than responses reported for exposures to similar concentrations of $O_3$, indicating no enhanced response due to the presence of the other pollutants in the mixtures.

### 7.2.6.2  Ozone and Nitrogen-Containing Pollutants

Adams et al. (1987) reported on the responses of 20 males and 20 females (18 to 30 years of age), all healthy nonsmokers, exposed to (1) FA, (2) 0.3 ppm $O_3$, (3) 0.6 ppm $NO_2$, and (4) 0.3 ppm $O_3$ + 0.6 ppm $NO_2$.  Subjects were exposed via mouthpiece for 1 h, during which they exercised continuously at a $\dot{V}_E$ of about 70 L/min for males and 50 L/min for females.  The exposures were presented in random order, a minimum of 5 days apart. There were no differences in any pulmonary function ($FEV_1$ decrement of about 22%) between the $O_3$ and $NO_2$ + $O_3$ exposures, except for $SR_{aw}$, which was lower following $NO_2$ + $O_3$ (+7.3% for females and $\square$9.6% for males) than following $O_3$ alone (+15.3% for females and +4.0% for males).

Koenig et al. (1988) exposed 14 male and 10 female adolescents to FA, 0.30 ppm $NO_2$, 0.12 ppm $O_3$, and 0.30 ppm $NO_2$ + 0.12 ppm $O_3$.  Twelve of the subjects were healthy normals, and the other 12 were allergic asthmatics.  The asthmatics, except for one who took no regular medications, used one or more of beta-adrenergic agents, theophylline, and antihistamines.  Asthmatic subjects took their morning medications if needed, but refrained from medication use for at least 4 h prior to the exposures.  The mouthpiece exposures were 1 h in duration, during which the subjects exercised in 15-min periods (mean $\dot{V}_E = 32.8 \pm 6.0$ L/min), alternated with 15-min rest periods.  No changes in any measure of pulmonary function were observed in normal or asthmatic subjects following $O_3$ or $NO_2$ + $O_3$ exposure.

Sequential exposure to 0.6 ppm $NO_2$ or FA for 2 h, followed 3 h later by a 2-h exposure to 0.3 ppm $O_3$ was investigated by Hazucha et al. (1994) in 21 healthy, nonsmoking females (18 to 34 years of age).  Subjects alternated 15-min periods of exercise ($\dot{V}_E = 20$ L/min/m$^2$ BSA) and 15-min rest periods while in the exposure chamber, and rested in ambient air during the 3-h interexposure period.  The 2 exposure days were separated by at least 2 weeks.  Ambient conditions in the exposure chamber were 21 $\square$C and 40% RH.  Group mean decrements following the FA/$O_3$ exposure sequence were $\square$10.8, $\square$7.0, $\square$10.2, and $\square$14.9% for PEFR, FVC, $FEV_1$, and $FEF_{25\ 75\%}$, respectively.  Following the $NO_2$/$O_3$ exposure sequence, the group mean decrements were $\square$14.5, $\square$8.5, $\square$12.0, and $\square$19.5%, respectively, for PEFR, FVC, $FEV_1$, and $FEF_{25\ 75\%}$.  Although small, the differences in $FEV_1$ and $FEF_{25\ 75\%}$ between the FA/$O_3$ and $NO_2$/$O_3$ exposure sequences were statistically significant.  There were no differences in the changes in $SR_{aw}$ or symptomology between the two exposure sequences.  The most striking finding of this study was that, although both exposure sequences increased airway responsiveness to methacholine, responsiveness was potentiated by the $NO_2$/$O_3$ exposure sequence compared to the FA/$O_3$ exposure sequence.

Aris et al. (1991) examined pulmonary function responses to a 3-h exposure to 0.2 ppm $O_3$ following a 2-h exposure to 0.54 mg/mL nitric acid ($HNO_3$; volume mean diameter = 6.0 $\pm$ 0.2 $\square$m) or 0.55 mg/mL water ($H_2O$; volume mean diameter = 6.47 $\pm$ 0.4 $\square$m) fog.  This is a common pattern of pollutant exposure in coastal California areas.  Subjects were 10 healthy adults 21 to 31 years of age; they were prescreened for a decrement of 10% or

greater in $FEV_1$ following 3 h of exposure to 0.2 ppm $O_3$, during which they exercised for 50 min of each hour ($\dot{V}_E$ = 40 L/min). Decrements in $FEV_1$ following the screening $O_3$ exposure ranged from 15 to 49%. The three exposures (FA + $O_3$, $H_2O$ fog + $O_3$, and $HNO_3$ fog + $O_3$) were presented in random order, and were separated by a minimum of 2 weeks. The authors hypothesized that exposure to acidic fog, followed by $O_3$ exposure, would induce greater decrements in FVC and $FEV_1$ than $H_2O$ fog or air followed by $O_3$ exposure. In fact, both $HNO_3$ and $H_2O$ fog exposure seemed to ameliorate the effect of subsequent $O_3$ exposure on $FEV_1$ and FVC, although only the difference between the $FEV_1$ responses to FA + $O_3$ (28.5%) and $H_2O$ fog + $O_3$ (18.5%) was significant. Group mean comparisons of methacholine responsiveness and $O_3$ responsiveness (defined as a minimum of a 10% decrement in $FEV_1$ following the prescreening $O_3$ exposure) suggest that the subjects classified as $O_3$ sensitive, on the average, had lower methacholine $PC_1$ $_{Sraw}$ doses. The individual data, however, do not always support this conclusion. Two of 10 $O_3$-sensitive subjects had methacholine $PC_1$ $_{SRaw}$ concentrations above the author's cut-off for airway hyperresponsiveness, and 3 of 10 $O_3$ nonsensitive subjects had hyperreactive airways based on the authors' criteria for methacholine $PC_1$ $_{SRaw}$.

Aris et al. (1993b) further examined pulmonary responses to combined $O_3$ and $HNO_3$ exposures. Ten healthy, nonsmoking adults, 19 to 41 years of age, were exposed to FA, 500 $\Box$g/m³ of $HNO_3$ gas plus 0.2 ppm $O_3$, or to 0.2 ppm $O_3$ alone. The exposure protocol was 4 h in duration, with 50 min IE at 40 L/min alternating with 10-min rest periods each hour. Pulmonary function was measured during each rest period, whereas BAL, proximal airway lavage, and bronchial biopsies were performed 18 h after completion of each exposure. Mean $FEV_1$ and FVC decreased, and mean $SR_{aw}$ and respiratory symptom scores increased across both the $HNO_3$ + $O_3$ and the $O_3$ exposures. The results indicated, however, that $HNO_3$ combined with $O_3$ did not exacerbate the pulmonary function decrements or respiratory symptoms caused by $O_3$ alone. Similarly, there were no statistically significant differences between the $HNO_3$ + $O_3$ and the $O_3$ exposures in the cellular or biochemical constituents in either the BAL or proximal airway lavage fluids or in the bronchial biopsy specimens. The authors concluded that $HNO_3$ does not potentiate the inflammatory response produced by $O_3$ in healthy individuals.

The objective of a study by Koenig et al. (1994) was to investigate possible interactions between oxidants (0.12 ppm $O_3$ + 0.30 ppm $NO_2$) and an $H_2SO_4$ aerosol (70 $\Box$g/m³) with a mass median aerodynamic diameter (MMAD) of 0.6 $\Box$m ($\pm\Box_g$ = 1.5). Twenty-two adolescent allergic asthmatics who also had exercise-induced bronchospasm and a positive response to a standardized methacholine bronchochallenge test completed all exposures. Subjects inhaled FA, $O_3$ + $NO_2$, $O_3$ + $NO_2$ + $H_2SO_4$, or $O_3$ + $NO_2$ + $HNO_3$ through a mouthpiece for 90 min on 2 consecutive days. Each pair of exposures was separated by at least 1 week. Subjects exercised ($\dot{V}_E$ about 10 times FVC) and rested in alternating 15-min periods. Pulmonary functions (FVC, $FEV_1$, $\dot{V}_{max5\ \%}$, $\dot{V}_{max75\%}$, and $R_T$) were measured before and after each exposure and on the day following the second consecutive exposure, at which time only pulmonary function was evaluated and a methacholine bronchochallenge was performed. Six additional subjects began the study, but dropped out before completion because of uncomfortable symptoms associated with the exposures; none dropped out following an FA exposure. There were no statistically significant changes in any measured parameter of pulmonary function following the three pollutant-containing exposures, compared to the FA exposure, contrary to expectations. (Also see Section 7.4 for related epidemiological studies.)

### 7.2.6.3 Ozone, Peroxyacetyl Nitrate, and More Complex Mixtures

Horvath et al. (1986) exposed 10 healthy young women (19 to 36 years of age) to (1) FA, (2) 0.48 ppm $O_3$, (3) 0.27 ppm PAN, and (4) 0.48 ppm $O_3$ + 0.27 ppm PAN. The chamber exposures were 2 h in duration, during which subjects alternated 20-min exercise periods ($\dot{V}_E$ = 25 L/min) and 15-min rest periods. Exposures were completed in random order and were at least 1 week apart. Exposure to PAN alone did not induce any significant changes in pulmonary function. Both $O_3$ and PAN + $O_3$ exposure induced significant decrements in FVC, $FEV_1$, and $FEF_{25-75\%}$; however, the decrements following the PAN + $O_3$ exposure were significantly larger (average of about 10%), suggesting interaction between PAN and $O_3$. It should be noted that typical peak ambient PAN concentrations are about 0.05 ppm. Symptom reports indicated that $O_3$ + PAN exposure induced greater subjective stress than did exposure to $O_3$ alone.

Drechsler-Parks et al. (1987b) exposed eight healthy young adults (mean age 24 years) to a mixture of 0.30 ppm PAN + 0.45 ppm $O_3$ on 5 consecutive days to evaluate possible attenuation. Subjects were reexposed to the PAN + $O_3$ mixture on the third and seventh days following the last consecutive day of exposure. Attenuation occurred with the same pattern and time sequence as has been reported for $O_3$ alone. The largest group mean decrements occurred following the second exposure, and the subjects became progressively less responsive with subsequent exposures. Two subjects failed to return to baseline values with 5 consecutive days of exposure. Pulmonary function changes after the follow-up exposures indicated that the attenuation response is relatively short lived, in that it began to abate within 3 to 7 days following the fifth consecutive day of exposure. These results are consistent with those of similar studies using exposure to $O_3$ alone (Horvath et al., 1981; Kulle et al., 1982), suggesting that PAN had no additional effect on attenuation to $O_3$. A greater number of symptoms was reported following all PAN + $O_3$ exposures than following exposure to $O_3$ alone.

Drechsler-Parks et al. (1989) studied 16 older men and women (51 to 76 years of age) and 16 young men and women (19 to 26 years of age) who each completed 2-h chamber exposures to FA, 0.45 ppm $O_3$, and mixtures of 0.45 ppm $O_3$ with 0.60 ppm $NO_2$ and/or 0.13 ppm PAN. Subjects alternated 20-min exercise ($\dot{V}_E$ about 25 L/min) and rest periods. Exposure to $O_3$ alone and in all combinations induced significant decrements in FVC (14 to 17%), $FEV_1$ (19 to 22%), and $FEF_{25-75\%}$ (28 to 30%) in the younger group. In the older group, these same three variables were significantly decreased only with $NO_2$ + $O_3$ exposure (7.3% for FVC, 8.4% for $FEV_1$, and 12% for $FEF_{25-75\%}$). Exposure of the older subjects to PAN + $O_3$ induced significant decrements only in FVC (4.2%) and $FEV_1$ (8.3%). The PAN + $NO_2$ + $O_3$ exposure induced a significant decrement only in FVC (6.4%) in the older subjects. All subjects reported more symptoms following the mixture exposures than following exposure to $O_3$ alone. These pulmonary function results following the exposure to $O_3$ + PAN are in contrast to those reported by Drechsler-Parks et al. (1984) and Horvath et al. (1986) on young adults exposed to 0.45 ppm $O_3$ + 0.30 ppm PAN. The results of both earlier studies suggested an interaction between $O_3$ and PAN, in that pulmonary function decrements following the mixture exposure were approximately 10% larger than those following exposure to $O_3$ alone, whereas there were no significant pulmonary function effects with exposure to PAN alone. A likely explanation for this discrepancy is that the PAN concentration used by Drechsler-Parks et al. (1989) was slightly less than half that used by Drechsler-Parks et al. (1984) and Horvath et al. (1986). Thus, if the additional effect of PAN is linear, an additional

effect of PAN + $O_3$ would be expected to be less than 5%, which probably would not be detected because it is within the variability of the pulmonary function measurements. In any case, ambient PAN concentrations are considerably less than 0.13 ppm. This indicates that, even if PAN and $O_3$ do interact in some way in their effects on pulmonary function, at typical ambient concentrations of $O_3$ and PAN, effects can be attributed to $O_3$ alone.

### 7.2.6.4 Summary

Information on interactive effects between $O_3$ and other pollutants remains sparse at this time. However, it is clear that $O_3$ is responsible for the largest share of observed effects when subjects are exposed to the mixtures of $O_3$ and other pollutants that have been studied to date. There is no evidence that simultaneous exposure of healthy individuals to ambient concentrations of $O_3$ plus $NO_2$, PAN, $H_2SO_4$, $HNO_3$, or $SO_2$ results in significant interaction. However, Aris et al. (1991) have reported that $HNO_3$ and $H_2O$ fog exposure ameliorates the pulmonary function effects of a subsequent $O_3$ exposure. Koenig et al. (1990) found that preexposure to $O_3$ induced significant pulmonary function decrements in allergic asthmatic adolescents following a sequential $SO_2$ exposure. Both the $O_3$ and $SO_2$ concentrations were at subthreshold levels for the experimental design used.

Both studies that reported potentially significant effects have involved sequential exposure protocols, in contrast to the simultaneous exposure protocols, which generally have not shown effects beyond those that would be expected at the $O_3$ concentration used. It may be that certain preexposures predispose an individual to responses following a subsequent exposure; however, this question remains far from being resolved. Further, these results are related only to spirometry and plethysmography and may not be applicable to other possible endpoints.

# 7.3 Symptoms and Pulmonary Function in Controlled Studies of Ambient Air Exposures

Controlled $O_3$ exposure studies under a variety of different experimental conditions have generated a large amount of informative exposure-effects data. However, complete laboratory simulation of the pollutant mix present in ambient air is impossible on practical grounds. Thus, the exposure effects of one or several artificially generated pollutants (i.e., a simple mixture) on symptoms and lung function may not be comparable to those in ambient air where complex mixtures of pollutants likely exist. This section reviews two types of studies that utilize a mobile laboratory or a hypobaric chamber to investigate the acute effects of $O_3$ during exposures to ambient air or altitude, respectively. These studies can be designed to determine the independent effects of $O_3$ as well as possible interactions among many pollutants and other conditions present in typical ambient air.

## 7.3.1 Mobile Laboratory Studies

Quantitatively useful information on the effects of acute exposure to photochemical oxidants on symptoms and pulmonary function originated from field studies using a mobile laboratory, as presented in the previous criteria document (U.S. Environmental Protection Agency, 1986). These studies offer the advantage of studying the effects of ambient air on a local subject population by combining the experimental methods of both epidemiology and

controlled-exposure studies. Field studies using mobile exposure chambers involve subjects exposed to ambient air, FA without pollutants, or FA containing artificially generated concentrations of $O_3$ that are comparable to those measured in the ambient environment. The exposure air can also be conditioned to a desired temperature and humidity. As a result, measured health responses in ambient air can be compared to those found in more artificial or controlled conditions. The mobile laboratory shares many of the same limitations of stationary exposure laboratories (e.g., limited number of both subjects and artificially generated pollutants for testing). Ambient air studies in the mobile laboratory are dependent on ambient conditions, which can be unpredictable, uncontrollable, and not completely characterizable. Logistical problems (space, power, and locations with local interfering outdoor conditions) limit access to many ambient pollution sites of interest.

As summarized in Table 7-14, investigators at the Rancho Los Amigos Medical Center in California used a mobile laboratory and demonstrated that respiratory effects in Los Angeles residents are related to $O_3$ concentration and level of exercise (Linn et al., 1980, 1983b; Avol et al., 1983, 1984, 1985a,b,c, 1987). Such effects include pulmonary function decrements at $O_3$ concentrations of 0.144 ppm in healthy exercising adolescents (Avol et al., 1985a,b) and increased respiratory symptoms and pulmonary function decrements at 0.153 ppm in heavily exercising athletes (Avol et al., 1984, 1985c) and at 0.174 ppm in lightly exercising normal and asthmatic subjects (Linn et al., 1980, 1983b). The observed effects were typically mild, and generally no substantial differences were seen between asthmatic and nonasthmatic subjects. Postexposure pulmonary function decrements appeared to last several hours longer in the asthmatics, but no statistical test was reported for this difference (Avol et al., 1983; Linn et al., 1983b). The medication status of the asthmatic subjects during the studies was not reported, although medications were temporarily withheld prior to exposures. The subjects' clinical severity typically was mild, based on their baseline lung function and exercise capability. Many of the normal subjects with a history of allergy appeared to be more responsive to $O_3$ than "nonallergic" normal subjects (Linn et al., 1980, 1983b), although a standardized evaluation of atopic status was not performed. Direct comparative studies of exercising athletes (Avol et al., 1984, 1985c) with chamber exposures to oxidant-polluted ambient air (mean $O_3$ concentration of 0.15 ppm) and purified air containing a controlled concentration of generated $O_3$ at 0.16 ppm showed no significant differences in lung function and symptoms, suggesting that coexisting ambient pollutants had minimal contribution to the measured responses under the typical summer ambient conditions in Southern California. Effects of copollutants in other regions of the country remain to be investigated with the mobile laboratory. These field studies emphasize the importance of adequate characterization of subjects and the ambient air, exercise levels, duration of exposure, and individual variations in sensitivity in interpreting observed exposure effects. Although these factors need to be investigated over a wider range of experimental conditions, the results from these field studies are, so far, consistent with those from controlled human exposure studies. Short-term respiratory effects of summer ambient oxidant pollution in Southern California are predominantly, if not entirely, caused by ambient $O_3$ in typical healthy or asthmatic residents, according to mobile laboratory studies (Avol et al., 1984, 1985c). Overall, the symptoms and decrements in lung function were generally modest and, while statistically significant in some cases, were probably not clinically significant.

**Table 7-14. Acute Effects of Ozone in Ambient Air in Field Studies with a Mobile Laboratory[a]**

| Mean Ozone Concentration[b] 6ppm | $\mu$g/m³ | Ambient Temperature[c] (°C) | Exposure Duration | Activity Level ($\dot{V}_E$) | Number of Subjects | Observed Effect(s) | Reference |
|---|---|---|---|---|---|---|---|
| 0.113 ± .033 | 221 ± 65 | 33 ± 1 | 1 h | CE (22 L/min) | 66 healthy children, 8 to 11 years old | No significant changes in forced expiratory function and respiratory symptoms after exposure to 0.113 ppm $O_3$ in ambient air. | Avol et al. (1987) |
| 0.144 ± .043 | 282 ± 84 | 32 ± 1 | 1 h | CE (32 L/min) | 59 healthy adolescents, 12 to 15 years old | Small significant decreases in FVC (□2.1%), $FEV_{0.75}$ (□4.0%), $FEV_1$ (□4.2%), and PEFR (□4.4%) relative to control with no recovery during a 1-h postexposure rest; no significant increases in symptoms. | Avol et al. (1985a,b) |
| 0.153 ± .025 | 300 ± 49 | 32 ± 2 | 1 h | CE (53 L/min) | 50 healthy adults (competitive bicyclists) | Mild increases in lower respiratory symptom scores and significant decreases in $FEV_1$ (□5.3%) and FVC; mean changes in ambient air were not statistically different from those in purified air containing 0.16 ppm $O_3$. | Avol et al. (1984, 1985c) |
| 0.156 ± .055 | 306 ± 107 | 33 ± 4 | 1 h | CE (38 L/min) | 48 healthy adults, 50 asthmatic adults | No significant changes for total symptom score or forced expiratory performance in normals or asthmatics; however, $FEV_1$ remained low or decreased further (□3%) 3 h after ambient air exposure in asthmatics. | Linn et al. (1983b) Avol et al. (1983) |
| 0.165 ± .059 | 323 ± 115 | 33 ± 3 | 1 h | CE (42 L/min) | 60 "healthy" adults (7 were asthmatic) | Small significant decreases in $FEV_1$ (□3.3%) and FVC with no recovery during a 1-h postexposure rest; TLC decreased and □$N_2$ increased slightly. | Linn et al. (1983b) Avol et al. (1983) |

## Table 7-14 (cont'd). Acute Effects of Ozone in Ambient Air in Field Studies with a Mobile Laboratory[a]

| Mean Ozone Concentration[b] | | Ambient Temperature[c] ($°C$) | Exposure Duration | Activity Level ($\dot{V}_E$) | Number of Subjects | Observed Effect(s) | Reference |
|---|---|---|---|---|---|---|---|
| ppm | $µg/m^3$ | | | | | | |
| 0.174 ± .068 | 341 ± 133 | 33 ± 2 | 2 h | IE (2 times resting) at 15-min intervals | 34 "healthy" adults, 30 asthmatic adults | Increased symptom scores and small significant decreases in $FEV_1$ ($□2.4\%$), FVC, PEFR, and TLC in both asthmatic and healthy subjects; however, 25/34 healthy subjects were allergic and "atypically" reactive to polluted ambient air. | Linn et al. (1980, 1983b) |

[a]See Appendix A for abbreviations and acronyms.
[b]Ranked by lowest level of $O_3$ in ambient air, presented as the mean ± SD.
[c]Mean ± SD.

### 7.3.2  High-Altitude Studies

Symptoms and pulmonary function resulting from exposure to $O_3$ in commercial aircraft flying at high altitudes and in altitude-simulation studies were reviewed in the previous criteria document (U.S. Environmental Protection Agency, 1986).  Attention has focused on the health effects in flight crew, specifically flight attendants because of their physical activities at altitude and exposure patterns to peak levels of cabin $O_3$.  The most quantitatively useful information was based on a series of hypobaric studies of normal nonsmoking subjects who were exposed to 1,829 m (6,000 ft) and $O_3$ at concentrations of 0.2 and 0.3 ppm for 3 or 4 h (Lategola et al., 1980a,b).  Increased symptoms and pulmonary function decrements occurred at 0.3 ppm but not at 0.2 ppm under light exercise conditions.  However, the exposure conditions did not reflect higher (peak) $O_3$ concentrations reported to occur in certain aircraft at high altitudes or the higher cabin altitudes attained by new-generation commercial aircraft.

No reports have appeared subsequently in the literature that specifically study the health effects of aircraft cabin $O_3$.  However, $O_3$ levels were reported to be very low (average concentration 0.01 to 0.02 ppm) during 92 randomly selected smoking and nonsmoking flights in 1989 (Nagda et al., 1991).  None of the flights exceeded the time-weighted average standard of 0.10 ppm (during any 3-h interval) promulgated by the U.S. Federal Aviation Administration, perhaps related to the use of $O_3$-scrubbing catalytic filters (Melton, 1990).  However, in-flight $O_3$ exposure is possible because catalytic filters are not necessarily in continuous use during flight.

# 7.4  Field and Epidemiology Studies
## 7.4.1  Acute Effects of Ozone Exposure
### 7.4.1.1  Introduction

Field and epidemiology studies addressing the acute effects of $O_3$ on lung function decrements and increased morbidity and mortality in human populations involve those combinations of environmental conditions and copollutant and activity levels present under real-world conditions of $O_3$ exposure.  This real-world relevance is an advantage over animal or human chamber studies.  Thus, results of such studies are essential components of an understanding of overall effects of $O_3$.  However, the conditions under which epidemiologic studies are carried out cannot be controlled in the same way that they can in experimental studies.  Parameters that may be difficult or impossible to estimate or control outside the laboratory include actual $O_3$ exposures, levels of temperature, RH, allergens, correlated pollutants other than $O_3$, and breathing rates and activity patterns of subjects.  Variations in these factors can be important sources of variability in data and results and may, under certain conditions, lead to biases (e.g., confounding) in results.  These and other issues of importance in the interpretation of epidemiology study results are discussed in the sections below.

The limitations of epidemiologic studies of $O_3$ health effects noted above were highlighted in the previous $O_3$ criteria document (U.S. Environmental Protection Agency, 1986), which reached the conclusion that, because of such factors, epidemiologic studies on the acute effects of $O_3$ on lung function available at that time did not provide information that is quantitatively useful in the standard-setting process.  Since publication of the 1986 $O_3$ criteria document, however, results have become available from a substantial number of well-conducted, individual-level studies and aggregate-level, time-series studies.  New statistical

techniques also have become available to deal with confounders that were not appropriately considered when the data were first analyzed. In the following sections, the more recent studies and reanalyses of older studies will be evaluated collectively.

### 7.4.1.2 Individual-Level Studies

The studies discussed in this section fall into three main categories: (1) summer camp studies, (2) exercise studies, and (3) daily life studies. Summer camp studies involve collection of sequential (usually daily) data on lung function, respiratory symptoms, and environmental conditions over the course of 1 or 2-week attendance at camps. Exercise studies are unique in that lung function and respiratory symptoms are measured before and after each of a series of discrete exercise events in the presence of ambient air pollution. Daily life studies measure lung function, respiratory symptoms, and exacerbation of existing respiratory diseases, along with environmental variables at regular intervals in the course of normal daily activities of a population. These include studies of healthy adults and school-aged children as well as studies of individuals with preexisting disease (e.g., asthma). Medication use also may be monitored in asthmatics. Studies of this kind that focus on exacerbation of asthma symptoms usually have been referred to as panel studies.

The important differences among the three study types relate primarily to issues of exposure assessment. Because subjects usually are out-of-doors or in well-ventilated cabins, exposure estimation errors are minimized in camp and exercise studies. In contrast, larger exposure estimation errors may occur in daily life studies. Camp and daily life studies enable assessment of the effects of cumulative $O_3$ exposures, whereas exercise studies limit attention to rather brief exposures. Exercise studies offer the potential of assessing individual $\dot{V}_E$ values and $O_3$ concentrations during the relevant exposure period, whereas such assessments are more difficult in camp and daily life studies.

Although the study designs differ in some ways, the central design feature of all of these study types is the collection of repeated measurements on individuals. This feature is exploited in data analysis by having each subject serve as his or her own control. For continuous outcomes such as lung function, subject-specific linear regressions are usually performed with lung function (or change in lung function) as the outcome variable and $O_3$ or other environmental factors as the explanatory variable. The regression slope is a measure of individual lung function response to $O_3$. The mean slope across individuals often is used as a measure of the average population response. A more statistically valid approach involves computing the mean slope with weighting proportional to the inverse variances of the individual slopes. An alternative approach has been to use analysis of covariance methods to fit a population-pooled slope and separate, subject-specific y-intercepts. To date, no studies have used nonlinear (e.g., quadratic) models in relating lung function decrements to $O_3$ exposures, which in chamber studies have been shown to better describe the functional relationship between $O_3$ exposures and lung function decrements (see Chapter 9, Section 9.3.4).

### Issues in the Interpretation of Individual Level Studies

The most basic question affecting the interpretation of acute $O_3$ epidemiology studies is whether (and if so, to what extent) the associations observed between $O_3$ and decreased pulmonary function are causally related to $O_3$ and not merely due to confounding by some other factor (e.g., temperature, allergens, time trends in spirometry, or other pollutants).

By definition, a confounder is an unmeasured or unaccounted-for variable that has an effect on the measured outcome and also is correlated with $O_3$ concentrations.  Variables that satisfy only one of these two conditions are not confounders.  For example, a variable that affects lung function but is independent of $O_3$ would add variation to lung function measurements but would not confound an $O_3$/lung function analysis, and a variable that correlates with $O_3$ but does not directly affect lung function (in the range of measurements) would not confound an analysis of $O_3$ effects.  Other variables might modify the effect of $O_3$ on lung function, thereby increasing or decreasing the $O_3$ effect under the conditions of study.  Epidemiologists refer to this latter phenomenon as "effect modification".  The presence of effect modification does not bias the results of a study, but can provide insights into the range of effect magnitudes (e.g., slope of lung function decrement on $O_3$ level) that occur under varying environmental conditions.

Ambient air temperature often exhibits a moderate to high correlation over time with $O_3$ in acute epidemiology studies due, in part, to the dependence of $O_3$ formation rate on light intensity.  Among the studies reviewed in this section, correlations ranging from □0.06 to 0.90 (mean = 0.51) have been reported.  Correlations between $O_3$ and RH, when reported, have been in the range □0.4 to □0.6.  Several human chamber studies have examined the possible direct effects of temperature and RH on lung function independent of $O_3$, with somewhat mixed results (Stacy et al., 1982; Folinsbee et al., 1985; Eschenbacher et al., 1992).  Two studies reported increases in $FEV_1$ at high temperature (30 and 37 □C) and 60% RH (Stacy et al., 1982; Eschenbacher et al., 1992), whereas the other reported no effect on $FEV_1$ at 35 □C, and a decrease at 40 □C (Folinsbee et al., 1985).  Referring to results of acute $O_3$ epidemiology studies, Eschenbacher and colleagues (1992) concluded,  based on their own results, that "the associations found between ambient $O_3$ and daily changes in ventilatory function cannot be attributed to the heat and humidity stress often associated with high $O_3$ concentrations."  Temperatures observed in the epidemiology studies reviewed in the present section primarily have been below 30 □C, with occasional peaks as high as 35 □C.  It should be noted that subjects studied epidemiologically usually will have had an opportunity to acclimate to ambient temperatures prior to or soon after the start of the study.  In any event, given the laboratory findings, a significant confounding role for temperature in these studies seems unlikely.  The possibility that changes in ambient temperature may introduce biases in measured lung volumes (e.g., through inaccurate correction of volumes to body temperature) is an issue that deserves further study.

Exposure to specific allergens can influence lung function in individuals who have diseases characterized by IgE-mediated, Fc interactions (i.e., atopy) and may also affect individuals who have an atopic tendency (e.g., as assessed by positive prick skin test or serum levels of total IgE) without diagnosed clinical disease.  Raizenne et al. (1989) detected positive reactions to one or more allergens by skin prick in 49% of 96 young nonasthmatic females enrolled in a summer camp study.  Few data are available on the correlation between $O_3$ and allergen levels during acute epidemiology studies.  However, because both variables to some are extent influenced by weather patterns, some correlation seems likely.  Thus, a possible confounding role of airborne allergens in such studies cannot be ruled out.  Because of the specific nature of individual antigen sensitization and uncertainty regarding the full set of relevant allergens in a given setting, attempts to measure and to control statistically for allergen levels on a group level in epidemiology studies may not be very effective.

The potential effects of time trends in spirometry due to training effects are also of concern. There have been several recent studies that have looked at time trends in serial lung function measurements (mainly $FEV_1$ and PEFR) independent of air pollution effects (Raizenne et al., 1989; Avol et al., 1990; Hoek and Brunekreef, 1992). In each case, average $FEV_1$ measurements have been observed to decline steadily over the first few measurements and then to stabilize or recover slightly to a flat pattern. Average FVC measurements follow a similar pattern. In contrast, PEFR often has been observed to increase steadily over successive measurements. Similar patterns have been observed in studies with intervals between lung function measurements ranging from 12 h to 1 week. The consistency of these observations across studies suggests that they represent real phenomena that should be recognized in designing and analyzing studies involving repeated lung function measurements. However, time trends will result in confounding of $O_3$ effects only if, by chance, the trend correlates with temporal variations in $O_3$ concentrations. Such chance correlations could be either positive or negative and, if present, would have a larger impact (i.e., produce an undesirable degree of confounding) on studies in which all subjects begin the study simultaneously and have few follow-up measurements. Studies that focus on daily changes in lung function may be less impacted by this phenomenon.

It is also important to consider the roles of other pollutants as possible confounders or effect modifiers. In the studies to be reviewed in this section, most copollutants (e.g., $SO_2$, $NO_2$, sulfate, and acid aerosols) were present at levels well below those that have produced lung function decrements in healthy subjects following short-term exposures in chamber studies (see Section 7.2.6). In contrast, an extensive and growing database is available from chamber studies documenting the independent acute effects of ambient-level $O_3$ on lung function (see Section 7.2.1). Although direct lung function effects of other pollutants at typical ambient concentrations seem unlikely, it has been suggested that the effects of $O_3$ may be potentiated by coexposure or previous exposure to other pollutants, most notably acid aerosols (Spektor et al., 1988b). Some data from animal studies suggest interactive effects of $O_3$ and acid exposures for certain pulmonary outcomes (see Chapter 6). However, to date, analyses directed towards this phenomenon in field studies of human lung function (via analysis of the relationship between acid aerosol levels and residuals from regressions of lung function on $O_3$) have proven negative (Spektor et al., 1988a,b). That is, after controlling for the influence of $O_3$, no significant association between acid aerosol peaks and lung function decrements has been observed. Acid aerosol episodes, which often occur coincident with high $O_3$ levels in the summer in the northeastern United States, may extend for several hours or days. However, the possible potentiating effects of prolonged acid peaks on $O_3$ effects are still poorly understood. Some recent epidemiological studies (Pope et al., 1991; Pope and Dockery, 1992; Koenig et al., 1993; Roemer et al., 1993) have reported significant associations between lung function decrements and ambient particulate matter (PM) concentrations. Although no supporting evidence for lung function effects due to ambient-level particle exposure is yet available from human or laboratory animal controlled studies, the possibility of some confounding by particles in the studies reviewed here cannot be ruled out.

In epidemiologic studies, activity levels are difficult to control and to measure, although this varies with study type (see below). Chamber studies have shown clearly that lung $O_3$ doses and associated functional effects increase as a function of physical activity level (Hazucha, 1987). Epidemiologic study designs often have been chosen that result in relatively

high subject activity levels (exercise studies and camp studies), but generally the studies have been carried out without quantitative information on $\dot{V}_E$ distributions across subjects and time.

Variations in activity levels will introduce variability in the relationship between personal exposure and personal dose. If this variability occurs primarily between subjects, it will result in differing $O_3$ doses to people exposed to the same $O_3$ level and yield differences in response that may be misinterpreted as $O_3$ sensitivity variations. If variability in activity levels occurs over time for a given subject, it will add error to the functional relationship linking lung function and $O_3$ exposure. In either case, the influence of activity level variability is to add dose estimation error (or misclassification). Estimates of $\dot{V}_E$ based on heart rate measurements can be derived using subject-specific calibrations under representative ranges of exercise levels and types (Samet et al., 1993; Raizenne and Spengler, 1989). However, the utility of such $\dot{V}_E$ estimates for reducing dose-misclassification errors in acute $O_3$ epidemiology studies has not yet been demonstrated (Kinney, 1986; Spektor et al., 1988b; Raizenne and Spengler, 1989). This is partly due to the logistical difficulties associated with collecting accurate data and also may be due to the fact that, for a given subject, $\dot{V}_E$ variations across days are usually small in comparison to $O_3$ concentration variations. The same issues arise in the context of $O_3$ exposure misclassification in "daily life" studies (see below), where outdoor $O_3$ concentrations are used to estimate exposures of subjects who spend substantial amounts of time indoors during the period over which lung function measurements take place.

### *Camp Studies of Lung Function in Children*

Summer camp studies provide the most extensive and reliable information on the acute pulmonary effects of $O_3$ under natural conditions. Camp studies involve the collection of sequential (usually daily) data on lung function on each of a large number of children, along with concurrent measurements of $O_3$ exposures and other environmental factors over the course of a single-week or multiweek summer camp. Data analyses usually consist of estimating the linear association between lung function and environmental variables on an individual basis (allowing each subject to serve as his/her own control) and then testing the mean population association for statistical significance. As noted, summer camps offer the significant advantage that subject exposures are especially well estimated because they are based on on-site, outdoor $O_3$ monitoring. In addition, these studies assess the pulmonary effects of natural diurnal patterns of $O_3$ exposures, which often involve broad daytime peaks.

Since the last $O_3$ criteria document (U.S. Environmental Protection Agency, 1986), eight camp studies have been reported. Design characteristics and results are summarized in Table 7-15. Six of these studies have focused solely on normal (i.e., nonasthmatic) children, one focused on asthmatics exclusively (Thurston et al., 1995), and one used both normal and asthmatic children (Raizenne et al., 1987). Although methods and results varied somewhat across studies, this group of studies collectively provides substantial evidence for associations between ambient $O_3$ exposures, together with other pollutants, and acute decrements in lung function. Interpretation of these associations as causal is supported by evidence of biological plausibility. For example, the well-documented direct effects of $O_3$ on lung function in human chamber studies; the evidence, also from chamber studies, indicating a lack of direct effects of other collinear environmental factors (e.g., temperature and acid aerosols) at the levels at which these factors occur in the camp studies; exposure-response relationships; and consistency across studies all provide strong support. Camp studies involving asthmatic

children generally have yielded lung function/$O_3$ associations that are similar in absolute magnitude to those observed in nonasthmatics (Raizenne et al., 1987;

## Table 7-15. Acute Effects of Photochemical Oxidant Pollution: Lung Function in Camp Studies[a]

| Pollutants/Environmental Variables | Study Description | Results and Comments | Reference |
|---|---|---|---|
| Hourly $O_3$ ranged from 10 to 110 ppb. $SO_2$, $NO_x$, $O_3$, $SO_4^=$, $H_2SO_4$, pH, $PM_{10}$, $PM_{2.5}$, RH, temperature, barometric pressure, and wind speed and direction also were measured. | Effects of pollutants and other environmental variables on symptoms and lung function were examined in children attending a summer camp at Lake Couchiching, about 100 km north of Toronto, ON. Study was conducted June 30 through July 8, 1983; n = 52, 23 nonasthmatics (11 males, 12 females) and 29 asthmatics (16 males, 13 females), avg. age = 12.1 years. Symptom questionnaire and function tests given twice daily to each child between 7:30 and 9:30 a.m. and 4:30 and 6:30 p.m. Children's activity levels not estimated. | Strongest association between lung function and environmental variables was in nonasthmatics, with FVC decrements significantly correlated (p < 0.01) with lagged-avg $SO_4$, $PM_{2.5}$, and temperature. Unlagged PEFR significantly correlated with 1 h $O_3$. Also, significant association of temperature with all lung function indices in nonasthmatics, but not in asthmatics. Coefficient of variation stable across morning and evening tests. | Raizenne et al. (1987)[b] |
| 1-h $O_3$ ranged from < 10 to 143 ppb; max 1-h $O_3$ > 100 ppb on 14 days of total study (6 weeks). For other pollutants and variables measured, see Raizenne et al. (1987) because same protocol used here as in that study. | (a) Effects of pollutants and other environmental variables on lung function were examined in girls attending one of three 2-week Girl Guide camp sessions on the north shore of Lake Erie. Cohort (n = 104) screened by MC and skin-prick tests for 10 common respiratory allergens; five asthmatics withdrawn from the study (n = 99). Lung function tests administered twice daily. Children's activity levels not estimated. <br><br> (b) Subset of 12 girls (7 MC+, 5 MC-) studied pre- and postexercise on 1 low-pollution (control) day and 1 peak-pollution day (episode, 1 h $O_3$ > 139 ppb, $SO_4^=$ > 80 g/m³). | (a) Associations between aerometric data and lung function measurements were not reported by pollutant in this reference. Aggregate analysis for full study not reported. Lung function changes reported for 5 episode days only. $FEV_1$ decrements statistically significant on 2 episode days for methacholine- nonresponsive subjects. <br><br> (b) Group mean FVC increased postexercise in the n = 12 subset by 40 mL, 71 mL in MC and 17 mL in MC+. Pollution effect not statistically significant. | Raizenne et al. (1987, 1989)[b] |
| Continuous 1-h $O_3$, $SO_2$, $NO_2$, and acid aerosols (as $H_2SO_4$); 1-h $O_3$ range = 40-143 ppb; max 12-h acid particle concentration = 28 g/m³ in one episode; FP $SO_4^=$ 100 g/m³ for peak hour. | Time-activity model used to evaluate likely cumulative (6 h) $O_3$ and $H_2SO_4$ exposures/doses experienced by children in above Lake Erie Girl Guide camp study, summer 1986. See Raizenne et al. (1987, 1989) for protocol and related information. Dosimetry model was developed for relating heart rate (from a 12-min, graded, cycle ergometer test) to ventilation and then to $O_3$ and $H_2SO_4$ concentration. Also, five randomly selected children wore portable heart-rate monitors, providing data for use in the dosimetric model. | Application of the dosimetry model used to estimate individual 6-h cumulative doses for $O_3$ and $H_2SO_4$ exposures on 1 control and 1 episode day indicated negative trend in lung function (PEFR) as cumulative dose increased for both $O_3$ and $H_2SO_4$, although slopes for each did not differ significantly from zero (p > 0.10). | Raizenne and Spengler (1989)[b] |

**Table 7-15 (cont'd).  Acute Effects of Photochemical Oxidant Pollution:
Lung Function in Camp Studies[a]**

| Pollutants/Environmental Variables | Study Description | Results and Comments | Reference |
|---|---|---|---|
| Max 1 h $O_3$ ranged from 40 to □100 ppb, with max 1 h > 80 ppb on 9 of 27 days of $O_3$ recorded.  $O_3$, $SO_4$, $H_2SO_4$, $PM_{15}$, $PM_{2.5}$, temperature, humidity, and wind speed and direction measured.  Levels not reported for $SO_2$, pH, $NO_3$, and $NH_4^+$. | Effects of pollutants and other environmental variables on respiratory functions in 91 children (53 boys, 38 girls; ages 8-15) attending 2 to 4 weeks of summer camp at Fairview Lake, NJ.  Subsets were n = 37 for all 4 weeks, n = 34 for first 2 weeks only, n = 20 for last 2 weeks only.  Symptom questionnaire; FVC, $FEV_1$, MMEF, and PERF (by spirometry) were measured once each test day (most of days in camp) sometime between 11:00 a.m. and 6:30 p.m.  All children had validated spirometric data for □7 days of their 2- or 4-week camp stay.  Activity levels of the children were not estimated.  Respiratory health status determined by parental questionnaire only.  Children slept in screened-in shelters but otherwise were exposed to ambient air 24 h/day.  Average regression slopes for respiratory function vs. max 1-h $O_3$ concentration reported for the full cohort, for boys and girls separately, and for subsets in attendance for all 4 weeks and for respective 2-week sessions.  Regressions also repeated for data below 80 and 60 ppb 1-h $O_3$, and for data with THI <78 □F. | Average regression slopes ($\pm$ SE) were □1.03 $\pm$ 0.24 and □1.42 $\pm$ 0.17 mL/ppb for FVC and $FEV_1$, respectively; and □6.78 $\pm$ 0.73 and □2.48 $\pm$ 0.26 mL/s/ppb for PEFR and MMEF, respectively.  Most slopes of regression significant at $p < 0.05$ (differences from zero).  Not clear if slopes for data subsets significantly different from each other (e.g., function vs. $O_3$ < 60 ppb and function vs. $O_3$ < 80 ppb).  No formal analysis performed for possible concentration threshold. | Spektor et al. (1988a)[b] |

# Table 7-15 (cont'd).  Acute Effects of Photochemical Oxidant Pollution: Lung Function in Camp Studies[a]

| Pollutants/Environmental Variables | Study Description | Results and Comments | Reference |
|---|---|---|---|
| Maximal 1 h $O_3$ concentrations ranged from approximately 40 to 150 ppb over the course of the study.  12-h average aerosol acidity measurements ranged from near 0 to 18.6 $\mu g/m^3$ ($H_2SO_4$ equivalent).  Temperature and RH measured, but levels not reported.  THI reached a maximum of 81 ⬜F.  All environmental measurements were made on site. | Effects of $O_3$ and other environmental variables on lung function studied in a group of 46 children (13 girls, 33 boys; ages 8-14) at a 4-week, 1988 summer camp in southwestern New Jersey (Fairview Lake).  Same location used in previous camp study by same investigators.  Subjects had no history of lung diseases or atopy.  Two lung function measurement periods each day (a.m. and p.m.) along with collection of respiratory symptom data.  Data collected during or after periods of rain were excluded from analysis.  Results for FVC, $FEV_1$, $FEV_1/FVC$, $FEF_{25-75\%}$, and PEFR reported.  Linear day-of-study trends were examined for lung function.  Subject-specific linear regressions were performed relating lung function in a.m., p.m., and p.m. ⬜ a.m. differences to $O_3$ averaged over various periods.  Average slopes across subjects were tested for significant differences from zero.  Regressions were repeated after excluding days with $O_3$ at or above 120 ppb.  Regression residuals were tested for correlation with THI and $H^+$ concentrations. | No significant linear day-of-study effect seen for any of the lung function variables tested, but the linear model may not have been optimal for testing this effect.  In a subset of 35 subjects with at least 2 consecutive days of lung function measurements, mean regression slopes of a.m. lung function variables on previous-day mean or 1-h maximum $O_3$ were all significantly negative (e.g., mean slope of $FEV_1$ on 1-h maximum $O_3$ was ⬜0.50 $\pm$ 0.12 mL/ppb).  These results suggest a possible carry-over effect from previous-day $O_3$ exposures.  In the full set of 46 subjects, regressions of p.m. lung function on previous-hour $O_3$, maximum 1-h $O_3$ for same day, or average $O_3$ for day were significantly negative in most cases (e.g., mean slope of $FEV_1$ on previous-hour $O_3$ was ⬜1.60 $\pm$ 0.30 mL/ppb).  All regressions of the p.m. ⬜ a.m. lung function differences on intervening $O_3$ concentrations were significantly negative (e.g., mean slope of $FEV_1$ on mean $O_3$ between a.m. and p.m. measurements was ⬜0.63 [$\pm$0.09] mL/ppb).  No correlation seen between regression residuals and THI or $H^+$ concentrations, indicating there was no remaining effect of these variables with lung function after accounting for $O_3$.  However, no models were fit that included $O_3$ and these variables simultaneously, nor were interaction effects tested for.  The strong and consistent associations between lung function decrements and $O_3$ concentrations in this study contrast with results reported from studies in Canada and California at similar levels of $O_3$. | Spektor et al. (1991) Spektor and Lippmann (1991) |

## Table 7-15 (cont'd).  Acute Effects of Photochemical Oxidant Pollution: Lung Function in Camp Studies[a]

| Pollutants/Environmental Variables | Study Description | Results and Comments | Reference |
|---|---|---|---|
| 1-h $O_3$ preceding lung function measurements ranged from 25 to 245 ppb.  Pollutants measured on site included $O_3$; $NO_2$ (range: 0 to 40 ppb), $SO_2$ (range:  1 to 8 ppb); and fine (mean = 23.9 $\mu g/m^3$), coarse (mean = 36.6 $\mu g/m^3$), and total (mean = 59 $\mu g/m^3$) $PM_{10}$ mass.  Temperature averaged 21.5 $°C$ (range: 13.5 to 25.5 $°C$) and RH averaged 43.3%. | Effects of $O_3$ and other environmental factors on lung function examined in 43 children (24 female, 19 male; ages 7-13) attending 1 of 3 sequential weeks (three subjects stayed an additional week) of summer camp in the San Bernardino Mountains of California.  Camp was at 5,710 ft above sea level.  Lung function measured by spirometry up to three times daily on each subject; analytical measures included FVC, $FEV_1$, and PEFR.  No report of respiratory data derived from questionnaires. Subject activity levels prior to lung function testing were not characterized.  Campers slept in well-ventilated cabins. Subjects came mostly from homes in the Los Angeles Basin, and thus were likely to have been exposed to high $O_3$ levels prior to camp.  Simple linear regression models were fit on an individual basis (subject-specific slopes) and by pooling across individuals (common population slope) to determine the linear relations between the three lung function variables and various $O_3$ metrics (1-h average preceding hour of spirometry, 1-h average 2 h previous to hour of spirometry, or 6-h average preceding spirometry). The common slope model was repeated separately for morning, noon, and evening lung-function measurements, and separately for data with 1-h $O_3$ levels above and below 120 ppb.  Multiple regression models were fit that included $O_3$ along with temperature, RH, and coarse and fine PM mass. | The population-pooled regression slopes ($\pm$SE) of FVC and $FEV_1$ on previous hour $O_3$ were $-$0.40 ($\pm$0.10) and $-$0.38 ($\pm$0.09) mL/ppb, respectively (p < 0.0001 in both cases); for PEFR, the regression slope was $-$0.13 ($\pm$0.36) mL/s/ppb (not significant).  Similar, though slightly more negative, slopes were obtained using 2-h and 6-h average $O_3$.  Interpretation of differences across the three $O_3$ metrics is substantially hampered by the high correlations among them (r $\geq$ 0.90).  When temperature, RH, and coarse and fine PM mass were included with $O_3$ in multiple regression models, the $O_3$ slopes increased in absolute magnitude to $-$0.68 ($\pm$0.16) and $-$0.76 ($\pm$0.15) mL/ppb for FVC and $FEV_1$, respectively, and to $-$1.91 ($\pm$0.63) for PEFR. Technical problems with the temperature sensor in the first week of the study did not appear to influence these results.  Data were split on the basis of whether or not the maximum 1-h $O_3$ concentration in the 6 h preceding spirometry was above 120 ppb.  Regression slopes relating lung function and previous 1-, 3-, and 6-h average $O_3$ were more negative in the high concentration stratum.  This result is consistent with the nonlinear (e.g., quadratic) relationships between lung function and $O_3$ exposure observed in chamber studies.  Because levels of pollutants other than $O_3$ were quite low ($NO_2$ and $SO_2$), and/or were uncorrelated with $O_3$ levels (PM), the regression results reported from this well-conducted study are likely to represent real influences of $O_3$ on lung function. | Higgins et al. (1990); Gross et al. (1991) |

# Table 7-15 (cont'd).  Acute Effects of Photochemical Oxidant Pollution:
## Lung Function in Camp Studies[a]

| Pollutants/Environmental Variables | Study Description | Results and Comments | Reference |
|---|---|---|---|
| Daily maximum $O_3$ concentrations ranged from approximately 60 to 160 ppb (derived visually from figure presented in paper).  Other pollutants measured on site included $SO_2$, $NO_2$, CO, total hydrocarbons, and size-segregated PM mass.  Aside from $O_3$, all gaseous pollutant levels reported to be very low (data not presented).  24-h TSP concentrations ranged from 18 to 54 $\mu g/m^3$.  Airborne allergen data collected.  Temperature ranged from 10 to 15 °C at night and from 25 to 35 °C during day.  RH ranged from 30 to 45% at night and from 5 to 20% during day. | Effects of $O_3$ and other environmental variables on lung function examined in 293 children (139 girls, 154 boys; ages 8-17) attending one of six 1-week camp sessions at a summer camp located in the mountains near Idyllwild, CA, 190 km southeast of Los Angeles (altitude: 1,570 m).  Lung function measured twice daily on each camper (a.m.: 0730 to 0930; p.m.: 1600 to 1930).  Analyses presented for FVC, $FEV_1$, PEFR, and $FEF_{25-75\%}$.  Symptom questionnaires completed prior to each test.  Used repeated measures analysis of variance model to test for day-of-study and a.m./p.m. effects on lung function independent of pollution concentrations.  Linear regressions of morning, afternoon, and p.m. − a.m. difference of lung function on $O_3$ were performed with simultaneous control of day and a.m./p.m. effects.  Upper and lower quartiles of distribution of individual $FEV_1/O_3$ regression slopes were examined with respect to subject characteristics.  Changes in $FEV_1$ over several days analyzed in relation to intervening integrated $O_3$ concentrations. | Significant day-of-study effect observed for FVC and $FEV_1$ characterized by steady drop over first few days of measurement, followed by partial reversal later in week.  For PEFR, p.m. measurements were significantly higher than a.m. measurements.  Controlling for day and a.m./p.m. effects, the authors reported that no consistent $O_3$ effects on lung function were observed.  The a.m. lung-function measurements had a significant positive correlation with $O_3$ averaged over the previous 1, 8, or 24 h.  The p.m. measurements reported to have no correlation with $O_3$.  The p.m. − a.m. lung function differences were negatively correlated with previous 8-h average $O_3$ concentrations, but not with previous 1-h $O_3$ concentrations.  No quantitative results reported for the above lung function/$O_3$ findings.  There were no discernable differences between subjects in the upper and lower quartiles of the distribution of individual regression slopes of a.m. − p.m. $FEV_1$ difference on previous 1 h $O_3$.  Regressions of change in $FEV_1$ over several days (four separate intervals ranging from approximately 8 h to approximately 80 h) with integrated $O_3$ concentrations yielded negative slopes ranging from −0.41 to −1.46 mL/ppb, one of which was statistically significant.  The time-trends in FVC and $FEV_1$ measurements observed in this study are qualitatively consistent with those seen in some other summer camp studies.  The lack of consistent negative slopes relating lung function with $O_3$ concentrations contrasts with other, eastern U.S., summer camp studies at similar $O_3$ levels. | Avol et al. (1990) Avol et al. (1991) |

## Table 7-15 (cont'd).  Acute Effects of Photochemical Oxidant Pollution: Lung Function in Camp Studies[a]

| Pollutants/Environmental Variables | Study Description | Results and Comments | Reference |
|---|---|---|---|
| $O_3$ data collected at a site 8 mi from camps. Daily 1-h $O_3$ maxima ranged from approximately 40 ppb to approximately 200 ppb.  12-h aerosol acidity concentrations ranged between 14 and 360 neq/m³. Temperature and RH data obtained from a nearby site. | Report of data collected during two simultaneous summer camps located 2 mi apart in central New Jersey in 1988. 34 subjects were studied, including 20 camp counselors (ages 14-35) and 14 campers (ages 9-13).  Study spanned 19 days.  Spirometry and respiratory symptom data collected each afternoon.  Analysis of FVC, $FEV_1$, and PEFR in relation to $O_3$ and temperature using linear regression within camps and subject types (i.e., counselors vs. campers). | Regressions of lung function on 1-h and 8-h average $O_3$ within several subject subsets yielded inconsistent results, with some mean slopes apparently significantly positive, and one negative mean slope, highlighted by authors, of borderline significance ($p < 0.10$). | Berry et al. (1991) |
| Daily 1-h maximum $O_3$ concentrations ranged from 70 to 160 ppb in 1991 and from 10 to 63 ppb in 1992.  On-site measurements also made for acid aerosols (approximately 20 to 110 nmoles/m³ in 1991 and 15 to 55 nmoles/m³ in 1992) and temperature (between 21 and 32 °C over 2 years). | Effects of $O_3$ and acid aerosols on peak flow, respiratory symptoms, and medication usage in asthmatic children evaluated at two 1-week summer camps (June of 1991 and 1992) in the Connecticut River Valley.  Fifty-two and 55 subjects were studied in 1991 and 1992, respectively, ranging in age from 7-13.  Peak flow measured twice daily (approximately 9:00 a.m. and 5:00 p.m.).  Combining data from the two studies, individual regressions of daily change in $FEV_1$ on $O_3$ or $H^+$ concentrations were performed. | In subjects without asthma exacerbations during the camps, statistically significant, negative mean slopes were found relating PEFR and $O_3$ or $H^+$ concentrations. The correlation between these two pollutants was not reported.  The mean slopes were 2.3 ($\pm 0.7$) mL/s/ppb for $O_3$, and 1.2 ($\pm 0.6$) mL/s/nmol/m³ for $H^+$.  In the case of $O_3$, a scatter-plot with PEFR demonstrated an apparently linear trend.  In contrast, the $H^+$ regression results appeared to be driven entirely by one data point. | Thurston et al. (1995) |

[a]See Appendix A for abbreviations and acronyms.
[b]Cited in U.S. Environmental Protection Agency (1992).

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Thurston et al., 1995); however, the health significance of a given drop in $FEV_1$ may be greater for those with preexisting, compromised respiratory function.

Although similar study designs have been employed in most of the camp studies summarized in Table 7-15, differences in analytical methods have made quantitative comparisons between studies difficult to interpret. In particular, it has not been clear to what extent differences in results across studies may be due to differences in study characteristics (e.g., $O_3$ effect potentiation by other pollutants and activity levels) as opposed to differences in data analysis methods.

For better comparison in this document, data from six of the camp studies summarized in Table 7-15 were reanalyzed using uniform analytical methods. For each study, afternoon lung function data ($FEV_1$) were regressed on concurrent 1-h $O_3$ concentrations using an analysis of covariance model that included subject-specific intercepts and a single, pooled $O_3$ slope. Although intersubject variation in responses to $O_3$ would be expected on the basis of controlled chamber study results (see Section 7.2), a common-slope model was chosen for this analysis because emphasis was placed on estimating the average response in each study population. The study-specific slopes computed with this model ranged from 0.19 to 1.29 mL/ppb across the six studies (Table 7-16). All but one of these slopes were statistically significant (p < 0.02). When data for all six studies were pooled, a slope of 0.5 mL/ppb was observed. The slope from the 1988 Fairview Lake, NJ, study (1.29 mL/ppb) was greater in absolute magnitude than the slopes from the other studies (which ranged from 0.19 to 0.84 mL/ppb). Overall, however, these pooled results indicate a quantitative consistency among studies that is not as readily apparent in the absence of the combined analysis.

### Table 7-16. Slopes from Regressions of Forced Expiratory Volume in One Second on Ozone for Six Camp Studies[a]

| Study Name | Slope ± SE (mL/ppb)[b] | p-Value | Reference |
|---|---|---|---|
| Fairview Lake, 1984 | 0.50 ± 0.16 | 0.002 | Spektor et al. (1988a) |
| Fairview Lake, 1988 | 1.29 ± 0.27 | 0.0001 | Spektor et al. (1991) Spektor and Lippmann (1991) |
| Lake Couchiching | 0.19 ± 0.44 | 0.66 | Raizenne et al. (1987) |
| Lake Erie | 0.29 ± 0.10 | 0.003 | Raizenne et al. (1987, 1989) |
| San Bernardino Mountains | 0.84 ± 0.20 | 0.0001 | Higgins et al. (1990) Gross et al. (1991) |
| Pine Springs Ranch | 0.32 ± 0.13 | 0.013 | Avol et al. (1990, 1991) |
| All studies | 0.50 ± 0.07 | < 0.0001 | |

[a]For each study, data were analyzed in one regression model that included a pooled $O_3$ slope and separate subject-specific intercepts. See Appendix A for abbreviations and acronyms.
[b]Slope is the weighted mean of six study-specific slopes. The SE is the weighted SE of mean slope.

It is not clear why the 1988 New Jersey study yielded a larger slope than the other studies. Possible explanations include greater subject activity levels (resulting in higher $O_3$ doses at a given exposure level), potentiation of the $O_3$ effect by other pollutants (such as acid aerosols), the relative absence of $O_3$ tolerance in the New Jersey study, or confounding by

airborne allergens.  There are no firm data on activity levels across the six studies.  Thus, whereas this factor surely contributes to the random variability within and between studies, it is not known whether activity levels were substantially and systematically higher in the 1988 New Jersey study.  Potentiation of the $O_3$ effects on lung function in asthmatics by acid aerosols has been demonstrated in a chamber study in which $O_3$ exposure was administered 1 day following a 3-h exposure to 100 $g/m^3$ $H_2SO_4$ (Utell et al., 1994).  Although the relevance of these data to the nonasthmatic subjects who experienced much lower acid levels at northeastern summer-camps is not clear, they do demonstrate that potentiation can occur between these pollutants.  However, this factor alone cannot explain the observed differences across camp results, because a camp study in southern Ontario (Raizenne et al., 1989), which yielded relatively low $FEV_1$ slopes on $O_3$, experienced sulfate aerosol levels that were comparable to those seen in New Jersey.  Similarly, whereas tolerance due to prior exposures to high $O_3$ levels has been suggested as an explanation for the smaller slopes seen in the California studies, a lower subject activity level has been suggested to explain the smaller slopes in southern Ontario.  Data have not been reported on comparative levels of airborne allergens during the various camp studies.  None of the subjects in the 1988 New Jersey study reported a history of asthma or atopy, minimizing the likelihood of confounding by airborne allergens.  However, given the lack of allergen data and the potential for substantial numbers of "silent hyper-responders" (Raizenne et al., 1989), this possibility cannot be completely discounted.  Thus, no one factor seems adequate to explain the differences in results across studies.  Quite possibly, these differences reflect the combined influence of several of the factors discussed above.  Indeed, given the many possible sources of camp-to-camp variability, it is surprising that results are as consistent as they are across six studies by three investigative groups.

Several investigators have reported regression results for 1-h average $O_3$ and for longer averaging times (e.g., 6 to 8 h) (Higgins et al., 1990; Avol et al., 1990, 1991; Spektor et al., 1988a, 1991).  In general, similar results have been obtained regardless of the averaging time.  Attempts to draw conclusions regarding the relative importance of short-term peaks and longer term averages from such analyses have been hampered by the high degree of correlation between 1-h and multihour averages.  Until better analytical methods are found for dealing with this problem, comparative results will remain difficult to interpret.

### *Lung Function in Exercising Subjects*

This subsection discusses studies involving lung function measurement immediately before and after a series of discrete outdoor exercise activities in the presence of air pollution.  This design is similar in principle to the ambient chamber studies conducted in the early 1980s (see Section 7.3), in which subjects exercised under a specified protocol in a chamber ventilated with ambient air.  Here, however, there is typically less control imposed over exercise duration and intensity, and less assessment of achieved $\dot{V}_E$.  Compensating to some extent for this diminished control is the relative ease of collecting numerous repeated measurements at varying ambient $O_3$ levels for the same subjects, improving the precision of concentration-response estimation.  In contrast to camp studies, duration of relevant $O_3$ exposure is assumed to be known, as it is defined by the length of each exercise event.

Results from five exercise studies (Selwyn et al., 1985; Spektor et al., 1988b; Hoek and Brunekreef, 1992; Hoek et al., 1993a; Braun-Fahrlander et al., 1994; Brunekreef et al., 1994) are summarized in Table 7-17.  One of the studies (Selwyn et al., 1985) was discussed

in the previous $O_3$ criteria document (U.S. Environmental Protection Agency, 1986) but is reviewed again here because of its apparent consistency with the more recent study of Spektor et al. (1988b).

Certain design variations across studies are worth noting. In the Houston study, each of 24 recreational runners performed spirometry before and after a series of approximately 28 runs on a track from late spring to early fall (Selwyn et al., 1985). Each run was 3 mi long, and each subject attempted to maintain a similar heart rate across all runs. Minute ventilation was not assessed. In the study carried out in Tuxedo, NY, adult runners and walkers were allowed to choose their own exercise level and duration, but again were encouraged to maintain a steady heart rate for the duration of the study (Spektor et al., 1988b). Minute ventilation of each subject while running was estimated by measurement of $\dot{V}_E$ during a treadmill test that achieved a heart rate typical of that subject's experience while running. In the study of 128 Swiss school children (Braun-Fahrlander et al., 1994), 10-min exercise periods on a cycle ergometer were utilized on four to six occasions over a 6-mo period.

## Table 7-17.  Acute Effects of Photochemical Oxidant Pollution: Lung Function in Exercising Subjects[a]

| Pollutants/Environmental Variables | Study Description | Results and Comments | Reference |
|---|---|---|---|
| 1-h $O_3$ concentration ranged from 21 to 124 ppb, max THI = 78 □C; max acidic aerosol (as $H_2SO_4$) = 9 □g/m$^3$ during study. $SO_2$, $NO_x$, $PM_{15}$, $PM_{2.5}$, $SO_4^=$, $NO_3$, $NH_4^+$, temperature, and RH measured but not reported. | Effects of $O_3$ on respiratory function and symptoms examined in 30 nonsmoking adults (2 of 10 non-Caucasian females) exercising almost daily outdoors (Tuxedo, NY) for 15 to 55 min (average ca. 30 min) from July to early August 1985.  Pre- and postexercise lung function measured, and questionnaire answered postexercise.  Pulse rate, calibrated to $V_E$ indoors, taken postexercise.  Exercise regimen self-selected but constant for each subject over the course of study.  Dosimetry estimated and linear regressions done for pulmonary function changes vs. (1) mean $O_3$ concentration during exercise and (2) inhaled $O_3$ dose.  Persistence of effects tested by linear regressions of before-exercise lung function on previous-day $O_3$ during exercise.  Subjects screened only by questionnaire; two with previous history of asthma but asymptomatic. | Significant (p < 0.01) decrements in FVC, $FEV_1$, PEFR, $FEF_{25-75\%}$, and $FEV_1$/FVC associated with $O_3$. For example, the mean slope of □$FEV_1$ on $O_3$ across all subjects was □1.35 mL/ppb ($\pm$0.35).  No persistence of effects seen.  No symptoms reported by subjects.  Mean decrements showed unexpected inverse relationship with calculated $V_E$ levels, as indicated by regressing pulmonary function changes and postexercise function against inhaled $O_3$ during exercise.  $V_E$ ranges given, but not group or subset means.  Subjects not screened for atopy.  Exercise done in Sterling Forest, wooded research park, on paved roads or trails. | Spektor et al. (1988b) |
| 15-min peak $O_3$ measured during runs averaged 47 ppb (range:  4 to 135 ppb).  Ambient T averaged 29.4 □C (range:  18.0 to 37.8 □C). RH averaged 62.6% (range:  37.0 to 88.0%). Levels of other pollutants were low, median values were $SO_2$, 3 ppb; $NO_2$, 6 ppb; FP, 10 □g/m$^3$.  Median of subject-specific correlations of $O_3$ and RH correlated was -0.42. | Effects of $O_3$ on lung-function change during running outdoors were examined in 24 conditioned, recreational runners (6 women, 18 men, ages 29-47) at a track 30 mi southeast of Houston, TX, from May to October, 1981. All runs were 3 mi in length, and each subject performed at a near-constant heart rate for the duration of the study. An average of 28 runs completed by each subject during the study.  Spirometry carried out before and after each run, with analysis of FVC, $FEV_1$, $FEF_{25-75\%}$, and $FEF_{0.2-1.2L}$.  Change in each lung function variable was regressed, for each subject, on 15-min maximum $O_3$ measured during the run.  The mean slope across subjects was tested for significance.  The regression was repeated with temperature and RH in the model. | Mean slope of $FEV_1$ on $O_3$ alone was □0.4 mL/ppb (p = 0.03).  In regressions that included temperature and RH, the $O_3$ slope dropped to □0.07 (not significant). Although temperature reached high levels during the study, a substantial direct effect of temperature or RH on lung function, relative to that of $O_3$, seems unlikely.  A possible potentiating role of high temperature and RH on $V_E$, and corresponding $O_3$ dose, cannot be ruled out. Lung function effect observed in simple $O_3$ model seem likely to be a valid reflection of $O_3$ effects under varying environmental conditions. | Selwyn et al. (1985) |

In contrast to these studies, early investigation of $O_3$ effects in The Netherlands involved lower and more variable exercise levels, without any specific attempt to control exercise intensity (Hoek and Brunekreef, 1992; Hoek et al., 1993a). Here, children engaged in sports training and skills development activities that were characterized by the investigators as low to moderate in intensity. Lung function change after exercise was assessed using peak flow meters. Later studies in The Netherlands investigated the effects of heavy exercise levels of variable duration in amateur cyclists, but lung function was evaluated by spirometry (Brunekreef et al., 1994).

Although the designs varied somewhat, $O_3$ exposure levels were similar in most of the studies: in Houston, 15-min peaks while running varied from 4 to 135 ppb; in Tuxedo, 1-h $O_3$ levels ranged from 21 to 124 ppb; and in The Netherlands, 1-h maxima on study days ranged from 10 to 120 ppb. The Swiss study observed $O_3$ levels between 20 and 80 ppb during the exercise period.

The studies in adults (Selwyn et al., 1985; Spektor et al., 1988b; Brunekreef et al., 1994) involving fairly intense exercise yielded statistically significant mean slopes of $\Box FEV_1$ (i.e., $FEV_1$ after exercise minus $FEV_1$ before exercise) regressed on $O_3$ levels measured during exercise, whereas the studies in children did not. The mean slope observed in the Tuxedo study across all subjects was $\Box 1.35$ mL/ppb ($\pm$ 0.35), but was reduced to $\Box 0.55$ mL/ppb ($\pm$ 0.45) in the group of 10 runners who achieved the highest $\dot{V}_E$ values ($>100$ L/min) during exercise. The mean slope reported from the Houston study was similar to the latter number, $\Box 0.4$ mL/ppb ($\pm$ 0.16). The large effect level observed in the Tuxedo study led Spektor et al. (1988b) to speculate that $O_3$ effects may have been potentiated by other pollutants such as acid aerosols; however, this phenomenon was not demonstrated analytically from the available acid monitoring data. In the Houston study, the $O_3$ effect became small and nonsignificant when temperature and RH were added to the model. Effects of temperature and $O_3$ on lung function were highly correlated and hard to separate in the Dutch amateur cyclists (Brunekreef et al., 1994), although adjustment for humidity did not change the findings. Given the available knowledge base on the independent effects of $O_3$ and temperature on lung function, it seems reasonable to interpret the results from these studies as demonstrating acute effects of low concentrations of ambient $O_3$ on lung function with moderate to heavy exercise. The predominantly negative findings

## Table 7-17 (cont'd).  Acute Effects of Photochemical Oxidant Pollution: Lung Function in Exercising Subjects[a]

| Pollutants/Environmental Variables | Study Description | Results and Comments | Reference |
|---|---|---|---|
| 1-h maximum $O_3$ concentrations during study ranged from 50 to 240 $\mu g/m^3$ (25 to 120 ppb). The highest 4-h average $PM_{2.5}$ level was 70 $\mu g/m^3$, the highest 4-h average sulfate concentration was 21 $\mu g/m^3$, the highest 24-h average $NO_2$ concentration was 51 $\mu g/m^3$. Temperature data were collected but levels were not reported. | The relationship between lung function change and $O_3$ exposures during outdoor exercise examined in a population of 83 children (43 girls, 40 boys; ages not given) in Wageningen, The Netherlands.  Study covered the period from late May to mid-July, 1989.  Lung function assessed using hand-held peak-flow meters before and after various outdoor, sports-training exercises lasting approximately 1 h.  Change in PEFR regressed on $O_3$, $O_3$ × exercise duration, and temperature for each subject; and distribution of slopes were examined.  Postexercise PEFR analyzed in relation to same and previous day 1-h $O_3$ maximum, and temperature.  Analyses repeated in subsets of subjects with varying levels of correlation between $O_3$ and temperature during their series of exercise events. | For 55 children with at least four sets of before and after exercise peak flow measurements, the mean slope of the PEFR change on $O_3$ during exercise was 0.035 ($\pm 0.030$) mL/s/$\mu g/m^3$.  For 65 subjects with at least four postexercise measurements, the mean slope of PEFR on previous-hour $O_3$ was 0.080 ($\pm 0.023$), which is statistically significant, but in the nonplausible direction.  Adjustment for temperature resulted in negative mean slopes, but these are difficult to interpret because of the high statistical correlation between same-day $O_3$ and temperature (r = 0.86).  Exercise events were of low intensity as compared with chamber studies and with the Tuxedo runners study (Spektor et al., 1988b).  Significant exposures may have occurred prior to the exercise period.  $H^+$ levels were low ($< 5$ $\mu g/m^3$) as measured simultaneously at three other nonurban sites in The Netherlands.  The possibility of a physical effect of temperature on mini-Wright peak flow meter measurements was noted by authors. | Hoek and Brunekreef (1992) Hoek et al. (1993a) |
| 1-h maximum $O_3$ concentrations during the exercise period ranged from 0.02 to 0.08 ppm. The highest pollutant levels measured during the study period were 0.13 ppm for 1-h mean $O_3$ and 70 $\mu g/m^3$ for the mean $NO_2$.  No measurements of particulates were available. | The acute effects of ambient $O_3$ on lung function were examined in 128 Swiss children, aged 9 to 11 years, after 10 min of outdoor exercise on a cycle ergometer (60 W). Study covered the period from May through October 1989. Changes in lung function were regressed on current $O_3$ concentration, with or without adjustment for temperature, RH, and other factors. | Elevated $O_3$ levels were significantly associated with decreased peak flows (PEFR), but not FVC or $FEV_1$, after exercise.  The average adjusted regression slope for PEFR was $\square 1.14$ mL/s/ppm.  This corresponds to an average decrease in PEFR of $\square 7.8$ and $\square 11.7$ at 0.08 and 0.12 ppm $O_3$, respectively.  The significant association for PEFR, but not FVC or $FEV_1$, is not consistent with other studies.  The low $O_3$ levels and short exercise period raise a question of plausibility regarding the results. | Braun-Fahrlander et al. (1994) |

## Table 7-17 (cont'd). Acute Effects of Photochemical Oxidant Pollution: Lung Function in Exercising Subjects[a]

| Pollutants/Environmental Variables | Study Description | Results and Comments | Reference |
|---|---|---|---|
| During exercise, the maximum hourly $O_3$ concentration averaged 87 $\mu g/m^3$ (0.04 ppm), with a range of 26 to 195 $\mu g/m^3$ (0.01 to 0.10 ppm). Temperature averaged 17.9 $°C$, with a range of 7.1 to 30.2 $°C$. $NO_2$ and $SO_2$ concentrations were low; 24-h averages were 26.0 and 7.5 $\mu g/m^3$, respectively. No measurements of $PM_{10}$ were made. | The relationship between lung-function change and $O_3$ exposure was investigated in 23 amateur cyclists, 18 to 37 years of age, during training sessions and races between June 4 and August 18, 1981, in The Netherlands. Lung function was measured with spirometry 30 min before and between 10 and 60 min after cycling in rural locations. Acute respiratory symptoms were recorded in a diary before and after exercise. The difference between pre- and post-exercise lung function was regressed on the mean $O_3$ concentration during exercise. Time trend, pollen, ambient temperature, and absolute humidity were taken into account as potential confounders. Regression slopes were pooled, and mean and median slopes were calculated. The effect of $O_3$ during exercise on mean symptom scores was determined by a logistic regression model; all coefficients were converted to estimated odds ratios. | Lung function was negatively related to $O_3$ concentration during exercise; effects were stronger in midsummer than in the late summer. Mean regression coefficients were $-1.16 \pm 0.33$, $-0.52 \pm 0.26$, $-2.96 \pm 1.06$, and $0.44 \pm 0.46$ mL/s/$\mu g/m^3$ for FVC, $FEV_1$, PEF, and $FEF_{25-75\%}$, respectively. For all but $FEF_{25-75\%}$, the mean coefficients were significantly different from zero. Adjustments for air humidity resulted in slightly more negative coefficients for $FEV_1$ and PEF. Acute respiratory symptoms of shortness of breath, chest tightness, and wheeze were positively related to $O_3$. | Brunekreef et al. (1994) |

[a]See Appendix A for abbreviations and acronyms.

of the studies in children are more difficult to interpret, but may be related to the low exercise intensities achieved, low exposures, and, perhaps, associated $O_3$ tolerance that occurred prior to the exercise period under study or to some subtle effect of confounders on the peak flow measurements.

*Lung Function in Daily Life Studies*

This set of studies is characterized by the assessment of lung function, respiratory symptoms, and environmental factor associations in the course of people's daily lives. This section discusses only the lung function data from these studies. For logistical reasons, studies of this kind usually have involved either spirometry conducted at regular intervals (every 1 to 3 weeks) in schools (Kinney et al., 1989; Castillejos et al., 1992; Hoek et al., 1993b) or self-administered peak flow measurements in subjects of various ages over various periods (Vedal et al., 1987; Krzyzanowski et al., 1989). Although daily life studies have the worthwhile goal of characterizing air pollution effects on respiratory health in the real world, they suffer from significant exposure assessment uncertainties owing to the use of outdoor $O_3$ monitoring, the incomplete and variable penetration of $O_3$ indoors, and the preponderance of time spent indoors by study subjects. This problem is probably less severe for the studies involving schoolchildren, who often spend substantial time outdoors after school, when $O_3$ levels may be elevated. Indeed, three of the school-based studies have found statistically significant associations between lung function and previous-day $O_3$ levels (Castillejos et al., 1992; Kinney et al., 1989; Hoek et al., 1993b). Another difficulty in interpreting the results of these studies is the possible role of seasonal factors (e.g., pollens, epidemics of respiratory infection, changes in activity patterns) as potential confounders of the analyses.

In addition to these general limitations inherent in the study design, several of the studies summarized in Table 7-18 have other problems that limit their utility for assessing $O_3$ effects on lung function. The study of Vedal et al. (1987), although well conducted, took place from September through May, a period when $O_3$ levels generally are low, and other potential respiratory insults may dominate. The statistical significance of results from a study carried out in Tucson, AZ, is difficult to interpret because of the multiple statistical tests performed (Krzyzanowski et al., 1989).

The remaining studies, although subject to the general criticisms noted previously, provide suggestive evidence that ambient $O_3$ may play a role in short-term lung function declines among children engaged in their normal daily routines (Kinney et al., 1989; Castillejos et al., 1992; Hoek et al., 1993b). The Mexico City study of Castillejos et al. (1992) is especially noteworthy because of the novel observation of $FEV_1$ and $FEF_{25-75\%}$ decrements that were strongly related to $O_3$ levels averaged over 24 to 168 h previous to spirometry, but not to previous-hour $O_3$ levels. The strength of these associations (measured by the ratio of the regression slope to its standard error) increased steadily as averaging time increased. Ozone levels observed throughout this 6-mo study were high by U.S. standards; 1-h average $O_3$ concentrations in the hour preceding lung function measurements ranged from 14 to 287 ppb, with a mean of 99 ppb. The authors suggested these results may reflect an inflammatory response in the airways rather than the well-known acute physiological response. However, further studies will be necessary to test this hypothesis.

*Panel Studies of Symptom Prevalence*

Many field and epidemiological studies reviewed both in the last criteria document (U.S. Environmental Protection Agency, 1986) and in the previous section of this document

**Table 7-18. Acute Effects of Photochemical Oxidant Pollution:
Daily Life Studies of Lung Function and Respiratory Symptoms[a]**

| Pollutants/Environmental Variables | Study Description | Results and Comments | Reference |
|---|---|---|---|
| Max $O_3$ (1-h) concentrations ranged from 3 to 63 ppb. Other ambient pollutants measured were $NO_2$, TSP, IP, RSP, FP, $SO_2$, and FP $SO_4^-$. | Lung function measured by spirometry for 154 children ages 10-12 years (90 males, 64 females) in Kingston and Harriman, TN. Spirometry done between 10 a.m. and 1 p.m. on up to 6 days at least 1 week apart during February to April 1981. Child-specific linear regression models of FVC, $FEV_{0.75}$, MMEF, and $V_{max75\%}$ fit on 1-h $O_3$ max and 24-h FP and FP $SO_4^-$. Means $\pm$ SD of distributions of estimated child-specific slopes computed and tested for significance by $t$-test. | Significantly negative mean slopes on $O_3$ for all lung function variables. For example, mean slope of $FEV_{0.75}$ on $O_3$ was $\square 0.99$ mL/ppb ($\pm 0.36$). Among regressions on FP and FP $SO_4^-$, only one statistically significant mean slope (i.e., positive mean slope of MMEF on FP). Results insensitive to outlier audits and inconclusive for sensitivity variation. Association between fitted slopes and individual characteristics not significant. Low $O_3$ levels raise plausibility questions. | Kinney (1986)[b] Kinney et al. (1989)[b] |
| 1-h average $O_3$ concentrations in hour preceding spirometry ranged from 14 to 287 ppb, with mean of 99 ppb. No other pollutants measured. Temperature ranged from 3.9 to 27.8 $\square$C. RH ranged from 18.9 to 92.3%. | Effects of $O_3$ on lung function examined during regular school hours in a group of 148 children (65 girls, 83 boys; ages 7-9) from three schools in Mexico City. Spirometry and symptom data (cough/phlegm) collected between 0800 and 1400 hours every 2 weeks over the period January through June 1988. To account for lung growth over the study period, residuals from lung function prediction equations were used in analyses. Analyses limited to 143 subjects with at least seven valid measurements. Schools were not air conditioned, and windows were usually open. Schools and subject residences all within 5 km of $O_3$ monitoring site. Associations between $O_3$ and lung function (FVC, $FEV_1$, and $FEF_{25-75\%}$) examined by computing the weighted mean of subject-specific regression slopes relating these variables. Various $O_3$ averaging times (from 1 h to 168 h) were tested. After analyzing population as a whole, regressions were repeated in subject subsets defined by sex, report of chronic symptoms, and maternal smoking. Overall regressions repeated with temperature and RH in model with $O_3$. | Only FVC had a statistically significant negative mean slope in relation to previous hour $O_3$ concentration ($\square 0.059 \pm 0.23$ mL/ppb). This slope is approximately one order of magnitude lower than those observed in some camp studies. Both $FEV_1$ and $FEF_{25-75\%}$ had significant negative associations with $O_3$ averaged over the previous 24, 48, and 168 h. For example, the mean slope of $FEV_1$ on 48-h average $O_3$ was $\square 0.592 \pm 0.109$ mL/ppb. The authors speculated that the FVC result reflects the acute, reversible effects of $O_3$ on one's ability to take a deep breath, whereas the $FEV_1$ and $FEF_{25-75\%}$ observations may reflect inflammatory effects of more prolonged $O_3$ exposures. It should be noted that both FVC and $FEV_1$ had significant negative slopes on 1-h maximum $O_3$ measured in the previous 24 h. Adjustment for temperature and RH diminished somewhat the associations between lung function and $O_3$. Associations between lung function decrements and $O_3$ exposure often appeared larger in children with chronic respiratory symptoms than in those without, and in children of mothers who were current smokers; however, these results were not statistically confirmed. | Castillejos et al. (1992) |

## Table 7-18 (cont'd).  Acute Effects of Photochemical Oxidant Pollution: Daily Life Studies of Lung Function and Respiratory Symptoms[a]

| Pollutants/Environmental Variables | Study Description | Results and Comments | Reference |
|---|---|---|---|
| Daily maximum 1-h $O_3$ concentrations on days prior to lung-function testing ranged from 7 to 206 $\mu g/m^3$ (3.5 to 103 ppb).  Levels of other pollutants measured ($SO_2$, $NO_2$, $PM_{10}$, and aerosol $H^+$) were reported to be low during study.  Ambient temperature (range:  5 to 31 $\,^\circ C$) and some pollen data also were collected. | Associations between morning lung function and previous day $O_3$ examined during school in 533 children (ages 7-11) from seven schools in three towns in The Netherlands. Towns were selected without local pollution sources and with low levels of pollutants other than $O_3$.  Study spanned the period from March through July, with lung-function measurements collected every 2-3 weeks.  An overall time trend was fit to the lung- function data to account for lung growth.  Data on FVC, $FEV_1$, PEFR, and $FEF_{25-75\%}$ analyzed in relation to previous-day 1-h maximum $O_3$ concentrations using subject-specific linear regressions followed by analysis of mean slopes.  Intersubject variations in responsiveness to $O_3$ were tested via an F-test.  The influence of chronic respiratory symptoms and other subject characteristics (e.g., age, sex) on $O_3$ responsiveness was examined.  Models that included other pollutants were also considered. | Negative, usually statistically significant mean slopes seen for lung function regressed on previous-day 1-h maximum $O_3$ for the seven individual schools.  Over all 533 subjects, mean regression slopes for FVC and $FEV_1$ were $-0.20 \pm 0.05$ and $-0.21 \pm 0.04$ mL/$\mu g/m^3$, respectively; and for PEFR and $FEF_{25-75\%}$ were $-0.72 \pm 0.22$ and $-0.45 \pm 0.12$ mL/s/$\mu g/m^3$, respectively.  These coefficients may be doubled to convert to slopes in terms of parts per billion.  The authors report that adding $SO_2$, $NO_2$, or $PM_{10}$ did not materially change the $O_3$ slopes. There was evidence for inter-subject variation in $O_3$ responsiveness, but this variation was not statistically related to available subject characteristics data. Temperature data not included in models, perhaps due to high correlation with $O_3$.  The lung function/$O_3$ relationships noted above are qualitatively similar to those reported in the 1988 Fairview Lake camp study and the Mexico City school children's study. | Hoek and Brunekreef (1992) Hoek et al. (1993b) |
| 1-h maximum $O_3$ concentrations on PEFR measurement days ranged from 20 to 103 ppb. No other pollutants assessed, but ambient temperature data included. | Relationship between daily peak flow measurements and ambient $O_3$ concentrations in a population sample of 732 subjects (both adults and children) over 2-week periods during normal daily activities in Tucson, AZ. Peak flow assessed using hand-held peak-flow meters up to four times per day.  PEFR measurements on initial 2 days for each subject dropped to avoid possible learning effects, leaving a series of up to 12 measurement days per subject. Population-pooled regression slopes computed for PEFR on 1- and 8-h average $O_3$ for children (ages $\leq$ 15) and adults (ages > 15), controlling for residual auto-correlations.  Outcome measures included PEFR diurnal variability and afternoon PEFR levels.  Besides $O_3$, potential explanatory variables included temperature, average time outdoors, acute respiratory infections, asthma, and environmental tobacco smoke exposure. | Significant positive associations observed between $O_3$ concentrations and PEFR diurnal variability; the effect magnitude was greatest in asthmatic subjects. In children only, noon PEFR was suppressed on days with higher $O_3$ levels.  The uncertain relationship between central site $O_3$ levels and personal exposures in this southwestern community was not addressed. Although the statistical models employed were appropriate and well chosen, it appears that a substantial amount of exploratory data analysis was performed prior to selection of results to present in the paper, leading to uncertainties regarding the statistical validity of the hypothesis tests presented. | Krzyzanowski et al. (1989) |

**Table 7-18 (cont'd).  Acute Effects of Photochemical Oxidant Pollution:
Daily Life Studies of Lung Function and Respiratory Symptoms[a]**

| Pollutants/Environmental Variables | Study Description | Results and Comments | Reference |
|---|---|---|---|
| Means and range of max daily 1-h values: $O_3$ mean = 32.4 $\mu g/m^3$, range = 0-129 $\mu g/m^3$; $SO_2$ mean = 51.2 $\mu g/m^3$, range = 18-176 $\mu g/m^3$; $NO_2$ mean = 40.5 $\mu g/m^3$, range = 12-79 $\mu g/m^3$; CoH mean = 0.38 CoH units, range = 0.1-1.3 CoH units; temperature mean = 1.3 $\square$C, range = $\square$22$\square$ to +22 $\square$C. | Follow-up study (September 1980 through April 1981) of pollutant-respiratory symptom relationships in subsets of children from 1979 Chestnut Ridge cross-sectional study of more than 4,000 elementary school children.  Subsamples selected from six schools in study area with consistently higher levels of air pollution during previous 4 years.  Subsamples (three) stratified by reported symptoms.  One or more of following measures taken for 144 children: diaries, symptom questionnaire, spirometry.  Telephone follow-up each 2 weeks on diaries, spirometry done at school, pollutants (including $O_3$) measured at one monitor (data from 17 monitors for $SO_2$ generally reflected in data at single monitor).  Diary panel study covered 8 mo; successive PEFR spirometry studies of 9 weeks each done in respective groups of the three subsamples. | Relationships of maximum hourly $SO_2$, $NO_2$, $O_3$, and CoH and minimum temperature for each 24-h period to daily upper and lower respiratory illness, wheeze, and PEFR were evaluated using multiple regression models adjusted for illness occurrence or levels of PEFR on preceding day.  No air pollutant was strongly associated with respiratory illness or with PEFR.  Authors concluded that this study can best be interpreted as showing no acute effects of studied pollutants on respiratory symptoms or PEFR in children at levels lower than the current NAAQS, but also noted that conclusion must be tempered by relatively low levels of pollutants encountered and possibility of exposure misclassification. | Vedal et al. (1987) |

[a]See Appendix A for abbreviations and acronyms.
[b]Cited in U.S. Environmental Protection Agency (1992).

reported results that indicated associations between ambient oxidant exposures and various measures of respiratory effects (e.g., irritative respiratory symptoms and acute pulmonary function decrements) in children and adults. The aggregation of individual studies provides reasonably good evidence for an association between ambient photochemical oxidants and acute respiratory effects and a database that is generally coherent, consistent, and biologically plausible. In addition, other studies of irritative symptoms in children and adults also were reported in the 1986 document. For example, Hammer et al. (1974) reported qualitative associations between ambient oxidant levels and symptoms such as eye and throat irritation, chest discomfort, cough, and headache at total oxidant levels greater than 0.15 ppm in young adults (nursing students). Wayne et al. (1967) reported a high correlation ($R^2 = 0.89$) between ambient total oxidant levels (1 h prior to competition) and impaired exercise performance (running time) in high school students during cross-country track meets in Los Angeles, CA. Symptoms were not measured, but Wayne speculated that chest discomfort from oxidant inhalation impaired exercise performance. Although results such as these are consistent with evidence from controlled human exposure studies, precise characterization of ambient pollutants and environmental conditions and rigorous statistical analyses were lacking in the studies. Thus, the primarily qualitative data from these and other studies were not satisfactory to provide quantitative conclusions about the relationship of ambient $O_3$ concentrations and acute respiratory illness.

Schwartz (1992), Schwartz and Zeger (1990), and Schwartz et al. (1988) reanalyzed the original diary data of student nurses reported earlier by Hammer et al. (1974) (Table 7-19). The nurses were told that the diaries were part of a prospective study of viral infections. Logistic regression models including time series analyses were used to control for autocorrelation effects that are frequently present in time series data. The reanalysis for daily prevalence rates of symptoms (Schwartz et al., 1988) confirmed that ambient oxidants were significantly associated with cough and eye discomfort. However, earlier reported associations between oxidants and headache or chest discomfort were not confirmed. Cough was the one symptom that showed an apparent threshold near 0.20 ppm total oxidants, which approximates the threshold value reported by Hammer et al. (1974). Further reanalysis of the diary data (Hammer et al., 1974) by Schwartz (1992) and by Schwartz and Zeger (1990) for the effects of air pollutants on the risk of new episodes of respiratory and other symptoms and on their durations revealed interesting findings. The mean plus or minus standard deviation (SD) level of oxidants was $0.102 \pm 0.074$ ppm. In logistic regression models, an increase in oxidant concentration by one SD (0.074 ppm) was associated with a 17% increased risk of chest discomfort and a 20% increased risk of eye irritation. These associations were highly significant ($p < 0.001$). In addition, photochemical oxidants were significantly ($p < 0.0001$) associated with the duration of episodes of cough, phlegm, and sore throat.

Krupnick et al. (1990) and Ostro et al. (1993) reanalyzed daily health data from over 5,000 children and adults living in the Los Angeles area during a 6-mo period (September 1978 to March 1979) (Table 7-19). The original study was reported by Flesh et al. (1982). The presence or absence of daily respiratory symptoms associated with daily exposure to ambient $O_3$ and other air pollutants was analyzed in a pooled, cross-sectional, time-series model. Krupnick et al. (1990) reported statistically significant effects of $O_3$ levels on daily reported respiratory symptoms in healthy nonsmoking adults, but not among smokers, children, and patients with chronic respiratory disease. Ostro et al. (1993) evaluated the daily reports of 321 nonsmoking adults and, using a logistic regression model,

# Table 7-19.  Acute Effects of Photochemical Oxidant Pollution:
## Symptom Prevalence[a]

| Pollutants and Environmental Variables | Study Description | Results and Comments | Reference |
|---|---|---|---|
| Total oxidant, CO, $SO_2$, NO, and $NO_2$ measured; total oxidant concentrations reached episodic levels (maximum 1-h/day < 0.4 to 0.5 ppm); mean daily temperature was 71.8 °C. | Reanalysis of daily diary study of student nurses working and living at schools in Los Angeles (see U.S. Environmental Protection Agency, 1986, for details of Hammer et al., 1974).  This series of papers reexamines the nurses' data using logistic regression models and time-series methods to account for serial correlation (autocorrelation) of symptoms on successive days.  The effects of total oxidants on daily prevalence rates of symptoms, risks of developing new symptoms (episodes), and duration of episodes were analyzed. | Associations found between total oxidants and prevalence of cough and eye irritation, confirming part of findings of original study.  Association with cough only at oxidant concentrations above approximately 0.20 ppm.  Previously reported associations between oxidants and chest discomfort and headache (Hammer et al., 1974) not confirmed.  Oxidants associated with increased risk (incidence) of chest discomfort and eye irritation and duration of episodes of cough, phlegm, and sore throat.  Duration of symptoms showed concentration-response relationships even below 0.12 ppm.  Findings suggest different effects of oxidants on symptom characteristics.  Lack of daily particulate measurements, small number of subjects, and heterogeneous individual responses restrict quantitative interpretation of results.  Lung function was not measured. | Schwartz (1992) Schwartz and Zeger (1990) Schwartz et al. (1988) |
| Daily $O_3$, $NO_2$, $SO_2$, and CoH and every sixth-day sulfates measured at one site (Azusa). 1-h daily maximum $O_3$ 0.1 ppm, 7-h average $O_3$ 0.07 ppm; sulfates 8.43 µg/m³; maximum temperature was 22.4 °C. | Reanalysis of daily diaries completed during 181-day survey period (September 1978 to March 1979) by 756 children and 572 adults (Krupnick et al., 1990) and 321 nonsmoking adults (Ostro et al., 1993) living in Glendora, Covina, or Azusa, CA (see Flesh et al., 1982 for details).  Presence or absence of 19 (upper and lower) respiratory and two nonrespiratory symptoms recorded daily.  Presence or absence of symptoms analyzed in a pooled cross-sectional time-series model.  Nonpollution factors, including sex, gas stove use, day of study, and a chronic disease indicator were included in final regression models used to measure effects of ambient air pollution.  Logistic regression analyses for entire sample to determine effect of each pollutant on health endpoints.  Lagged effects of each pollutant and effects in individuals (n = 74) without air conditioners and those with preexisting respiratory infection were analyzed. | Logistic regression model indicated significant associations between incidence of lower respiratory symptoms and healthy nonsmoking adults (but not among smokers, children, or patients with chronic respiratory disease); 1-h daily maximum $O_3$ levels (OR = 1.22, 95% CI of 1.11-1.34, for a 0.1 ppm change), 7-h average $O_3$ level (OR = 1.32, 95% CI of 1.14-1.52), and ambient sulfates (OR = 1.30, 95% CI of 1.09-1.54, for a 10 µg/m³ change).  CoH was significantly related to daily symptoms in children.  Gas stove in the home was associated with lower respiratory tract symptoms (OR = 1.23, 95% CI of 1.03-1.47), as were the effects of $O_3$ in subgroups without residential air conditioner (OR = 1.24) and with preexisting respiratory infection (OR = 1.24).  All the above increased risks were statistically significant (p < 0.05).  Interpretation of results limited by selection of sample; undersampling of young adults; aggregation of symptoms of all severity levels into one measure; possible reporting bias; and absence of indoor exposure, aeroallergen, and lung function data. | Krupnick et al. (1990) Ostro et al. (1993) |

[a]See Appendix A for abbreviations and acronyms.

found a statistically significant association between the incidence of lower respiratory tract symptoms and 1-h daily maximum and 7-h average $O_3$ levels (22 and 32% increased risk, respectively, with 0.1-ppm increase in $O_3$) and ambient sulfates (30% increased risk with a 10-$\mu g/m^3$ change). The lower respiratory tract effects of $O_3$ were greater in the subgroups with gas stoves, without residential air conditioners, and with preexisting respiratory infection. Interpretation of the results is limited by the selection of the sample for analysis; undersampling of young adults; aggregation of symptoms of all severity levels into one measure; possible reporting bias; and absence of indoor exposure, outdoor aeroallergen, and lung function data.

The results from the above panel studies suggest a modest but biologically plausible relationship between short-term exposure to ambient oxidants/$O_3$ and respiratory symptoms. The interpretation of these recent reanalyses is limited by several factors. Heterogeneous individual responses occur, and analyses of grouped data possibly may miss susceptible subgroups. The lack of specific measurements of $O_3$ and other pollutants (especially particles) and of personal exposure or risk variables (e.g., time-activity data) weaken the assessment of confounders and effect modifiers. In addition, the overall data analysis pertains to small and very selected samples that have uncertain representativeness to the general population.

### *Aggravation of Existing Respiratory Diseases*

Prior epidemiological data on the effects of ambient $O_3$ levels in subjects with existing respiratory disease have been difficult to interpret due to methodological limitations (U.S. Environmental Protection Agency, 1986). Exacerbation of asthma and other health endpoints subsequently has been evaluated, and more recent studies have observed possible increases in symptom aggravation or changes in lung function of asthmatic subjects in relation to increased $O_3$ or total oxidant levels, as well as interactions between $O_3$ concentrations and temperature. However, no consistent pattern of findings for aggravation of symptoms or lung function changes has been reported for patients with other types of chronic lung disease. Some of the major issues in interpreting results from studies of respiratory exacerbations have been inadequate sample size and characterization of the study subjects, lack of information on the possible effects of medications, the absence of records for all days on which symptoms could have occurred, inadequate interpretation of the clinical significance of measured changes, the role of confounders and effect modifiers (e.g., temperature, humidity, particles, aeroallergens), and personal or group characterization of indoor-outdoor exposures. For example, Whittemore and Korn (1980) and Holguin et al. (1985) found small increases in the probability of asthma attacks associated with previous attacks, decreased temperature, and incremental increases in oxidant and $O_3$ concentrations. Lebowitz et al. (1982, 1983, 1985) and Lebowitz (1984) reported effects in asthmatics, such as decreased PEFR and increased respiratory symptoms, that were related to the interaction of $O_3$ and temperature. None of these studies adequately assessed possible effect modification by other pollutants, particularly inhalable particles, which may have independent effects.

Epidemiological studies published since the 1986 criteria document (U.S. Environmental Protection Agency, 1986) have attempted to control for many methodological issues (e.g., with [1] better estimates of exposure to pollutants [as well as $O_3$] and environmental variables that can confound or modify responses, [2] serial measurements of pulmonary function for determining correlations with pollutants and other environmental variables, [3] better biomedical characterization of cohorts, and [4] more robust analytical

approaches that control for autocorrelation of environmental variables and health responses). Recent studies generally have provided further evidence that supports a relationship between ambient $O_3$/oxidant concentrations and respiratory morbidity in asthmatic subjects (Table 7-20).

Gong (1987) studied the relationship between air quality and respiratory status of 83 asthmatic subjects living in a high-oxidant area of Los Angeles County. The study covered February to December 1983, but data analyses were limited to a 230-day period (April 15 through November 30) because of staggered entry of subjects into the study and the high frequency of missing or incomplete data encountered in the earlier part of the study period. Regression and correlation analyses between $O_3$ and average symptom scores, asthma medication index (AMI), and day and night PEFR across subjects showed weak, nonsignificant relationships. These daily outcome variables were compared across days with maximum 1-h-average $O_3$ in three ranges: $<0.12$ ppm, 0.12 to 0.19 ppm, and $>0.20$ ppm; "no statistical or clinical significance was detected." Individual exposures and activity patterns were not estimated in these two analyses. Multiple regression analyses also indicated the lack of a significant overall relationship between $O_3$ (and their independent variables) and respiratory status, despite the use of lagged variables and the inclusion of other pollutants, meteorological variables, aeroallergens, and AMI. Total suspended particles directly affected PEFR, but the relationship was not consistent in the analysis. Aeroallergens showed significantly negative relationships to respiratory variables, but only the effect of certain molds was considered clinically relevant. Temperature and humidity showed no significant effect on the respiratory variables on this study.

Although there was no significant overall effect of $O_3$ on respiratory variables in the 83 asthmatic subjects, multiple regression analysis of subjects whose $O_3$ coefficients on various days were in the top quartile for dependent variables (respiratory measures) showed significant and consistent effects of $O_3$ on Day t and the previous day (Day t $\square$ 1). Multiple regression testing of subsets for associations of symptom score or day or night PEFR on the same-day $O_3$ and previous-day values of the same responses showed highly significant $O_3$ coefficients for all three respiratory measures.

The clinical significance of responses in symptom scores and day and night peak flow was evaluated for all subjects by individual regression analyses. No subject had evidence of significant worsening of symptoms attributable to $O_3$ during the study. Adult subjects with high scores in fatigue, hyperventilation, dyspnea, congestion, and rapid breathing in the Asthma Symptom Checklist had more negative slope coefficients for $O_3$ than subjects with low-to-moderate scores on the checklist. "Responders" (statistically identified by multiple regression analysis) scored consistently higher in the factors representing fatigue, hyperventilation, and rapid breathing. The higher scores of these responders, however, "were apparently not associated with differences in ambient $O_3$ concentrations since the test scores were similar during relatively low (first test) and high (second test) $O_3$ days. The significance of the psychological results is unclear at this time" (Gong, 1987).

Lebowitz et al. (1987) performed a time series analysis to evaluate daily respiratory responses to outdoor and indoor air pollutant and aeroallergen exposures in potentially sensitive adults living in a dry climate (Tucson, AZ). Daily symptoms and PEFR were recorded in well-characterized groups of asthmatics, allergic subjects, patients with chronic airways obstruction, and asymptomatic healthy controls (total sample size of 204) over 2 years. Daily diaries included acute symptoms, medication use, and doctors' visits.

## Table 7-20. Aggravation of Existing Respiratory Diseases by Photochemical Oxidant Pollution[a]

| Pollutants and Environmental Variables | Study Description | Results and Comments | Reference |
|---|---|---|---|
| Air pollutant measurements for April to November 1983 used in statistical analyses. Daily maximum of $NO_x$, $SO_2$, CO, THC less than California standards or NAAQS. $SO_4^=$ > 25 $\mu g/m^3$ on 4 days; TSP > 100 $\mu g/m^3$ on 78% of days with data. Daily maximum 1-h average $O_3$ concentrations (from continuous monitoring) = 0.01-0.11 ppm on 103 days, 0.12-0.19 ppm on 65 days, 0.2-0.34 ppm on 60 days, and 0.35-0.38 ppm on 3 days. Outdoor aeroallergens sampled with Roto-Rod: spores, pollens, grasses, molds, miscellaneous debris; all generally low except for group of common molds (rusts, smuts, mushroom) present in thousands per square centimeter on sampler. Mean ($\pm$ SD) daily temperature at 1 p.m. during 200 days: 26 $\pm$ 11 $\degree$C, range 13-41 $\degree$C; 128 days with 24 $\degree$C. | Effects of pollutants and other environmental variables on respiratory symptoms and PEFR evaluated in 11-mo population study of asthmatics living in high-$O_3$ area (Glendora) of Los Angeles County, CA. Detailed questionnaires given at outset on medical/occupational histories and personal factors, including general activity patterns; psychological testing (Asthma Symptom Checklist, State-Trait Anxiety Inventory, etc.) also given, once during good air period and once during smoggy period. Lung function (spirometry) and bronchodilator responses measured at outset in all subjects. Daily diaries (checked 2×/week), mini-Wright peak flow meters, and Nebulizer Chronolog attached to metered-dose inhaler used to record symptoms, day and night PEFR, and medication use, respectively. Multiple regression analyses for overall group; then subsets (two groups of "responders") analyzed separately and compared with rest of cohort. | Eight of 91 subjects completing study (of 109 recruited) showed no variability in asthma status during the 230-day study. Respiratory status of final study population (n = 83 with generally mild or stable asthma), as a whole, not related, either clinically or statistically, to maximum 1-h average $O_3$ on Days t, t-1, t-2, or t-3 for any respiratory variable even when adjusting for medication use, symptoms, and PEFR on Day t-1. Subset analyses showed association of $O_3$ with symptoms and with day and night PEFR in subjects in top quartile for respiratory measures, but association did not follow a consistent relationship with ambient $O_3$ concentrations. $\dot{V}_E$ levels during outdoor time not estimated. Outcomes not related to time outdoors vs. indoors or to outdoor time on "clean" vs. "smoggy" days. Subsets ("responders") differed from rest of cohort mainly in scores of Asthma Symptom Checklist for factors representing fatigue, hyperventilation, and rapid breathing, but there was no difference in responders between clean and smoggy periods. Aeroallergens from maple, oak, beech, and elm trees showed significant (and clinically relevant) relationships to respiratory variables. Exposure assessment limited by outdoors-only monitoring and lack of time-activity data. | Gong (1987) Gong et al. (1985) |
| Hourly outdoor $O_3$, CO, $NO_2$, and TSP measured from three stations. Hourly maxima used for $O_3$ and CO; daily CO and $NO_2$ derived as weighted measures for each cluster sampling site, and daily values used. Sample of homes monitored inside and outside for particulates and gases and evaluated for housing characteristics (e.g., gas stove usage). Meteorological variables measured daily. Temperature data not reported. | Effects of outdoor and indoor air pollutants and aeroallergens evaluated in a 2-year study of 22 subjects with asthma, 33 with airway obstructive disease, 30 atopics, and 14 normals living in an arid environment (Tucson, AZ). Subjects part of a community population sample of 117 families (see U.S. Environmental Protection Agency, 1986, for details of Lebowitz et al., 1982, 1983, 1985; Lebowitz, 1984) and had well-characterized symptoms, medication use, lung function, methacholine response (in a subsample), and immunological status. Daily diaries (acute symptoms, medication use, and doctors' visits) and daily PEFR (2×/day) performed for 3 mo, 2-4×/study period. Duration of time spent outdoors recorded. Spectral time series analyses used to evaluate each respiratory response variable for periodic tendencies and covariance (dependent and independent) functions as processes in time in the different groups. | Asthmatics had greatest number of respiratory complaints, which were related to the presence of gas stoves, active smoking, humidity, and temperature. $O_3$ was associated with peak flow and temperature (late spring), wheeze (Day t-3 with humidity), and productive cough (Day t-2). $O_3$ (Day t-3) was related to productive cough during the summer in allergic subjects. Outdoor gases and meteorological variables significantly related to symptoms and PEFR, both independently and as effect modifiers. No significant $O_3$ effect in patients with obstructive disease or in normals. Small number of subjects and study days and lack of indoor $NO_2$ and $PM_{10}$ measurements, measured pollutant values, and effect estimates limit quantitative interpretation of study. | Lebowitz et al. (1987) |

## Table 7-20 (cont'd). Aggravation of Existing Respiratory Diseases by Photochemical Oxidant Pollution[a]

| Pollutants and Environmental Variables | Study Description | Results and Comments | Reference |
|---|---|---|---|
| Outdoor $O_3$ levels measured hourly by three stations and maximum 1- and 8-h average values were used to represent $O_3$ levels for all subjects on a given day. For each day of the study, the mean of the maximum 8-h $O_3$ average for the 4 preceding days was calculated to be an index of cumulative exposure. $PM_{10}$ was measured daily at one station. Mean $\pm$ SD of maximum 1-h $O_3$ concentrations was $0.055 \pm 0.014$ ppm (range: 0.015-0.092 ppm), moving average maximum 8-h $O_3$ levels were $0.046 \pm 0.013$ ppm (0.09-0.082 ppm). Maximum daily outdoor temperature was 87 °F (30 °C) per person-day, maximum $PM_{10}$ was 187 $\mu$g/m$^3$ (mean 42 $\mu$g/m$^3$). | Temporal effect of ambient $O_3$ concentration on PEFR during 30-mo study period in 287 children (13% physician-diagnosed asthmatics) and 523 nonsmoking adults (9% asthmatics) in the Tucson community population sample. Mini-Wright peak flow meters used four or fewer times per day but only for 2-week periods, and only one meter was assigned/household. Children's tests were supervised by adult, and initial 2 days of observation were eliminated from analysis. Symptoms from daily diaries were also used in analysis. Random-effects longitudinal model was used for analyses to account for autocorrelation of PEFR values. Multifactorial ANCOVA was used to analyze day-to-day changes in daily average PEFR and symptom prevalence rates (the dependent variables) in relation to 8-h $O_3$ values on the same day and previous days (lags of 0 and 1). | Analyzed PEFR data limited to at least 12 measurements for at least 6 days in 78% of children and 74% of adults. Noon PEFR in nonasthmatic and asthmatic children was lower with higher 1-h maximum $O_3$ levels: □11.9 L/min/0.1 ppm $O_3$ (p < 0.05) and □31.0 L/min/0.1 ppm $O_3$ (p < 0.1), respectively. Effect of 8-h $O_3$ mean on evening PEFR seen only in asthmatic children, possibly reflecting a cumulative $O_3$ response during course of day. Among adults, evening PEFR was decreased in asthmatics who spent more time outdoors on days with higher $O_3$ concentrations (C × T effect). The ANCOVA model showed significant interactive effects of $O_3$ × temperature × $PM_{10}$ on daily average PEFR. Daily rates of allergic-irritant symptoms increased with the maximum 8-h $O_3$ average (>0.056 ppm) on the previous day and increased more with interactions of $O_3$ × temperature × $PM_{10}$. Missing PEFR data, possible overestimation of outdoor $O_3$ exposure, large variability of responses in asthmatics, medication use on days with high $O_3$ levels, relatively low $O_3$ levels, and uncertain effects of indoor and outdoor allergens and respiratory infections limit interpretation. | Lebowitz et al. (1991) Krzyzanowski et al. (1992) |

## Table 7-20 (cont'd). Aggravation of Existing Respiratory Diseases by Photochemical Oxidant Pollution[a]

| Pollutants and Environmental Variables | Study Description | Results and Comments | Reference |
|---|---|---|---|
| Hourly $O_3$, twice daily (9:00 a.m. and 9:00 p.m.) acidic aerosols (sulfates, $SO_4$, and $H^+$), and pollen counts were measured on site. Hourly temperature, RH, and $O_3$ measured from nearby monitors. In 1991, pollution levels increased daily until Day 5, when maximum 1-h $O_3$ reached 0.154 ppm and daytime $H^+$ and sulfate levels were 245 nm/m³ and 26.7 □g/m³, respectively. In 1992, air quality was better (e.g., the highest daily 1-h maximum $O_3$ was 0.063 ppm). Temperature data not reported. | Effects of ambient summertime haze air pollution on asthmatic children (ages 7-13) attending 1-week asthma camp in Connecticut River Valley were evaluated during June 1991 (n = 50) and 1992 (n = 55). PEFR and symptoms (2×/day) and number of as-needed (p.r.n.) inhaled bronchodilator treatments given by on-site physician during each study day were recorded. Correlations between health outcomes and air pollutants were performed. | In 1991, daily total number of p.r.n. treatments highly correlated (r > 0.80) with maximum $O_3$, $SO_4$, daytime $H^+$, and maximum temperature, but only $SO_4$ (r = 0.97) and $H^+$ (r = 0.985) were significant (p < 0.05) and remained so after temperature was included in the analysis. Daily pollen counts were not associated with treatments p.r.n. Afternoon chest symptoms (cough, phlegm, and wheeze) and changes in morning-afternoon PEFR values (excluding children given medication) were significantly correlated (p < 0.05) with $O_3$ and $H^+$, respectively. Scheduled medications did not apparently provide a protective effect ($X^2$ = 3.25, p = 0.067), although the failure to achieve statistical significance is not unexpected given the small sample size. In 1992, change in PEFR (magnitude not reported), chest symptoms, and the fewer daily exacerbations (maximum 27 vs. 37 in 1991) were not significantly correlated with pollution, pollen, or temperature. Only sore throat, runny nose, and eye irritation were correlated with pollen counts. Although the data are only in preliminary form, the 1991 results appear consistent with an effect of summertime haze air pollution on PEFR, chest symptoms, and asthma exacerbations. The 1992 results are consistent with less health effects owing to cleaner ambient conditions. Small number of subjects and study days and lack of results for other pollutants limit the interpretation of the studies. | Thurston et al. (1995) |

[a]See Appendix A for abbreviations and acronyms.

A sample of homes was evaluated for environmental characteristics and was monitored indoors and outdoors at the home for gases and particles, in addition to regional stationary outdoor monitors. Asthmatics showed the most respiratory responses. Outdoor $O_3$ levels were significantly ($p < 0.05$) related to wheeze, productive cough, and peak flow (late spring) in the asthmatic group. Statistical interactions between $O_3$ and smoking, presence of a gas stove, maximum temperature, and minimum humidity ($R^2 = 0.49$) were found. The other groups did not demonstrate an $O_3$ effect, except for the atopic group, which had increased summertime productive cough related to $O_3$ levels. Thus, these results indicate an $O_3$ effect on asthmatics and that statistical interactions between $O_3$ and other environmental factors are significantly related to symptoms and peak flow. On the other hand, the results are largely descriptive and qualitative without adequate effect estimators.

A subsequent analysis of the same community population sample in Tucson (Lebowitz et al., 1991; Krzyzanowski et al., 1992) evaluated the temporal relationship between PEFR and ambient $O_3$ in 287 children and 523 nonsmoking adults. During part of the study period, ambient particles with a MMAD of 10 □m or less ($PM_1$) were collected daily at one monitoring station. A random-effects longitudinal model and multifactorial analysis of covariance were used for analyses. During the study period, the maximum ambient $O_3$ concentrations were relatively low (i.e., the 1-h maximum never exceeded 0.092 ppm). In children, noon peak flows were decreased on days when there was a high $O_3$ concentration. Children with physician-confirmed asthma experienced the greatest decrease in noon peak flow. Evening peak flow also was significantly related to $O_3$ in children, especially asthmatic children, suggesting a cumulative $O_3$ response during the course of the day. Among adults, evening peak flows were decreased in asthmatics who spent more time outdoors on days when $O_3$ levels were high. After adjustment for covariates, significant statistical interactions of 8-h $O_3$ levels with $PM_1$ and temperature on daily PEFR were found. There was a significant increase in allergic-irritant symptom rates related to prolonged exposure to $O_3$ (maximum 8-h average on the previous day and the interactions of $O_3$, temperature, and humidity). The study had some methodologic problems (e.g., missing daily PEFR data in many subjects, lack of information about specific hours spent outdoors, medication usage, and relatively low $O_3$ levels during the study period). Nonetheless, the data analyses, control of confounders, and overall exposure assessment strengthen the conclusions of the study: the respiratory response to $O_3$ is acute, occurs more often in asthmatics, and increases as temperature and $PM_1$ increase.

The respiratory effects of ambient $O_3$ and other coexisting pollutants were evaluated during a 1-week asthma camp in the Connecticut River Valley in June of 1991 and 1992 (Thurston et al., 1995). Each child (age 7 to 13 years) participated in the same daily activities all week. Peak flow and symptoms were recorded twice a day, as well as the number of as-needed (p.r.n.) treatments of inhaled bronchodilator administered by an on-site physician during each day (each representing an exacerbation of asthma). Hourly measurements of $O_3$ and twice daily samples of acidic aerosols (sulfates [$SO_4$] and hydrogen ions [$H^+$]) were collected. The results indicate a strong association between the ambient air pollution mix and the occurrence of asthmatic exacerbations in children. During 1991, pollution levels progressively increased until Day 5, when the 1-h maximum $O_3$ concentration reached 0.154 ppm, and the daytime (9:00 a.m. to 9:00 p.m.) $H^+$ and $SO_4$ concentrations were 254 nm/m$^3$ and 26.7 □g/m$^3$, respectively. The correlations of the daily total number of p.r.n. treatments required with daily maximum $O_3$, daytime $SO_4$ and $H^+$, and maximum temperature were all high ($r > 0.8$), but only $SO_4$ ($r = 0.97$) and $H^+$ ($r = 0.98$) were significant ($p < 0.05$) given

the small number of days involved. Afternoon symptoms (cough, phlegm, and wheeze) and morning-afternoon change in PEFR (without medication) were significantly correlated ($p < 0.05$) with $O_3$ and $H^+$, respectively. During 1992, the local air quality was better (e.g., the daily 1-h maximum $O_3$ concentration was only 0.063 ppm). There were fewer asthmatic exacerbations (maximum of 27 versus 37 in 1991), and they were not significantly correlated with pollution, pollen, or temperature. Pollutants were not significantly correlated with symptoms or PEFR. Overall, the 1991 data indicate a coherence in the associations of summertime haze air pollution with peak flow, chest symptoms, and asthma exacerbations in children. The lack of correlation during 1992 likely was due to the improved air quality and indirectly supports the results of the previous year. An adequate interpretation of these preliminary results is limited by the small number of subjects and study days and the lack of results for other pollutants. These camp studies remain to be reported in more detail.

The above epidemiological studies have generally supported a direct association between ambient $O_3$/oxidant concentrations and acute respiratory morbidity in asthmatics. The recent studies have strengthened their conclusions by improvements or new approaches in the estimations of $O_3$ exposure, confounders, and effect modifiers; characterization of the subjects and serial measurements of their responses; and analytical approaches. Thus, the aggregate results can be viewed as biologically and temporally plausible, consistent, and coherent to some extent; however, some methodological problems persist. The studies share certain deficiencies such as small numbers of subjects (which may reduce statistical power) and the lack of time-activity measurements and significant data about individual responses and their distribution. The independent effect of ambient $O_3$, as estimated by statistical models in epidemiological studies, is difficult, at best, to clearly differentiate from those of copollutants because $O_3$ (or another pollutant such as $H^+$) may be acting only as an indicator of the toxic potency of the ambient mixture of pollutants. This, in combination with measurement error and uncontrolled associations with other factors, complicates analytical findings about the relationships among components of an ambient mixture and may not accurately disentangle the effects of $O_3$ in a biologically appropriate fashion.

### 7.4.1.3 Aggregate Population Time Series Studies

Aggregate population, or "ecological", time series studies are epidemiological investigations in which the associations between air pollution and human health outcomes are evaluated over time in the population as a whole (e.g., with respect to deaths per day in a given city) and for which outcomes and exposures are not matched for the individuals within the population. Indeed, aggregate population time series studies of extreme air pollution episodes have provided some of the clearest evidence of the adverse effects of air pollution on humans. For example, during the historic December 1952 London Fog episode, in which extremely high sulfur oxide and PM air pollution levels were experienced, total mortality in Greater London rose from roughly 300 to 900 deaths/day, and acute respiratory hospital admissions rose from 175 to 460/day (United Kingdom Ministry of Health, 1954). At more routine levels of air pollution, any effects of air pollution are necessarily less obvious, and, as shall be discussed below, methodological issues exist as to the proper analysis and interpretation of such aggregate population time series data.

The previous criteria document (U.S. Environmental Protection Agency, 1986) discussed several methodological issues with regard to the epidemiological studies of $O_3$ and photochemical oxidants available at that time. Limitations identified included interferences by

or interactions with other pollutants and meteorological factors in the ambient environment; lack of comprehensive exposure issue assessments, such as individual activity patterns and evaluation of pollutant monitor appropriateness; difficulty in identifying the responsible oxidant species; and inadequate characterization of the study population. However, most of these criticisms are not relevant to time series studies. For example, because the same population is being followed from day to day, the study population acts as its own control, obviating the need for a detailed population characterization. Also, central site monitoring data can be useful in these studies for two reasons: (1) although $O_3$ concentrations can vary spatially within an airshed, they usually are highly correlated across sites over time, so that correlational time series studies are not as dependent on detailed exposure assessments as are, for example, cross-sectional studies; and (2) if the ultimate use of these studies is to be included as criteria for ambient standards, the attainment of which is evaluated at central monitoring stations, then these are the data most relevant for analysis. However, the usually high correlation of the 1-h daily maximum $O_3$ concentration with other averaging times (e.g., an 8-h average daily maximum) inhibits the ability of such time series studies to discriminate the most biologically relevant $O_3$ averaging time.

Of the concerns raised by the previous criteria document regarding epidemiological studies in general, the most relevant to time-series studies is the potential for other serially correlated environmental factors (e.g., temperature or other pollutants) to confound the unique identification of $O_3$ as a critical causal factor in any environmental health effects identified via time series analyses of aggregate population data. As discussed by Thurston and Kinney (1995), either upward or downward bias in the $O_3$ effect estimate can result if the model is misspecified. In the case of underspecification, if another environmental factor that is both serially correlated with $O_3$ over time and also may be causally related with the effect under consideration (e.g., temperature stress effects on mortality) is excluded from the analysis, then $O_3$ may "pick up" that environmental factor's effect in the model, biasing the $O_3$ coefficient upward. Conversely, the inclusion of variables in the model that are correlated with $O_3$ concentrations but are unlikely to be causally related to the health outcome (e.g., the inverse of wind speed) results in model overspecification, which may bias the $O_3$ coefficient downward. Only variables that are biologically plausible should be included in a time-series model, and intercorrelations of the model coefficients should be low if model specification bias is to be minimized.

One aspect of evaluating time series epidemiologic studies of the health effects of air pollution that was not raised directly by the previous criteria document but which can be crucial to proper interpretation is the statistical question of how each study has addressed the potentially confounding influences of long-wave (e.g., seasonal) variations in the health outcome data. The seasonality of morbidity and mortality was mentioned explicitly in Hippocrates' treatise on "Airs, Waters, and Places" and has been studied over the years (Hechter and Goldsmith, 1961). In respiratory diseases such as asthma, this seasonality of admissions is very common, due in part to the multifactorial nature of these diseases. For example, spring and fall increases in pollen and winter influenza epidemics superimpose long-wave cycles on the day-to-day variations in respiratory hospital admission rates. Such long-wave cycles need to be addressed as part of any time series analysis for two reasons: (1) they result in strong autocorrelations that violate the underlying assumptions of most statistical approaches used to analyze such data; and (2) their inclusion can lead to misleading conclusions (i.e., confounding), in that the long-wave relationships would likely obscure the

acute (i.e., short-wave) effects being evaluated. The need to address seasonal cycles in respiratory disease time series data in order to avoid spurious long-wave dominated correlations has long been recognized (e.g., Ipsen et al., 1969) but too often has been ignored or inadequately addressed in the published literature. Autocorrelation, although often contributed to by seasonal cycles in the data, can be introduced by other causes as well. For example, Lipfert (1993) noted the need for hospitalization studies to take into account both weekly and seasonal temporal patterns in the data. Thus, an important criterion for the evaluation of aggregate population time series studies of the acute morbidity and mortality effects of $O_3$ is whether or not the authors have appropriately addressed all long-wave periodicities in the data as part of their analysis.

There are a variety of statistical approaches available to address all long-wave confounding in time series analyses, each having advantages and disadvantages. The primary goal in invoking such procedures is to eliminate the long-wave autocorrelation "noise" in the data without inadvertently removing any $O_3$-related health effects "signal" at the same time. In particular, steps that address autocorrelation in the model but also remove or explain short-wave variance in the health outcome variable of interest (e.g., by applying prefilters to the series that affect periodicities down to a few days or by analyzing the residuals from prior regressions of the outcome variable on "control" variables that are correlated with $O_3$, such as temperature) carry with them the risk of also removing short-wave associations of interest before the actual analysis has begun. Furthermore, although there are standard regression diagnostics available to determine whether autocorrelation remains a significant problem (e.g., the Durbin-Watson statistic), no such check exists to determine whether the autocorrelation removal methods also have inadvertently removed an $O_3$-health effects association of interest. Thus, although steps must be taken in time series analyses to address the potentially large biases resulting from long-wave (e.g., seasonal) autocorrelations, care must be taken not to also remove the signal of interest when dealing with the autocorrelation problem.

### *Emergency Room Visits and Hospital Admissions*

Many investigators have evaluated the associations between hospital emergency room visits or hospital admissions and air pollution. Hospital admissions are far more common (as counts per day) than, for example, mortality, thereby providing greater statistical reliability and avoiding the distributional complications that may be presented by low counts. Also, admission to the hospital is a well defined endpoint, having the desirable feature that every patient must have been seen by a physician and deemed sick enough to require hospitalization. Emergency room (ER) visits provide larger daily counts, but are not necessarily as severe an endpoint. In a well-designed study in Quebec, Canada, hospital admission diagnosis at discharge was found to be very reliable, with the study confirming the classification of respiratory admissions in general 92% of the time, and asthma admissions 95% of the time (Delfino et al., 1993). Similarly, a study by Martinez et al. (1993) of respiratory emergency room admissions in Barcelona, Spain, during 1985 to 1989 concluded that identification of asthma admissions was highly reliable, as was the discrimination of asthma and COPD diagnoses. Daily series of hospital admissions thus represent an especially useful research resource for the investigation of the human health consequences of $O_3$ exposure.

Hospital admission and ER visit studies that have considered $O_3$ associations are summarized in Table 7-21. In the previous criteria documents (U.S. Environmental Protection Agency, 1978, 1986), such studies were found to give inconsistent results for

## Table 7-21. Hospital Admissions/Visits in Relation to Photochemical Oxidant Pollution: Time Series Studies[a]

| Concentration(s) (ppm) | Pollutant | Study Description | Results and Comments | Reference |
|---|---|---|---|---|
| 0.11 to 0.28 avg max 1 h during low and high periods, respectively | Oxidant | Comparison of admissions to Los Angeles County Hospital for respiratory and cardiac conditions during smog and smog-free periods from August to November 1954. | No consistent relationship between admissions and high-smog periods; however, statistical analyses were not reported. Clear seasonal trends in admissions (increasing from summer to winter) not addressed. | California Dept. of Public Health (1955[b], 1956[b], 1957[b]) |
| 0.12 avg concentration 6 a.m. - 1 p.m. | Oxidant | Respiratory and cardiovascular admissions to Los Angeles County Hospital for residents living within 8 mi of downtown Los Angeles between August and December 1954. | Inconclusive results; partial correlation coefficients between total oxidants and admissions were variable. Method of patient selection was not given. Other pollutants were not considered. Seasonal trend not addressed. | Brant and Hill (1964)[b] Brant (1965) |
| (Not reported) | Oxidant | Admissions of Blue Cross patients to Los Angeles hospitals with > 100 beds between March and October 1961; daily average concentrations of oxidant, $O_3$, CO, $SO_2$, $NO_2$, NO, and PM by Los Angeles air pollution control districts. | Correlation coefficients between admissions for allergies, eye inflammation, and acute upper and lower respiratory infections and all pollutants were statistically significant; correlations between cardiovascular and other respiratory diseases were significant for oxidant, $O_3$, and $SO_2$; significant positive correlations were noted with length of hospital stay for $SO_2$, $NO_2$, and $NO_x$. Correlations were not significant for temperature and RH or for pollutants with other disease categories. Reported seasonal variations in admissions and pollution not addressed. | Sterling et al. (1966[b], 1967[b]) |
| (Not reported) | Oxidant | Admissions for all adults and children with acute respiratory illness in four Hamilton, Ontario hospitals during the 12 mo from July 1, 1970, to June 30, 1971; city-avg pollution monitoring for $O_x$ (KI), $SO_2$, PM, CoH, CO, $NO_x$, HC, temperature, wind direction and velocity, RH, and pollen. | Correlation found between admissions and an air pollution index for $SO_2$ and CoH; negative correlation between temperature and admissions; and nonsignificant negative correlations found with concentrations of $O_x$ (KI). However, clear, long-wave trends (e.g., seasonality) not addressed. | Levy et al. (1977)[c] |
| (Not reported) | O | Emergency room visits for cardiac and respiratory disease in two major hospitals in the city of Chicago from April 1977 to April 1978; 1-h concentrations of $O_3$, $SO_2$, $NO_2$, NO, and CO from an EPA site close to the hospital, 24-h concentrations of TSP, $SO_2$, and $NO_2$ from the Chicago Air Sampling Network. | No significant association between admissions for any disease groups and $O_3$, CO, or TSP; $SO_2$ and NO accounted for part of the variation of ER visits for respiratory and cardiovascular admissions. However, the analysis has a lack of control for confounding, possible unaddressed seasonality in admissions (time series not shown), and model overspecification (e.g., use of wind speed). | Namekata et al. (1979)[c] |
| 0.07 and 0.39 avg max 1 h during low and high periods, respectively | $O_3$ | ER visits and hospital admissions for children with asthma symptoms during periods of high and low air pollution in Los Angeles from August 1979 to January 1980; daily maximum hourly concentrations of $O_3$, $SO_2$, NO, $NO_2$, HC, and CoH; weekly maximum hourly concentrations of $SO_4^=$ and TSP; biweekly allergens and daily meteorological variables from regional monitoring stations. | Asthma positively correlated with CoH, HC, $NO_2$, and allergens on same day and negatively correlated with $O_3$ and $SO_2$; asthma positively correlated with $NO_2$ on Days 2 and 3 after exposure; correlations were stronger on Day 2 for most variables; nonsignificant correlation for $SO_4^=$ and TSP. Monthly admissions and pollution data indicate strong seasonality, which is not accounted for. This results in (seasonally driven) positive correlations with CoH, HC, and $NO_2$ and negative correlations with $O_3$. | Richards et al. (1981)[c] |

**Table 7-21 (cont'd).  Hospital Admissions/Visits in Relation to Photochemical Oxidant Pollution:  Time Series Studies[a]**

| Concentration(s) (ppm) | Pollutant | Study Description | Results and Comments | Reference |
|---|---|---|---|---|
| 0.03 and 0.11 avg max 1 h for low and high areas, respectively | Oxidant | Daily hospital ER admissions in four Southern California communities during 1974 and 1975.  Max hourly average concentrations of oxidant, $NO_2$, NO, CO, $SO_2$, CoH; 24-h average concentrations of PM and $SO_4^=$; and daily meteorological conditions from monitoring sites 8 km from the hospitals. | Admissions significantly associated with oxidant and temperature in all locations.  Long-term trends and day-of-week effects appropriately controlled, but not seasonality.  Path-analysis-guided regression used to discriminate among the intercorrelated pollutant and meteorological factors, indicating $O_3$ to be most important only at the highest $O_3$ site.  However, lack of catchment area population figures and inadequate seasonality adjustments prevent quantitative use of results. | Goldsmith et al. (1983)[c] |
| 0.03 to 0.12 avg of max 1-h/day for 15 stations | $O_3$ | Admissions to 79 acute-care hospitals in Southern Ontario for the months of January, February, July, and August in 1974 and 1976 to 1983.  Hourly average concentrations of particulate (CoH), $O_3$, $SO_2$, $NO_2$, and daily temperature from 15 air sampling stations within the region. | Excess respiratory admissions most strongly associated ($p \square 0.001$) with $O_3$, sulfate, and temperature during July and August with 24- and 48-h lag.  No such associations exist for nonrespiratory (control) diseases.  Seasonality minimized by selection of narrow study period, and day-of-week effects controlled.  $SO_4^=$ and $O_3$ highly intercorrelated (r = 0.65), making effect discrimination difficult.  A lack of independent regression coefficients prevents quantitative application of results. | Bates and Sizto (1983, 1987, 1989) Bates (1985) |
| 0.025 to 0.075 3-mo avg of monthly means from all city sites | $O_3$ | Analysis of quarterly hospital admission rates for childhood asthma in Hong Kong during 1983-1987 (n = 19).  Quarterly means of $SO_2$, $NO_2$, NO, $O_3$, TSP, and RSP considered. | Concludes that asthma is negatively correlated with $SO_2$, but not with $O_3$.  However, analysis uses quarterly means and lacks seasonality controls. | Tseng and Li (1990) |
| 0.001 to 0.085 mean 1-h max $O_3$ (avg of 11 sites) | $O_3$ | Analysis of emergency room visits, by cause, to acute care hospitals in the Vancouver, BC, area July 1984 to October 1986.  $SO_2$, $NO_2$, $O_3$, $SO_4$, and temperature considered. | Summer (May to October) total emergency (but not respiratory) visits significantly correlated with temperature and $O_3$.  Day-of-week effects addressed.  Seasonality reduced by study period selection, but opposing within season cycles in asthma visits and $O_3$ not addressed, which may have weakened reported $O_3$-respiratory visit relationship.  Also, $O_3$ levels much lower than in previously studied in Southern Ontario. | Bates et al. (1990) |
| 0 to 0.13 avg of max 1 h/day for two stations | $O_3$ | ER admissions for COPD in Barcelona, Spain, during 1985 to 1986.  24-h avg $SO_2$ and BS city-wide averages.  1-h max $SO_2$, CO, $NO_2$, and $O_3$ obtained from two stations. | A weak but statistically significant association found between COPD admissions and levels of $SO_2$, BS, and CO, after accounting for seasonality and autocorrelation and during season-specific analyses.  However, $O_3$ was eliminated from the analysis based on its seasonally driven negative correlation with admissions (prior to long-wave controls).  Thus, no conclusions regarding $O_3$ can be made from this work. | Sunyer et al. (1991) |
| 0 to 0.04 daily mean | O | Hospital admissions for asthma in Helsinki, Finland, from 1987 to 1989; 24 h average $SO_2$, $NO_2$, TSP, and $O_3$ city-wide averages. | After accounting for daily minimum temperature, $NO_2$ and $O_3$ were significantly correlated on the same day as admissions, whereas $O_3$ was most significant on the prior day (p = 0.006).  However, long-wave peaks (e.g., in April for asthma) were not addressed and autocorrelation was not assessed. | Ponka (1991) |

## Table 7-21 (cont'd).  Hospital Admissions/Visits in Relation to Photochemical Oxidant Pollution:  Time Series Studies[a]

| Concentration(s) (ppm) | Pollutant | Study Description | Results and Comments | Reference |
|---|---|---|---|---|
| 0.06 to 0.13 mean of 1000 to 1500 hours $O_3$ (0.12 1-h max was exceeded on 42 of 226 total study days, whereas 0.08 was exceeded on 102 days) | $O_3$ | ER visits for asthma, bronchitis, and finger wounds (a nonrespiratory control) at nine hospitals in central New Jersey were analyzed for the period May to August 1988 and 1989.  Daily values of $O_3$ and $SO_2$ obtained from nearest of five monitoring sites.  Barometric pressure, temperature, RH, and visibility (as an index of sulfate) obtained from a Newark measurement station. | Bivariate correlations indicated asthma visits to be strongly negatively correlated with temperature and weakly negatively correlated with $O_3$, suggesting a seasonality influence, despite limitation to the $O_3$ season.  However, simultaneous regression of asthma visits on all environmental variables yielded significant (positive) $O_3$ and (negative) temperature coefficients only, suggesting that temperature acted as a long-wave control variable, revealing the short-wave $O_3$ relationship with asthma.  Day-of-week effects on visits found unimportant.  No environmental associations seen with bronchitis or control cases (finger cuts). | Cody et al. (1992) |
| 0.00 to 0.05 avg of daily means from 22 stations | $O_3$ | Admissions to 79 acute-care hospitals in Southern Ontario for the months of January, February, July, and August in 1979 to 1985.  Hourly average $O_3$, $SO_2$, $NO_2$, temperature, RH, wind speed, barometric pressure, and daily average TSP and $SO_4^=$. | An elaborate reanalysis of the Bates and Sizto (1989) data set augmented to 1985.  Long-wave influences controlled using time period subsets and AR modeling.  Despite possible overspecification of models (e.g., use of wind speed) and AR filtering of the short wave, results confirm Bates and Sizto's overall conclusions regarding significant $O_3$ associations.  Response to air pollution estimated to be 19 to 24% of summer respiratory admissions, although the exact contribution by $O_3$ to the total was not estimated. | Lipfert and Hammerstrom (1992) |
| 0.01 to 0.05 3-mo avg of daily means from all city sites | $O_3$ | Age-specific quarterly asthmatic hospital discharge rates in Hong Kong from 1983 to 1989 examined in relation to quarterly mean levels of TSP, RSP, $NO_2$, $NO_x$, and $O_3$ (n = 27). | Concludes that asthma morbidity is correlated with particles, but not $O_3$.  However, analysis uses quarterly means and lacks seasonality controls. | Tseng et al. (1992) |
| 0.03 to 0.21 1-h daily max at central site in each area | $O_3$ | Daily emergency admissions to acute care hospitals for asthma, total respiratory, and control disease categories in the New York City, Albany, and Buffalo, NY, metropolitan areas from June to August 1988 and 1989; daily 1-h maximum $O_3$ and temperature and daily average sulfate and acid aerosols ($H^+$) considered. | Significant positive associations found for $O_3$, $SO_4^=$, and $H^+$ with asthma and total respiratory admissions, but not for control categories.  Long-wave and day-of-week effects removed, and temperature effects controlled.  Strongest $O_3$ associations in higher pollution year (1988) and in more urban population centers (Buffalo and New York, NY). | Thurston et al. (1992) |
| 0.01 to 0.16 1-h daily max at central site | $O_3$ | Daily admissions to 22 acute care hospitals in Toronto, Ontario, for asthma, total respiratory, and control disease categories during July and August 1986, 1987, and 1988; daily 1-h maximum $O_3$, $SO_2$, $NO_2$, temperature, and daytime (9:00 a.m. to 5:00 p.m.) $SO_4^=$ and $H^+$ considered. | Significant positive correlations found for $O_3$, $H^+$, $SO_4^=$, $PM_{10}$, and TSP with asthma and for total respiratory admissions, but not for $SO_2$ or $NO_2$, and not with control admissions.  Long-wave and day-of-week effects removed.  Multivariate regressions and sensitivity analyses suggested that $O_3$ was the pollutant of primary importance, but $H^+$ may potentiate $O_3$ effects.  Except for $H^+$, all PM metrics considered became nonsignificant when entered into regressions simultaneously with $O_3$.  Ozone significant even after dropping days >0.12 ppm. | Thurston et al. (1994) |

## Table 7-21 (cont'd).  Hospital Admissions/Visits in Relation to Photochemical Oxidant Pollution:  Time Series Studies[a]

| Concentration(s) (ppm) | Pollutant | Study Description | Results and Comments | Reference |
|---|---|---|---|---|
| 0.01 to 0.15 1-h daily max | $O_3$ | Daily emergency respiratory admissions to 168 acute care hospitals in Ontario, Canada, during May to August 1983 to 1988 were related to daily levels of $O_3$ and $SO_4$ at the nearest of 22 and 9 monitoring sites, respectively.  Admissions broken into 0 to 1, 2 to 34, 35 to 64, and 65+ age groups, and by geographical subregion. | Ozone and $SO_4^=$ positively and significantly associated with admissions for asthma and COPD in all age groups.  Associations consistent across regions.  Seasonal and day of week effects addressed prior to analysis.  Analyses also controlled for individual hospital influences.  No pollutant associations found for nonrespiratory control admissions.  Simultaneous regressions suggest $O_3$ to be more important than $SO_4^=$. | Burnett et al. (1994) |
| 0.01 to 0.11 1-h daily max averaged over seven sites in Montreal | $O_3$ | Daily urgent hospital admissions to 31 hospitals in Montreal, Canada, during May-October and August-July from 1984-1988 related to daily levels of $O_3$, $SO_4$, $PM_{10}$, temperature, and humidity.  Admissions broken into asthma, nonasthma respiratory, total respiratory, and a nonrespiratory "control" group of admissions categories. | Ozone and temperature positively and significantly correlated with total respiratory admissions during the July-August period, but not with control admissions categories.  However, $O_3$ and T are both nonsignificant when entered simultaneously. | Delfino et al. (1994a) |
| 0.02 to 0.16 1-h avg daily max 0.01 to 0.12 8-h avg daily max | $O_3$ | Daily numbers of emergency asthma visits by patients 1 to 16 years old to an inner city hospital in Atlanta, GA, from June to August 1990 were related to daily levels of $O_3$, $SO_2$, $PM_{10}$, pollen, and T. | Hospital visits were found to be significantly higher on days when the previous day's 1-h max $O_3$ exceeded 0.11.  No relationship was found below 0.11, or with 8-h avg daily maximum $O_3$.  Day-of-week effects were accounted for.  Seasonality effect reduced by study period selection, but probable long-wave seasonal cycles superimposed on the day-to-day fluctuations were not directly addressed, which probably weakened the reported $O_3$-admissions associations. | White et al. (1994) |
| 0.01 to 0.04 (10th to 90th percentile) 24-h daily avg | $O_3$ | Daily respiratory admissions by patients ≥ 65 years of age in Birmingham, AL, from 1986 to 1989 were related to daily levels of $O_3$, $PM_{10}$, temperature, and dew point.  COPD and pneumonia admissions examined.  Multiple $O_3$ monitoring sites averaged, but the numbers of sites varied over time. | COPD and pneumonia admissions positively correlated with $O_3$ and $PM_{10}$ over time.  A 50 ppb increase in 24 h average $O_3$ was associated with RR = 1.14 for pneumonia (95% CI = 0.94 to 1.38) and RR = 1.17 for COPD (95% CI = 0.86 to 1.60).  Seasonal fluctuations addressed using 48 monthly dummy variables.  Auto-regression methods employed to reduce autocorrelation.  Day-of-week effects not addressed. | Schwartz (1994a) |
| 0.01 to 0.04 24-h daily avg (10th to 90th percentile) 0.02 to 0.09 1-h avg daily max (10th to 90th percentile) | $O_3$ | Daily respiratory admissions for patients ≥ 65 years of age in Detroit, MI, from 1986 to 1989 were related to daily levels of $O_3$, $PM_{10}$, temperature, and dew point. | Pneumonia and COPD respiratory admissions were found to be significantly associated with both $PM_{10}$ and $O_3$, even after eliminating noncompliance days.  Monthly dummy variables were employed to account for seasonal variations, but day of week effects were not addressed.  Asthma admissions were not associated with pollution, but this was attributed to the very low counts in this category for the elderly. | Schwartz (1994b) |

**Table 7-21 (cont'd).  Hospital Admissions/Visits in Relation to Photochemical Oxidant Pollution:  Time Series Studies[a]**

| Concentration(s) (ppm) | Pollutant | Study Description | Results and Comments | Reference |
|---|---|---|---|---|
| 0.01 to 0.04 (10th to 90th percentile) 24-h daily avg | $O_3$ | Daily respiratory admissions for patients ⃞65 years of age in Minneapolis-St. Paul, MN, from 1986 to 1989 were related to daily levels of $O_3$, $PM_{10}$, temperature, and dew point. | Pneumonia respiratory admissions were significantly associated with $O_3$ and $PM_{10}$.  No $O_3$-COPD association was found.  The pneumonia RR associated with a 50-ppb increase in 24-h average $O_3$ was RR = 1.22 (95% CI = 1.02 to 1.47).  Excluding days with 1-h max $O_3$ above 120 ppb did not alter results.  Various methods, including the use of monthly dummy variables, were used to control for seasonality effects, all yielding similar results. | Schwartz (1994c) |
| 0.053 (±0.005) Mean (±SD) 10 a.m. to 3 p.m. avg | $O_3$ | ER visits for asthma at central New Jersey hospitals from May to August 1986 to 1989 related to daily levels of $O_3$ and temperature.  Other environmental variables considered include RH, sulfates, $NO_2$, $SO_2$, and visibility. | Asthma visits were significantly associated with $O_3$ and a.m. temperature, but not with other environmental variables considered.  $O_3$ coefficient implies a 44% mean effect, but unaddressed temperature effects may be a confounding factor.  An analysis limited to July and August reduces this concern, yielding a 16% mean effect by $O_3$. | Weisel et al. (1995) Weisel (1994) |

[a]See Appendix A for abbreviations and acronyms.
[b]Reviewed in U.S. Environmental Protection Agency (1978).
[c]Reviewed in U.S. Environmental Protection Agency (1986).

reasons that were not apparent.  A common weakness of many of those studies,  however, was a failure to control adequately for seasonal differences in hospital usage and $O_3$ concentration. Therefore, each of the updated critiques in this table now includes an evaluation of how the data were (or were not) controlled for long-wave influences (e.g., seasonality).  With this factor taken into account, the older studies' varying results are now more understandable.  In a number of these studies, documented long-wave periodicities in the data were ignored, resulting in nonsignificant associations (i.e., California Department of Public Health, 1955, 1956, 1957; Brant and Hill, 1964; Brant, 1965; Levy et al., 1977; Namekata et al., 1979) or even significant negative correlations between $O_3$ and hospital visits and admissions (Richards et al., 1981) as a result of the generally higher respiratory admission rates in the colder months, when $O_3$ levels are at their lowest.  Two studies that did not control for seasonality still reported significant positive correlations between hospital admissions and oxidants (Sterling et al., 1966, 1967; Goldsmith et al., 1983), although Sterling et al. excluded the winter months from the analysis and Goldsmith et al. did detrend the data.  Also, unlike any of the previously cited studies, both of these analyses controlled for day-of-week effects on hospital admission rates (e.g., due to consistently lower admissions on weekends), an important factor in hospital admissions variations that also must be addressed (see Sterling et al., 1966).  Moreover, the one previously reviewed study that adequately controlled for both long-wave and day-of-week influences (Bates and Sizto, 1983, 1987, 1989) reported very significant associations (p < 0.001) between $O_3$ levels and summertime (July and August) respiratory hospital admissions.  However, other intercorrelated environmental variables (e.g., acidic sulfates) also may have been cofactors in this association (Bates and Sizto, 1987). Overall, a review of these older studies suggests that, if the data are analyzed using newer statistical techniques, a significant association may be found  between elevated ambient $O_3$ concentrations and acute increases in daily respiratory hospital admissions.

Since the last criteria document (U.S. Environmental Protection Agency, 1986), a number of new ER visit and hospital admissions studies have been completed, a few of which share some of the same statistical flaws found in many of the older studies.  For  example, Tseng and Li (1990) and Tseng et al. (1992) failed to control for the seasonality of admissions and pollutants in their statistical analyses of quarterly hospital admissions in Hong Kong, causing them to report no associations with $O_3$, but a significant (and likely spurious) negative correlation of age-specific asthma admissions with quarterly mean $SO_2$ in the first of these papers and a significant (and also likely spurious) positive association with TSP in the second paper, but no association with $O_3$.  Sunyer et al. (1991) failed to consider seasonality in their initial evaluation of an $O_3$ relationship with COPD hospital admissions in Barcelona, Spain; causing them to eliminate $O_3$ from consideration in the study and any evaluation of possible health effects.  Also, Bates et al. (1990), using a largely descriptive approach, characterized the seasonal periodicities of Vancouver, BC, respiratory ER visits.  Their subanalysis of the warm season (May through October) included a dominant fall asthma peak, which would obscure any summertime $O_3$ associations, and therefore, little can be inferred from this data analysis about the existence or nonexistence of an acute relationship between $O_3$ and Vancouver hospital visits for respiratory causes.  Ponka (1991) showed significant $O_3$ associations with asthma hospital admissions in Helsinki, Finland, over a 3-year period. The model also included temperature, but did not address directly the noted long-wave variations in both admissions and pollution.  Thus, whether a study has adequately addressed statistical confounding by the prominent long-wave cycles in respiratory hospital admissions

series, which are clearly dominated by other causes (e.g., spring pollen, fall respiratory infection, winter influenza seasons), continues to be a crucial criterion in evaluating the usefulness of a study's results.

Fortunately, there are also a number of new studies that have addressed both long-wave and day-of-week influences in their analyses. Cody et al. (1992) did not control directly for seasonality, but they did narrow their analysis of central New Jersey hospital ER visits to the high $O_3$ season (May through August). Even so, their initial correlational analysis yielded negative associations between hospital visits and both temperature and $O_3$, which suggests that within-season long-wave effects existed (e.g., generally higher asthma visits in May, at the end of the pollen season, when $O_3$ and temperature are lower on average than in July or August). However, the authors did conduct subsequent regressions of respiratory visits on both temperature and $O_3$ simultaneously, yielding a significant positive coefficient for $O_3$ and a negative coefficient for temperature, which suggests that the inclusion of temperature may have indirectly accounted for the long-wave cycle, allowing the positive short wave $O_3$-visit relationship to be seen. Day-of-week influences were considered, but found to be unimportant for these ER visit data. No such pollution-hospital visit relationship was found for finger cut (i.e., control disease) visits.

Weisel et al. (1995) examined central New Jersey hospital ER visits for asthma (mean = 5.4/day) during the high $O_3$ season (May through August) for 1986 through 1990. Using a stepwise regression analysis, a significant positive coefficient for $O_3$ and a negative coefficient for morning temperature was found. Other environmental factors considered, including rate of temperature change, RH, every-sixth-day sulfates, $NO_2$, $SO_2$, and visibility (an index of fine particles [FPs]), were not found to be correlated with asthma visits. This study did not directly address long-wave confounding, instead following the same approach as Cody et al. (1992) in using temperature to indirectly control for such seasonal confounding and diminishing autocorrelation to nonsignificance (DW = 2). However, it is not clear to what extent $O_3$ may be inadvertently picking up short-wave temperature effects not modeled by this specification. These are likely to be opposite to the seasonal effect apparently being captured by the temperature variable (as indicated by its negative coefficient). The highest $O_3$ coefficient was found on the lowest $O_3$ year, which is consistent with unaddressed confounding. Thus, the $O_3$ effects reported (which imply an overall $O_3$ mean effect equal to 44% of all asthma visits) should be viewed as maximum effects estimates, possibly contributed to by colinear high temperature influences. Indeed, limiting the analysis to July and August of each year (thereby reducing long-wave confounding) resulted in a less negative temperature coefficient and an overall $O_3$ coefficient one-third of that for May through August (Weisel, 1994), implying approximately a 16% mean effect, which is more consistent with published hospital admissions study results. A covariance analysis presented indicates an average 28% increase in the number of hospital ER visits for asthma on high-$O_3$ days (above 0.06 ppm) versus low-$O_3$ days (below 0.06 ppm) after controlling for temperature, but seasonal cycles were again not directly accounted for in the analysis. Overall, these results are consistent with an $O_3$ effect on asthma morbidity.

Thurston et al. (1992) analyzed unscheduled (emergency) admissions to acute care hospitals in three New York State metropolitan areas during the summers of 1988 and 1989. Environmental variables considered included daily 1-h maximum $O_3$ and 24-h average $SO_4$ and acid aerosol ($H^+$) concentrations, as well as daily maximum temperature recorded at central sites in each community. Long-wave periodicities in the data were reduced by selecting a June

through August study period.  However, because of remaining within-season long-wave cycles in the data series (i.e., day-to-day fluctuations superimposed on an annual cycle in admissions), data were prefiltered using sine and cosine waves with annual periodicities.  Day-of-week effects also were controlled via regression.  These adjustments resulted in nonsignificant autocorrelations in the data series and also improved the pollution correlations with admissions.  For example, in New York City, the same-day $O_3$-asthma correlation rose from a nonsignificant r = 0.04 in the raw data to a significant r = 0.24 after prefiltering.  This shows the importance of addressing long-wave cycles in such data, even when these data come from a single season.  In contrast, correlations between the pollution data and hospital admissions for nonrespiratory control diseases were nonsignificant both before and after prefiltering.  The strongest $O_3$-respiratory admissions associations were found during the period of high pollution in the summer of 1988 and in the most urbanized communities considered (i.e., Buffalo and New York City).  After controlling for temperature effects via simultaneous regression, the summer haze pollutants (i.e., $SO_4^=$, $H^+$, $O_3$) remained significantly related to total respiratory and asthma admissions.  However, these pollutants' high intercorrelation prevented the clear discrimination of a single pollutant as the causal agent.  Depending on the index pollutant, the admission category, and the city considered, it was found that summer haze pollutants accounted for approximately 5 to 20% of June through August total respiratory and asthma admissions, on average, and that these admissions increased approximately 30% above average on the highest pollution days.

Lipfert and Hammerstrom (1992) reanalyzed the Bates and Sizto (1989) hospital admissions data set for 79 acute-care hospitals in southern Ontario, incorporating more elaborate statistical methods and extending the data set through 1985.  Long-wave influences were once again reduced by using the short study periods previously employed by Bates and Sizto (e.g., July and August only for summer), as well as by employing prewhitening and autoregressive procedures to the data.  Day-of-week effects also were controlled.  In addition, the models were specified much more extensively, to include a variety of new meteorological variables that may have caused some confounding with the pollutant variables (e.g., wind speed correlated at r = $\Box$0.55 with $NO_2$).  Despite possible model overspecification (e.g., the inclusion of wind speed), summer haze pollutants (i.e., $O_3$, $SO_4$, $SO_2$) were still found to have significant effects on hospital admissions in southern Ontario.  In contrast, pollution associations with hospital admissions for accidental causes became nonsignificant in these models.  Although air pollution concentrations were generally within U.S. air quality standards, the pollutant mean effect accounted for 19 to 24% of all summer respiratory admissions, although the "responsible" pollutants could not be selected by the authors with certainty.

Burnett et al. (1994) also employed the Ontario acute care hospital database to analyze the effects of air pollution on hospital admissions, but their analysis considered all of Ontario and analyzed the data from each individual hospital, rather than aggregating the counts by region.  Slow moving temporal cycles, including seasonal and yearly effects, were removed (via an 19-day, moving-average-equivalent, high-pass filter), and day-of-week effects were controlled prior to the analysis.  Poisson regression techniques were employed because of the low daily admission counts at individual hospitals.  Ozone displayed a positive association with respiratory admissions in 91% of the 168 hospitals, and 5% of summertime (May through August) respiratory admissions (mean = 107/day) were attributed to $O_3$ (mean = 50 ppb).  Positive associations were found in all age groups (0 to 1, 2 to 34, 35 to 64, and 65+).  A

parallel analysis of nonrespiratory admissions showed no such associations, which indicates the association specificity. Ozone was found to be a stronger predictor of admissions than $SO_4$, which accounted for an additional 1% of summertime respiratory admissions. Temperature had no effect on the pollution-respiratory admission relationship.

Thurston et al. (1994) focused their analysis of respiratory hospital admissions in the Toronto metropolitan area during the summers (July through August) of 1986 to 1988, when they directly monitored for strong particulate acidity ($H^+$) pollution on a daily basis at several sites in that city. Long-wave cycles, and their associated autocorrelations, were removed by first fitting sine and cosine series having annual periodicity (as well as day-of-week dummy variables) to the data via regression, and analyzing the resulting residuals. Strong and significant positive associations with asthma and respiratory admissions were found for both $O_3$ and $H^+$, and somewhat weaker significant associations with $SO_4^=$, $PM_{2.5}$, $PM_1$, and TSP, as measured at a central site in downtown Toronto. No such associations were found for $SO_2$ or $NO_2$, nor for any pollutant with nonrespiratory control admissions. Temperature was only weakly correlated with respiratory admissions and became nonsignificant when entered in regressions with air pollution indices. Simultaneous regressions and sensitivity analyses indicated that $O_3$ was the summertime haze constituent of greatest importance to respiratory and asthma admissions, although elevated $H^+$ was suggested as a possible potentiator of this effect. During multipollutant, simultaneous regressions on admissions, $O_3$ was consistently the most significant. Of the particle metrics, only $H^+$ remained statistically significant when entered into the admissions regressions simultaneously with $O_3$. Sensitivity analyses also showed that dropping all days above the current U.S. $O_3$ standard of 0.12 ppm (2 of a total 117 days) did not significantly change the $O_3$ coefficients. The simultaneous $O_3$, $H^+$, and temperature model indicated that $21 \pm 8\%$ of all respiratory admissions during the three summers were associated with $O_3$ air pollution, on average, and that admissions rose an estimated $37 \pm 15\%$ above that otherwise expected on the highest $O_3$ day (0.159 ppm). Moreover, despite differing health care systems, the Toronto regression results for the summer of 1988 were remarkably consistent with previously reported results for that same summer in Buffalo, NY, (see Table 7-22).

Delfino et al. (1994a) studied daily urgent hospital admissions for respiratory and other illnesses at 31 hospitals in Montreal, Canada during the warm periods of the year between 1984 and 1988. Respiratory admissions were considered as a whole and split into asthma and nonasthma categories, using definitions compatible with those previously used by Bates and Sitzo (1987) and by Thurston et al. (1994). Both 1-h and 8-h maximum $O_3$ concentrations were considered in the analyses, as well as weather variables (temperature and relative humidity) and PM measurements, although 83% (five out of every six) PM measurements were not directly measured but, instead, were estimated from other environmental variables including visibility, temperature, and $O_3$ concentration on those missing PM days (Delfino et al., 1994b). Seasonal cycles were addressed by applying a 19-day moving average high-pass filter to the health and environmental data before analysis for associations. Day-of-the-week and autocorrelation effects also were addressed, when present. For the months of July and August, during the study period, a significant association was found between all respiratory admissions and both 8-h daily maximum $O_3$ (p $\square$ 0.01) and 1-h daily maximum $O_3$ (p $\square$ 0.03) 4 days prior to admission, despite the fact that no day exceeded 0.12-ppm 1-h daily maximum $O_3$ (90th percentile $= 118 \; \square g/m^3$ or 0.06 ppm $O_3$). Of the significant bivariate environmental-admission associations found, the association with 8-h

maximum $O_3$ was the highest reported (r = 0.15), tied only by the 4-day lag in temperature. However, the addition into the regression of temperature on the

**Table 7-22. Comparison of Regressions of Daily Summertime Respiratory Admissions on Ozone and Temperature in Toronto, Ontario, and Buffalo, New York, for the Summer of 1988[a]**

| City and Year | Respiratory Admissions Category | Temperature, Pollutant Model Specification | Pollutant Regression Coefficient (Admissions/ppb/$10^6$ persons $\pm$ SE) | Pollutant Mean Effect (% $\pm$ SE) | Max/Mean Pollutant Relative Risk $\pm$ SE |
|---|---|---|---|---|---|
| Toronto (pop. = 2.4 $\times$ $10^6$) 1988 summer | Total respiratory (mean = 14.1/day) | T(LG2), $O_3$ (LG1)[b] | 0.022 $\pm$ 0.010[c] | 26.4 $\pm$ 11.8 | 1.34 $\pm$ 0.15 |
| Toronto (pop. = 2.4 $\times$ $10^6$) 1988 summer | Total asthma (mean = 9.5/day) | T(LG2), $O_3$ (LG1) | 0.014 $\pm$ 0.008[c] | 25.3 $\pm$ 14.9 | 1.32 $\pm$ 0.19 |
| Buffalo (pop. = 2.0 $\times$ $10^6$) 1988 summer | Total respiratory (mean = 25.0/day) | T(LG2), $O_3$ (LG2) | 0.030 $\pm$ 0.016[c] | 18.4 $\pm$ 9.9 | 1.25 $\pm$ 0.09 |
| Buffalo (pop. = 2.0 $\times$ $10^6$) 1988 summer | Total asthma (mean = 7.1/day) | T(LG2), $O_3$ (LG3) | 0.012 $\pm$ 0.004[d] | 23.9 $\pm$ 10.1 | 1.25 $\pm$ 0.14 |

[a]See Appendix A for abbreviations and acronyms.
[b]LG = lag between exposure and admission, in days.
[c]$p < 0.05$ (one-way test).
[d]$p < 0.01$ (one-way test).

Source:  Thurston et al. (1994).

same day as the $O_3$ reduced both the $O_3$ and the temperature associations to nonsignificance.  It should be noted that the authors also found a significant association between asthma admissions and their estimated $PM_1$ variable during May through October; however, because both temperature and $O_3$ were used to estimate these observations, it is difficult to interpret this association separately from that for $O_3$ and temperature.  No significant correlations were found between $O_3$ and nonrespiratory, control admissions (e.g., appendicitis).  The authors conclude that their findings "should be regarded as a reflection of the potential public health burden of respiratory disease attributable to photochemical air pollutants."

White et al. (1994) reported daily emergency room visit records from June through August 1990 at a large inner city hospital in Atlanta, GA.  Daily counts of visits for asthma or reactive airway disease by patients 1 to 16 years of age (mean = 6.6/day) were related to daily levels of $O_3$, $SO_2$, $PM_1$, pollen, and temperature.  Seasonality likely was reduced by the study period selection, although no effort was made to address possible within-season long-wave cycles in the data.  Day-of-week and temperature effects were controlled as part of a Poisson model employed to address the small admission numbers at a single hospital.  This model yielded a 1.42 admissions rate ratio (p = 0.057, 95% CI = 0.99 to 2.0) for the number of asthma visits following days with $O_3$ levels equal to or exceeding a 1-h maximum of 0.11 ppm, which is consistent with the relative risk values reported by Thurston et al. (1992, 1994).  No admissions relationship with $O_3$ was seen below 0.11 ppm or with 8-h average $O_3$.

In a study of Birmingham, AL, data, Schwartz (1994a) separately examined $O_3$ and $PM_1$ influences on hospital admissions by the elderly for pneumonia (mean = 5.9/day) and COPD (mean = 2.2/day) causes from 1986 to 1989.  Other potentially confounding pollutants (e.g., $SO_2$ and $NO_2$) were not considered, nor was any control admission category analyzed.  Poisson regression analyses were employed controlling for time trends, seasonal fluctuations, and weather, but day-of-week effects (which can be a large influence on such admissions) were not addressed.  Weather was controlled by including dummy variables for seven (unspecified) temperature and dew point range categories in the regression.  Seasonal fluctuations were controlled through the use of 48 monthly dummy variables, which raises the concern that within-month long-wave confounding may have remained.  However, autoregressive models were reportedly used whenever serial correlation was found in model residuals.  Base model results (excluding winter months) yielded a 2-day lag relative risk (RR) estimate of 1.14 for pneumonia admissions from a 50 ppb increase in 24-h average $O_3$ (95% confidence interval, CI = 0.94 to 1.38).  Excluding days exceeding 120 ppb yielded similar results (RR = 1.12, CI = 0.92 to 1.37).  For COPD, the basic model yielded a RR = 1.17 (CI = 0.86 to 1.60), whereas excluding days above 120 ppb similarly  gave RR = 1.18 (CI = 0.86 to 1.62).  No models considered $O_3$ and $PM_1$ simultaneously.  Two other comparative models (the inclusion of sine/cosine cycles of various periodicities up to 2 years in the regression and the analysis of deviations from a nonparametric smoothing of admission counts) were tested for $PM_1$, but not for $O_3$, so the model sensitivity of the $O_3$ effect was not tested.  Overall, even after excluding days exceeding the standard, this work indicated a fairly consistent $O_3$ effect across respiratory categories that approached, but did not reach, statistical significance.

Schwartz (1994b) analyzed $O_3$ and $PM_1$ air pollution relationships with daily hospital admissions of persons 65 years or older in the Detroit, MI, metropolitan statistical area from 1986 to 1989.  Daily counts for pneumonia (mean = 15.7/day), asthma (mean = 0.75/day), and all other COPDs (mean = 5.8/day) were regressed on the pollution variables and various seasonal, trend, and temperature dummy variables, using Poisson

modeling. However, day-of-week effects were not addressed. Ozone was analyzed with respect to both its daily 24-h average and 1-h maximum. Autoregressive analyses and residuals plots indicated no remaining autocorrelation in the model. Both $O_3$ and $PM_1$ were significant in simultaneous pollutant models for pneumonia and COPD but not for asthma (which was ascribed to the low daily counts for this category). These simultaneous coefficients were reportedly similar to those from the single pollutant models, although the correlations of the coefficients were not provided. Dropping all days exceeding the 1-h maximum $O_3$ standard did not change the size of the $O_3$ coefficients, which remained significant ($p < 0.01$). Based on the regression coefficients and data presented, it can be estimated that the mean effect for $O_3$ (11.6%) was double that for $PM_1$ (5.7%) in the pneumonia model, but comparable for COPD (12.2% for $O_3$ versus 10.2% for $PM_1$). On an absolute scale, these results imply that $O_3$ was associated with 1.7 ($\pm$0.2) respiratory admissions by the elderly/day/100 ppb (as a 1-h maximum) per million persons in the Detroit metropolitan area. This estimate does not include admissions by persons less than 65 years of age (which likely would have included higher asthma admissions, for example), so that the total respiratory admissions associated with $O_3$ in the entire population likely would be higher than estimated from this work.

Schwartz (1994c) evaluated the associations of both $PM_1$ and $O_3$ with respiratory hospital admissions by the elderly in Minneapolis-St. Paul, MN, from 1986 to 1989. Due to small counts, Poisson modeling methods were employed. Various modeling approaches were employed to address weather influences, including (1) the use of annual, monthly, temperature, and dew point dummy variables; (2) a stepwise spline approach to fit data dependence on time, temperature, and dew point (an indicator of the water content of the air); and (3) a generalized additive model using nonparametric smooth functions of time, temperature, and dew point temperature. Autoregressive methods were employed to eliminate autocorrelations, when significant. However, these various complex statistical manipulations were not sufficiently documented to permit critical review of these methods or replication of results (e.g., dummy variable ranges were not provided and statistical packages were not referenced). Although no association was found for COPD in the elderly, $O_3$ did make a significant independent contribution to hospital admissions by the elderly for pneumonia (mean = 6.0/day), even after controlling for weather and $PM_1$. Although all models gave similar results, the best data fit (as measured by analysis of deviance) and strongest $O_3$ association was reported for the stepwise spline model, which yielded a pneumonia admissions relative risk of 1.22 (95% CI = 1.02 to 1.47) for a 50 ppb increase in the 1-day lag of the 24-h average of $O_3$. The use of 1-h daily maximum $O_3$ in these analyses reportedly yielded less significant associations with admissions. However, eliminating days with either $PM_1$ above 150 $\mu g/m^3$ or a 1-h maximum $O_3$ above 120 ppb from the analysis did not alter results significantly.

Table 7-23 intercompares the $O_3$-respiratory hospital admissions effect estimates for the various studies providing sufficient information to allow the derivation of such pollutant-specific estimates. The estimates are presented in two ways: (1) as an absolute number of daily admissions per 100-ppb increase in 1-h $O_3$ concentration per million persons, total population, and (2) as a percent increase in the daily admission rate of the relevant admissions category, presented as a relative risk per 100-ppb increase in 1-h $O_3$ concentration. A reference increment of 100-ppb $O_3$ is employed here because this is

## Table 7-23. Summary of Effect Estimates for Ozone in Recent Studies of Respiratory Hospital Admissions[a]

| Location | Reference | Respiratory Admission Category | Effect Size ($\pm$ SE) [Admissions/100 ppb $O_3$/day/$10^6$ persons] | Relative Risk (95% CI)[b] [RR of 100 ppb $O_3$, 1-h max] |
|---|---|---|---|---|
| New York City, NY[c] | Thurston et al. (1992) | All | | |
| Buffalo, NY[c] | Thurston et al. (1992) | All | | |
| Ontairo, Canada[c] | Burnett et al. (1994) | All | | |
| Toronto, Canada[c] | Thurston et al. (1994) | All | | |
| Montreal, Canada[d] | Delfino et al. (1994a) | All | | |
| Birmingham, AL[e] | Schwartz (1994a) | Pneumonia in elderly | 0.73 ($\pm$ 0.54) | |
| Birmingham, AL[e] | Schwartz (1994a) | COPD in elderly | 0.83 ($\pm$ 0.33) | |
| Detroit, MI[e] | Schwartz (1994b) | Pneumonia in elderly | 0.82 ($\pm$ 0.26) | |
| Detroit, MI[e] | Schwartz (1994b) | COPD in elderly | 0.90 ($\pm$ 0.41) | |
| Minneapolis, MN[e] | Schwartz (1994c) | Pneumonia in elderly | 0.41 ($\pm$ 0.19) [f] | 1.117 (1.03 to 1.39) [f] |
| Minneapolis, MN[e] | Schwartz (1994c) | COPD in elderly | | |

[a]See Appendix A for abbreviations and acronyms.
[b]One-way ( $\pm$ 1.65 SE).
[c]1-h daily maximum ozone data employed in analysis.
[d]8-h daily maximum ozone data employed in analysis.
[e]24-h daily average ozone data employed in analysis.  (1 h/24 h avg ratio = 2.5 assumed to compute effects and RR estimates).
[f]Not reported (nonsignificant).

approximately the difference between the maximum and the mean 1-h daily maximum $O_3$ in these studies (e.g., in Toronto, the 1988 mean = 69 ppb; maximum = 159 ppb). The absolute effect estimates relative to total population have the advantages that the total effect can be readily "partitioned" into subcategories (e.g., by age group or disease subcategory), and it also can be applied easily to other situations (i.e., only the population and $O_3$ levels are required), but this may not be appropriate if the other population makeup is very different from the study populations (e.g., in age distribution). The relative risk estimates are intuitively interpretable but are not as readily applied elsewhere (i.e., the respiratory disease prevalence rates must be known), and the effect will vary depending on the prevalence, which differs widely between populations and even throughout the year within a single population (as respiratory morbidity is generally higher in winter than summer). For example, this accounts for much of the apparent inconsistency between the Burnett et al. (1994) and Thurston et al. (1994) relative risks, in that the Thurston et al. (1994) Toronto values are for July and August only (when the prevailing number of respiratory admissions per day are generally at an annual minimum), whereas the Burnett et al. (1994) Ontario values are relative to respiratory admissions averages over more months of the year, yielding one-fourth the effect as a relative risk, even though the absolute effect estimate is two-thirds of the Thurston et al. (1994) estimate. In the case of the Schwartz studies of the elderly, the assumption has been made, based on data presented by Schwartz (1994b), that the 1-h daily maximum $O_3$ is 2.5 times the 24-h average, and the 100-ppb 1-h maximum estimates provided for these studies therefore are derived from a 40-ppb increase in 24-h average $O_3$. The absolute effect size results from these particular studies suggest that a large portion of the $O_3$ effects noted in the previous total respiratory admissions studies are contributed by COPD and pneumonia cases in the elderly. Based on results presented by Thurston et al. (1992, 1994), the other major contributor is asthma admissions, which are usually more prevalent in younger age groups. Overall, the results presented in Table 7-23 collectively indicate that ambient $O_3$ often has a significant effect on hospital admissions for respiratory causes, ranging in these studies from 1 to 3 total respiratory admissions/day/100 ppb $O_3/10^6$ persons, or from a 1.1 to 1.36 relative risk/100 ppb $O_3$.

### *Daily Mortality*

Past studies of the possible association of $O_3$ (oxidants) with human mortality summarized in prior $O_3$ criteria documents (U.S. Environmental Protection Agency, 1978, 1986) were sometimes suggestive of an association, but each study was flawed in some way. These studies are included in Table 7-24, with annotation as to the document in which they were reported. Most of these studies considered daily mortality in Los Angeles, CA, during the 1950s and 1960s. Unlike most historical hospital admissions studies, many of these studies did recognize and attempt to control for seasonality in the data series. Notable exceptions are the California Department of Public Health studies (1955, 1956, 1957), which were further weakened by their qualitative treatment of the air pollution data. The Mills (1957a,b) analyses also employed a questionable exposure assessment method (the Standard Research Institute smog index), which diminishes its usefulness. Massey et al. (1961) reported no significant correlations between community differences in mortality and differences in oxidant levels over time, but the investigators compared two communities with very different populations (e.g., age distributions), a likely confounder in such cross-sectional comparisons. Mills (1960), while reporting mortality-oxidant associations and effects (370 respiratory and cardiovascular deaths/year), did not control for potential temperature

## Table 7-24.  Daily Mortality Associated with Exposure to Photochemical Oxidant Pollution[a]

| Concentration(s) (ppm) | Pollutant | Study Description | Results and Comments | Reference |
|---|---|---|---|---|
| ≤1.0 peak (undefined) | Oxidant | Relationship between daily concentrations of photochemical oxidants and daily mortality among residents of Los Angeles County aged 65 years and older during the periods August through November 1954 and July through November 1955. | Heat had a significant effect on mortality; no consistent association between mortality and high oxidant concentrations in the absence of high temperature. However, seasonal trends were not addressed, and pollution data treatment was qualitative. | California Department of Public Health (1955[b], 1956[b], 1957[b]) |
| ≤0.38 max 1 h/day | Oxidant | Data extended to include the period from 1956 through the end of 1959. | | Tucker (1962) |
| (Not reported)<br><br>0.10 to 0.42 (undefined) for 148 days of 1949 | Oxidant<br><br>O₃ | Relationship between daily maximum oxidant concentrations and daily cardiac and respiratory mortality in Los Angeles for the periods 1947 to 1949; August 1953 through December 1954; and January through September 1955. | Positive relationship between daily maximum oxidant concentrations and mean daily death rates on high-smog days vs. low-smog days.  Questionable exposure analysis, including use of the SRI smog index. | Mills (1957a[b],b[b]) |
| (Not reported) | Oxidant | Comparison of daily mortality in two Los Angeles County areas similar in temperature, but with different levels of daily maximum and mean oxidant levels (KI); SO₂ and CO concentrations were also measured. | No significant correlations between differences in mortality and differences in pollutant levels.  However, the populations differed in socioeconomic and age distribution characteristics. | Massey et al. (1961)[b] |
| 0.02 to 0.37 average of 1-h daily max from all Los Angeles sites | Oxidant | Daily respiratory and cardiac death counts for Los Angeles County, 1956 to 1958, related to daily maximum oxidant concentrations.  All days above 96 °F daily maximum temperature eliminated from analysis.  Each day's average of daily oxidant maxima was related to that day's deviation from monthly mean mortality. | A stratification of the mortality deviations vs. oxidant concentration revealed increasing mortality with increasing oxidant concentration, even in the cooler months.  The use of deviations addresses data seasonality. It is estimated that over 300 deaths/year in Los Angeles are associated with oxidants.  However, the lack of temperature controls below 96 °F is a major weakness. | Mills (1960) |

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**Table 7-24 (cont'd). Daily Mortality Associated with Exposure to Photochemical Oxidant Pollution[a]**

| Concentration(s) (ppm) | Pollutant | Study Description | Results and Comments | Reference |
|---|---|---|---|---|
| 0.05 to 0.21 monthly avg | Oxidant | Reanalysis of the relationship between KI and daily mortality from cardiac and respiratory diseases in Los Angeles for the years 1956 through 1958. | Used deviations from sine wave fit to reduce seasonality of pollution and mortality, but fit of monthly variations was inadequate. Significant correlations found between pollutants and mortality for cardiorespiratory diseases, but autocorrelation adjustments by authors reportedly reduced these associations to nonsignificance. | Hechter and Goldsmith (1961)[b] |
| 0.003 to 0.128 max 1 h/day | $O_3$ | Relationship between daily mortality and daily 1-h maximum concentrations of $O_3$ in Rotterdam, The Netherlands, during the months of July and August 1974 and 1975. | Mortality significantly higher during relatively high pollution ($0.05 < O_3 < 0.125$) and heat episodes in 1975. However, no significant mortality difference due to moderate $O_3$ episodes ($0.05 < O_3 < 0.08$) in 1974, in the absence of high temperature. Such aggregated analyses of serial data makes interpretation difficult. | Biersteker and Evendijk (1976)[c] |
| 0.02 to 0.29 six-site mean of daily 1-h max | $O_3$ | Total, respiratory, and cardiovascular mortality in Los Angeles County, 1970 to 1979, related to $O_3$, CO, $SO_2$, $NO_2$, HC, PM, daily max temperature, and RH. Low-pass filter used to eliminate short-wave associations so that only seasonal associations could be studied. | Frequency domain analysis indicated a significant short-wave $O_3$-mortality association, but this was not investigated further. The filtered (i.e., long-wave) data analysis indicated $O_3$ to be a nonsignificant contributor to seasonal variations in mortality. | Shumway et al. (1988) |
| 0.02 to 0.29 six-site mean of daily 1-h max | $O_3$ | Shumway et al. (1988) 1970 to 1979 Los Angeles mortality dataset reanalyzed using a high-pass filter to allow investigation of short-wave (acute) associations with environmental variables, after removing seasonality effects. Environmental variables considered included temperature, RH, extinction coefficient, carbonaceous PM, $SO_2$, $NO_2$, CO, and $O_3$. | Filtered environmental and mortality data analyses demonstrated significant associations between short-term variations in total mortality and pollution, controlling for temperature. Day-of-week effects found not to affect the relationships. Of the pollutants considered, $O_3$ had the strongest association with total mortality. Similar results found for cardiovascular deaths, but not for respiratory deaths (for which only temperature was significant). | Kinney and Ozkaynak (1991) |

## Table 7-24 (cont'd).  Daily Mortality Associated with Exposure to Photochemical Oxidant Pollution[a]

| Concentration(s) (ppm) | Pollutant | Study Description | Results and Comments | Reference |
|---|---|---|---|---|
| Not reported 1-h daily max | $O_3$ | Total daily deaths in Detroit, MI, 1973 to 1982, analyzed using Poisson methods. Environmental variables considered included TSP, $SO_2$, temperature, dew point, and $O_3$. | Significant associations found between mortality and PM, but not $O_3$.  However, $O_3$ data and results not presented, so it is difficult to evaluate reported conclusion. Seasonality controlled via multiple dummy weather and time variables, and autocorrelation addressed using autoregressive techniques.  Possible overspecification of weather controls may be a factor in the nonsignificance of $O_3$ in this analysis. | Schwartz (1991) |
| 0.000 to 0.064 24-h avg (in TN, no exceedances of 0.12 ppm 1-h max; in MO, five exceedances with max = 0.15 ppm) | $O_3$ | Associations between total daily mortality and air pollution were investigated in St. Louis, MO, and Kingston-Harriman, TN, during September 1985 through August 1986.  Environmental variables considered include temperature, RH, $PM_{10}$, $PM_{2.5}$, sulfate, aerosol acidity, $SO_2$, $NO_2$, and $O_3$. | Statistically significant daily mortality associations were found with $PM_{10}$, but not with $O_3$.  Autocorrelation removed via season indicators, multiple temperature/climate variables, and AR modeling.  The nonsignificant $O_3$ coefficient may have been contributed to by the more conservative autocorrelation removal measures taken, lower $O_3$ concentrations, and shorter study period, relative to other recent mortality studies. | Dockery et al. (1992) |

[a]See Appendix A for acronyms and abbreviations.
[b]Reviewed in U.S. Environmental Protection Agency (1978).
[c]Reviewed in U.S. Environmental Protection Agency (1986).

influences on mortality below 96 °F daily maximum.  Hechter and Goldsmith (1961) reanalyzed the Mills (1960) data using a simple annual sine wave seasonality correction and obtained significant oxidant correlations until an autocorrelation adjustment was applied; this reportedly caused the pollutant-mortality correlations to drop to nonsignificance (results not presented).  Biersteker and Evendijk (1976) conducted a t-test of difference analysis of two summers of time series data from Rotterdam for 1974 and 1975.  Although significant mortality differences could be seen during 1975 heat-pollution episodes $(0.05 < O_3 < 0.125$ ppm), no significant mortality increase could be seen during the cleaner and cooler summer episodes  $(0.05 < O_3 < 0.08$ ppm).  Statistical time series methods were needed to address probable confounding by temperature effects.  Overall, the various exposure assessment and statistical analyses weaknesses in the studies reported in previous $O_3$ criteria documents have prevented the drawing of definitive conclusions in those past documents as to whether or not there is a significant association between $O_3$ and human mortality.

Although relatively few $O_3$ mortality studies have been conducted and published since the last criteria document (U.S. Environmental Protection Agency, 1986), the statistical methods and pollution data employed in these studies have improved, compared with the older studies discussed above.  Shumway et al. (1988) focused on long-wave variations in  mortality, finding that $O_3$ was a nonsignificant contributor to seasonal variations in Los Angeles mortality during 1970 to 1979.  As might have been expected, temperature was found to be the principal environmental factor influencing seasonal mortality fluctuations.  This paper's exploratory frequency domain analysis did indicate a significant short-wave (i.e., cycles on the order of a few days in period) association between $O_3$ and mortality, but this result was not pursued in the subsequent regression analyses.

Kinney and Ozkaynak (1991) reanalyzed the 1970 to 1979 Los Angeles County mortality and environmental data set for short-wave pollution-mortality associations using seasonal and day-of-week controls.  After prefiltering the environmental and mortality time series using a high-pass filter, significant associations were demonstrated between air pollution and short-wave (acute) variations in total mortality, even after controlling for temperature influences.  Day-of-week effects also were accounted for but were found not to affect pollutant-mortality associations.  In the regression models considered, the 1-day lag of $O_3$ concentration gave the strongest pollutant associations with total mortality.  This $O_3$ coefficient was statistically separable from the other significant pollutants in the analysis $(CO, NO_2,$ and PM), although these other three pollutants were too intercorrelated to separate from each other.  Expressed as an elasticity, the $O_3$ regression coefficient ($0.03 \pm 0.01$ [SE] deaths/ppb) over all years indicated that a 1% increase in $O_3$ concentration was associated with a 0.015% increase in total mortality.  This result would imply an $O_3$ mean effect on the order of 1.5% of total mortality throughout the year (i.e., 830 total deaths/year).  Results for individual years varied widely in terms of the $O_3$ coefficient size and significance, which indicates the need for multiple years of data to discern an effect of such a small size, relative to other mortality causes.  Ozone regression results for cardiovascular deaths (average = 87/day) were qualitatively similar to those for total mortality (average = 152/day), but only temperature was significant for respiratory deaths (average = 8/day), probably due to low count number effects for this category (i.e., Poisson models may have been required).  Overall, although the Shumway et al. (1988) analysis of these 1970 to 1979 Los Angeles data indicates that disease factors and other pollutants dominate the overall seasonal cycles in mortality in Los Angeles, the Kinney and Ozkaynak (1991) short-wave analysis documents that

$O_3$ explained a small but statistically significant portion of day-to-day variations in total mortality in that city over a 10-year period.

Schwartz (1991) analyzed total daily human mortality in Detroit, MI, during the 10-year period from 1973 to 1982, primarily investigating the effects of PM using Poisson methods. Although actual results are not presented for $O_3$, it is stated in the discussion of results that $O_3$ was "highly insignificant as a predictor of daily mortality." Weather is controlled for extensively in the model specification before the introduction of the air pollution variables. The fact that $O_3$ is usually correlated over time with meteorology raises the concern that the model may be overspecified, but no diagnostics (e.g., correlations of the coefficients) are presented to allow for an evaluation. Although previous-day temperature was included in the model, the only direct seasonality control attempted was to limit the analysis to nonwinter months. Thus, it is not clear to what extent within-season long-wave confounding also may be influencing the results. If present, such long-wave confounding would be expected to bias the $O_3$ coefficient downward towards nonsignificance in this case (because $O_3$ is usually highest, and mortality lowest, in summer) and would result in autocorrelation in the model. No model residual diagnostics are reported (e.g., DW statistics or plots of the model residuals), so the extent of this problem, if present, cannot be evaluated directly. However, autoregressive methods were employed, which should have addressed any autocorrelation problems. Overall, the poor documentation of the mortality-$O_3$ modeling, especially regarding the lack of model specification details or model coefficient intercorrelations, makes the author's statement regarding $O_3$ and mortality difficult to evaluate.

Dockery et al. (1992) conducted an analysis of total daily human mortality in St. Louis, MO, and Kingston-Harriman, TN, during the 1-year period from September 1985 through August 1986 aimed primarily at assessing the effects of PM on mortality. One of the strengths of this study is the fact that multiple air pollutants were measured and considered. Thus, as part of the analysis, $O_3$ and other gaseous pollutants also were considered and found to have nonsignificant associations with mortality in these cities. The statistical analysis addressed autocorrelation in the mortality data through the use of multiple climate indices (i.e., daily mean temperature, hot day, cold day, humid day, hot and humid day, season, and interactive terms) and through the incorporation of autoregressive modeling. This approach is possibly more conservative than that employed by Kinney and Ozkaynak (1991), and the lack of a significant $O_3$ coefficient in this analysis may be due in part to the statistical modeling approach, which may or may not have affected an $O_3$ mortality relationship in the data in the process of addressing autocorrelation and so extensively controlling for temperature (which is usually correlated with $O_3$ over time). Also, the lack of any $O_3$ associations with total mortality may be due in part to the relatively low $O_3$ levels found in these particular communities (especially in Kingston-Harriman, where no $O_3$ exceedances occurred) during the study year (maximum 24-h mean $O_3$ < 0.065 ppm). Overall, this study did not show an association between $O_3$ and mortality, but this may in part be a product of the particular methodological and exposure characteristics of this study vis-ŕ-vis the identification of $O_3$ health effects.

### 7.4.1.4 Summary and Conclusions

Recent epidemiology studies addressing the acute effects of ambient $O_3$ have yielded significant associations with a wide range of health outcomes, including lung function decrements, aggravation of preexisting respiratory disease, and increases in daily hospital

admissions and mortality. Individual-level camp and exercise studies clearly indicate that lung function can decrease in a concentration-related manner in response to $O_3$ exposures occurring in ambient air. The combined results of these studies provide useful, quantitative information on the pulmonary effects of ambient $O_3$ exposures. Results from daily life studies, although more difficult to interpret quantitatively due to exposure assessment uncertainties, are qualitatively consistent with camp and exercise studies. There is limited evidence from several studies suggesting that ambient $O_3$-induced lung function decrements may persist for up to 24 h. Results from lung function epidemiology studies generally are consistent with those of human chamber studies. An $O_3$-related worsening of symptoms in selected groups of healthy individuals and detrimental changes in symptoms, lung function, and medication use in asthmatics have been observed qualitatively and, to a lesser extent, quantitatively. The relationship is consistent, temporally plausible, and moderately coherent.

Emergency room visit and hospital admission studies considered in this document collectively indicate that, when the major confounders to such analyses are addressed (e.g., seasonality, day-of-week effects), consistent associations are seen between acute occurrences of respiratory morbidity and $O_3$ exposure. The evidence is especially strong for hospital admissions, as the association has been seen by numerous researchers at a variety of localities using a wide range of appropriate statistical approaches. Although the absolute size of the effect varied somewhat across localities and statistical approaches, these analyses suggest that, in the summertime (when many other respiratory illness causes have abated), $O_3$ air pollution is associated with a substantial portion (on the order of 10 to 20%) of all respiratory hospital visits and admissions. Moreover, certain of these analyses also indicate that, on the highest $O_3$ days, this pollutant's estimated contribution can increase to the point where it is associated with nearly half of all respiratory hospital admissions. Moreover, significant associations also are seen between $O_3$ and hospital visits and admissions at exposures below 0.12 ppm 1-h daily maximum $O_3$.

As was also the case for the $O_3$-hospital admissions time series studies, many of the older $O_3$-mortality studies had methodological or statistical weaknesses that prevented clear conclusions. However, since the release of the previous criteria documents, one of the two most useful new studies (Kinney and Ozkaynak, 1991) indicated statistically significant effects by $O_3$ on short-term (acute) human mortality. The one relevant new study that did not show any $O_3$ association (Dockery et al., 1992) employed much more extensive climate and autocorrelation control methods and was conducted over a much shorter time period than the other study. Also, the study that showed an $O_3$-mortality association considered an urban area experiencing 1-h maximum $O_3$ concentrations above 0.15 ppm, whereas the other study areas (eastern Tennessee and St. Louis, MO) did not. Thus, although the analysis of daily series of human mortality and air pollution has yielded small but statistically significant associations with $O_3$ in one study, the sensitivity of this association to statistical modeling methods and to $O_3$ concentration level needs further investigation.

## 7.4.2 Chronic Effects of Ozone Exposure
### 7.4.2.1 Introduction

At the time of the publication of the previous EPA air quality criteria document (U.S. Environmental Protection Agency, 1986), little useful data were available on the chronic effects of $O_3$ exposure. Table 11-10 of that document summarized the limited number of studies available at that time and concluded "…it is unlikely that any of these studies can be

used to develop quantitative exposure-response relationships for ambient oxidant exposures. Further study of well-defined populations over long periods of time is required before any relationship between photochemical oxidants and the progression of chronic diseases can be conclusively demonstrated from population studies" (U.S. Environmental Protection Agency, 1986). The document noted that existing studies failed to demonstrate any consistent relationship between chronic oxidant exposure and changes in pulmonary function, chronic symptoms, chromosomal abnormalities, or chronic disease mortality.

The largest study that had been performed at the time of the 1986 criteria document was that of Detels et al. at the University of California at Los Angeles (UCLA) (Detels et al., 1979, 1981; Rokaw et al., 1980). This study employed a population-based sample of households in selected communities in the Los Angeles South Coast Air Basin. A standardized interview was administered, and individuals underwent various tests of lung function. Air pollution data were derived from a network of monitoring stations maintained by the South Coast Air Quality Management District of the California Air Resources Board (ARB). The usefulness of the findings of this study was considered to be limited due to a number of factors: (1) variable timing of testing in the several study communities over a 4-year period, (2) paucity of data on self-selection (completion rates between 70 to 79%) and migration in and out of the study communities, (3) inconsistent demonstration of reproducibility of the pulmonary function measurements, (4) mixed ethnicity of the study population, (5) inadequate data on individual exposure and failure to adjust exposure estimates for migration in and out of the study areas, and (6) methods employed for comparisons of health effects.

The 1986 criteria document also summarized the first of the Adventist Health Smog (AHSMOG) studies (Hodgkin et al., 1984) on the occurrence of COPD in relation to chronic air pollution exposures. However, the data from this first publication were felt to be of limited value because only symptom data were reported and the exposure assessment was insufficient.

## 7.4.2.2  Recent Epidemiological Studies of Effects of Chronic Exposure

By the very nature of the problem of the establishment of a link between chronic exposure to $O_3$ and the occurrence of chronic health effects, epidemiological studies remain the only approach for obtaining human data. As has been noted in the 1986 document, principal problems for such studies relate to (1) the specification of individual exposures over the relevant periods of life of the study subjects; (2) the coincident effects of other oxidant species (e.g., $NO_x$, derivative acid species) and other air pollutants (acid aerosols, particulate species); (3) seasonal effects that relate to pollutant and meteorologic factors, which affect specific pulmonary function measurements relevant during the course of longitudinal studies or over studies that utilize multiple cross-sectional samples; and (4) control for effects of factors such as occupational exposures, cigarette smoking, etc. In addition, past epidemiologic studies have not had access to any human histologic specimens in relation to the exposure groups under study nor have specific mechanisms been investigated to explain any of the symptom or functional outcomes observed.

### *Histologic and Immunologic Effects*

Sherwin has presented some provocative preliminary, histologic data and uses it to offer a hypothesis on the importance of pathologic changes in the centriacinar region (CAR) of the lung in relation to chronic pulmonary effects of oxidant air pollution (Sherwin, 1991; Sherwin and Richters, 1991). Only the publication that presents the primary data (Sherwin,

1991) is reviewed here, because there is some redundancy in the two available publications. Sherwin (1991) obtained lungs from 107 subjects, 15 to 25 years of age, who died of a sudden death without evidence of overt disease, lived in Los Angeles County, had no autopsy evidence or history of drug use, and had no lung trauma. Abnormalities of the CAR were evaluated by a pathologist who was "blinded" to basic demographic data. Centriacinar region disease was defined as the extension of a respiratory bronchiolitis into the proximal acinar structures (i.e., chronic inflammatory cells and histiocytes into alveolar ducts, sacs, and alveoli immediately adjacent to a respiratory bronchiole). The odds ratio for severe CAR disease in subjects who lived in metropolitan Los Angeles versus those who lived in other cities in Los Angeles County was 4.0 (95% confidence limit [CL], 1.4 to 11.3; a calculation based on data in Sherwin [1991] Tables 2 and 3).

Unfortunately, no exposure data (or lifetime residence data) were available for the subjects in the Sherwin study, nor were smoking histories, cotinine results, or occupational histories available. The smoking history data is of critical importance because respiratory bronchiolitis has been shown to be an early pathologic change found in the pulmonary airways of young smokers (Niewoehner et al., 1974). Additional problems for this study were the fact that most subjects were of low socioeconomic status, and only 10 of the subjects were female. Furthermore, the study is limited by a lack of quantitative morphometry on the lung specimens and by the lack of a control group from an ambient environment with low oxidant pollution. Therefore, although Sherwin's data are of considerable interest, particularly in relation to the primate $O_3$ exposure data that show similar effects (see Chapter 6, Section 6.2.4), they currently are not of value in the determination of appropriate human exposure levels for $O_3$, nor do they even establish the fact that the oxidant environment found in metropolitan Los Angeles, indeed, is responsible for the observed pathologic changes.

Zwick et al. (1991) carried out a study of allergic sensitization and cellular immune responses in children (median age of 11 years) from four schools in two Austrian cities. Two years of meteorologic data and continuously measured levels of $SO_2$, $NO_2$, and $O_3$ were available for both cities. Monitors were within 2 km of the study schools, except for one $O_3$ monitor that was 13 km from a school in the "high"-$O_3$ area. "Allergic diseases" (rhinitis, conjunctivitis, and asthma), response to prick test antigens, total IgE concentration, number of subjects with IgE >100 kU/L, and total IgG concentration did not differ between the subjects in the two cities. Adjustment for sex, age, active and passive smoking, and types of cooking and home heating did not alter the results. Children from the high-$O_3$ environment had small, but statistically significant, decreases in the absolute and relative numbers of OKT4+ (helper/inducer) T cells and OKNK+ (natural killer) cells and increases in OKT8+ (suppressor) T cells. Adjustment for active and passive smoking and recent respiratory illness did not alter the results. The frequency of subjects with a measurable $PD_2$ to histamine also was increased in the high-$O_3$ area. No relationship between the T-cell findings and $PD_2$ or any of the other immunologic markers are provided.

The Zwick et al. (1991) results are limited by lack of any exposure data and by lack of detail for the $O_3$ and other ambient air pollution data. Except for data on the average percentage time above specific levels of $O_3$, there are no useful data that can be applied to the observations reported. Moreover, the differences observed in the various T-cell subsets were relatively small and of questionable biological significance. There are no analyses that relate the T-cell findings to the clinical and functional data (see Table 7-25) that are reported. Finally, although the communities were said to be similar on all meteorologic and other

ambient pollution data, inspection of the author's Table 1 (Zwick et al., 1991) indicates that the mean (averaging time not given) $NO_2$ levels in the low-$O_3$ community were fourfold greater than those in the high-$O_3$ community (42 $\mu g/m^3$ versus 11 $\mu g/m^3$). No data on acid species or particles are provided, although both study cities were free of heavy industry and heavy traffic.

Calderon-Garciduenâs et al. (1992) have studied chronic exposure to the ambient air of southwestern metropolitan Mexico City in relation to histologic abnormalities of the nasal mucosa. The exposed group consisted of subjects who spent at least 8 h/day while working at a naval hospital in southwestern metropolitan Mexico City. Ninety-two percent of the group lived in the same area as the hospital, and all had lived in southwestern metropolitan Mexico City for >2 mo (n = 47). Controls consisted of (1) subjects who lived in Veracruz and who had not left this area over a period of at least 5 years before the onset of the study (n = 12) and (2) new arrivals (<30-day residence in southwestern metropolitan Mexico City) at the naval hospital who came from low-$O_3$, "non-polluted" ports (n = 17). Nasal biopsies were obtained for all subjects in May through June, 1990, as were histories on residence, smoking, occupation, allergies, etc. All three groups were matched for age, sex, and occupation. There were no differences in familial allergy history or personal smoking (specific data not given in paper). There was a progressive increase in both nasal symptoms and nasal histologic abnormalities in relation to presumed $O_3$ exposure (Veracruz < new arrivals < long-term residents of southwestern metropolitan Mexico City). The principal histologic change was basal cell hyperplasia, with squamous cell metaplasia and mucosal atrophy occurring less frequently. Only 11% of those with >60-day residence in southwestern metropolitan Mexico City showed normal mucosa.

Unfortunately, no ambient air data were presented for $SO_2$ or particles, which are said to be low relative to other parts of the city, or other pollutants that could be present. In addition, because the monthly average maximal $O_3$ concentrations are (and have been since late 1986) well above the current U.S. 1-h standard of 120 ppb, the Calderon-Garciduenâs et al. (1992) data are of limited value to understanding low ambient $O_3$ exposures. (This conclusion probably applies even if one considers the different concentrations represented by a given parts-per-billion value at different altitudes.) Subjects in southwestern metropolitan Mexico City are subjected to $O_3$ levels of between 100 and 400 ppb for several hours per day in the winter and spring. Despite the lack of data on other air pollutants and specific exposure data for individual subjects, this study does provide useful evidence to suggest upper respiratory damage as a consequence of prolonged exposure to ambient air mixtures.

### Pulmonary Function, Respiratory Symptoms, and Chronic Respiratory Disease

*The Adventist Health Smog Study*. Since the publication of the 1986 criteria document (U.S. Environmental Protection Agency, 1986), a number of studies have been published that attempt to define chronic respiratory system health effects in relationship to ambient $O_3$ concentrations (see Table 7-26). Among these, the series of publications from the AHSMOG study (Hodgkin et al., 1984; Euler et al., 1987, 1988; Abbey et al., 1991a,b) will be discussed first and as a set.

**Table 7-25. Pathologic and Immunologic Changes Associated with Chronic Ozone Exposure[a]**

| Concentrations(s) | | Pollutants and Environmental Variables | Study Description | Results and Comments | Reference |
|---|---|---|---|---|---|
| ppm | $\square$g/m | | | | |
| Not provided | | Not provided, Los Angeles County, not further specified | Autopsy study of lungs from sudden death victims 15 to 25 years old whose residence was Los Angeles County; examination of lungs for inflammatory changes in CAR of lungs. | Most severe CAR disease in residents of metropolitan Los Angeles County versus other county areas; data limited by lack of smoking history, personal exposure and occupational data; interesting hypothesis, but role of $O_3$ unknown. | Sherwin and Richters (1991) |
| 0.095 to 0.188, time metric not given | 186 to 368 | O | Study of allergic sensitization and cellular immune responses in children (median age, 11 years) in two Austrian cities, 1989. | Small increases in OKT4+ (helper/inducer) and OKT8+ (suppressor) T-cells and small decrease in natural killer cells in "high" ozone community; increase in number of subjects with measurable $PD_{20}$ histamine in "high" ozone area; no relationship between T-cell findings and any clinical immunologic measure, lung function, or $PD_{20}$; meaning of results unclear. | Zwick et al. (1991) |
| 0.150 to 0.275 monthly average | Approx. 294 to 539 | $O_3$ | Study of nasal histology in persons living in southwestern Mexico City and Veracruz; subjects matched on age, sex, occupation; similar allergy and smoking histories. | Increased occurrence of nasal dysplasia in southwestern Mexico City residents, especially those with more than 5 years residence; no data on other air pollutants; data not directly relatable to U.S. conditions because Mexico City residents are exposed to $O_3$ levels between 0.1 and 0.4 ppm for several hours each day, all year long, with relatively few days below 0.1 ppm. | Calderon-Garciduenâs et al. (1992) |

[a]See Appendix A for acronyms and abbreviations.

## Table 7-26. Effects of Chronic Ozone Exposure on Pulmonary Function, Respiratory Symptoms, and Chronic Respiratory Disease[a]

| Concentrations(s) | | Pollutants and Environmental Variables | | Study Description | Results and Comments | Reference |
|---|---|---|---|---|---|---|
| ppm | $\mu$g/m | | | | | |
| 0.033 median average annual hourly value | 65 | $O_3$ | | Study of relationship of air pollution to levels of FVC, $FEV_1$, and PEFR based on 1976 to 1980 supplement to NHANES and data from EPA SAROAD monitoring system; subjects 6 to 24 years of age; exposure values based on hourly $O_3$ values for previous 365 days; data for TSP, $NO_2$, and $SO_2$; and data for important demographic, smoking, and health covariates. | Nonlinear relationship between annual average $O_3$ and function measurements with threshold at approximately 0.040 ppm; findings limited by inability to control for multiple pollutant effects, relatively crude assignment of exposure; data consistent with effect on forced flow at $O_3$ levels at or below 0.12 ppm. | Schwartz (1989) |
| 0.034 to 0.050 90th percentile annual mean 1-h daily max | 67 to 98 | $O_3$ | | 1983 to 1984 cross-sectional study of 2nd- to 6th-grade students in Ontario and Manitoba, Canada; data on $SO_2$, $NO_2$, nitrates, and sulfates; respiratory health, demographic, smoking, and home cooking fuel data; and spirometry. | Ontario town had more $O_3$ days >0.080 ppm; small decrements ($\leq 2\%$) in FVC and $FEV_1$ were found in the Ontario town compared to the Manitoba town; any $O_3$ possible effects were completely confounded with $SO_4$ effects. | Stern et al. (1989) |
| 0.024 to 0.031 annual mean 1-h daily max | 47 to 61 | $O_3$ | | 1985 to 1986 cross-sectional study of 7- to 11-year-old children from (n = 3,945) five rural towns in Ontario and five towns in Saskatchewan, Canada; data on $SO_2$, sulfates, $NO_3$, $NO_2$, and $PM_{10}$; respiratory health multiple covariates; spirometry including flow at mid-lung volumes. | Ontario towns had higher levels of $O_3$ and $SO_4$ in summer months and for 90th and 99th-percentiles of distributions; 90th percentile mean 1-h maxima were 80 ppb vs. 47 ppb for $O_3$ and 11.5 $\mu$g/m³ vs. 3.1 $\mu$g/m³ for $SO_4$; magnitude of $FEV_1$ and FVC effects was similar to Stern et al. (1989); no effect for mid-volume flows, except for subjects with asthma; coincidence of increased $O_3$ and $SO_4$ precludes definite statements concerning $O_3$ effects. | Stern et al. (1994) |
| 0.008 to 0.118 average hourly concentrations, 1974 to 1979 | 16 to 231 | $O_3$ | | Study of chronic respiratory symptoms in adults with use of 1979 National Health Interview Survey data and 1974 to 1979 EPA SAROAD data; data on respiratory health, demography, and smoking; and data for TSP. | Data for only 29% of those eligible could be used; average hourly $O_3$ concentration over period 1973 to 1979 associated with report of sinusitis and hay fever after control for covariates and TSP; no association with asthma or emphysema; large amount of data reduction, lack of adequate exposure assignment, lack of occupational exposure histories, and lack of adequate data on other pollutants make results very difficult to interpret. | Portney and Mullahy (1990) |

## Table 7-26 (cont'd).  Effects of Chronic Ozone Exposure on Pulmonary Function, Respiratory Symptoms, and Chronic Respiratory Disease[a]

| Concentrations(s) | | Pollutants and Environmental Variables | Study Description | Results and Comments | Reference |
|---|---|---|---|---|---|
| ppm | $\mu$g/m | | | | |
| 0.015 to 0.052 average HMV | 29 to 102 | O | Cross-sectional study of children ages 6 to 15 years in a community in Austrian alps divided into three zones based on $SO_2$, $NO_2$, and $O_3$; respiratory health, demographic, and spirometry data. | Only difference in respiratory history was increased adjusted prevalence of asthma in zone with highest $O_3$ (6.4%; 0.052 ppm HMV) vs. the zones with lower $O_3$ concentrations (4.8%; 0.015 ppm HMV; 2.7%, 0.026 ppm HMV); no meaningful differences in spirometry indices; data limited by use of single monitoring site for 1,200 $km^2$ area; effects of $SO_2$ and $NO_2$ on asthma prevalence not well studied. | Schmitzberger et al. (1993) |
| 0.10 to 0.20 3-mo mean daily peak hourly values for Lancaster and Glendora, respectively | 196 to 392 | Oxidants | 5-year follow-up of Lancaster and Glendora, CA, cohorts; from UCLA population study of CORD restricted to nonsmoking, non-Hispanic whites, 7 to 59 years old. | No difference in respiratory symptoms over follow-up for either community; across all age groups, slope of Phase III of $N_2$ washout deteriorated more rapidly in Glendora; in subjects $\Box$14 years of age, more rapid decrease in spirometric indices in Glendora; interpretation hampered by large losses to follow-up, inability to disentangle multiple pollutant effects. | Detels et al. (1987) |
| 0.04 to 0.07 mean peak daily peak hourly values 1972 to 1981; Long Beach and Lancester, respectively | 78 to 137 | Oxidants | 5- to 6-year follow-up of Lancaster and Long Beach, CA, cohorts from UCLA CORD study; Long Beach with higher $NO_2$, $SO_4$, and TSP than Lancaster. | All reported excess functional decline for Long Beach likely due to bias in decline estimates between locations; data not useful with regard to possible $O_3$ effects. | Detels et al. (1991) |
| Not reported | | Oxidant | Prevalence of respiratory symptoms in nonsmoking Seventh Day Adventists residing for at least 11 years in high- (South Coast) and low- (San Francisco, San Diego) photochemical air pollution areas of California; ARB regional air basin monitoring data for oxidants, $NO_2$, $SO_2$, CO, TSP, and $SO_4$ from 1973 to 1976. | Slightly increased prevalence of respiratory symptoms in high pollution area; after adjusting for covariables, 15% greater risk for COPD due to air pollution (not specific to oxidants); past smokers had greater risk than never-smokers; when past smokers were excluded, risk factors were similar. In addition, insufficient exposure assessment and confounding by environmental conditions limit the quantitative use of this study. | Hodgkin et al. (1984) |

## Table 7-26 (cont'd). Effects of Chronic Ozone Exposure on Pulmonary Function, Respiratory Symptoms, and Chronic Respiratory Disease[a]

| Concentrations(s) | | Pollutants and Environmental Variables | Study Description | Results and Comments | Reference |
|---|---|---|---|---|---|
| ppm | $\mu$g/m^{3} | | | | |
| Not reported | | Oxidant | Cross-sectional analysis of above populations; uses hours above various "threshold" values for oxidants, TSP, SO$_2$ based upon California, EPA, and World Health Organization max levels; period covered, 1966 to 1976; data available for important covariates (sex, occupation, environmental tobacco smoke, race, age, education, past smoking). | OX (10) most significantly associated with COPD after adjustment for covariates; number of hours above higher thresholds less significant; when TSP, SO$_2$, and OX (10) entered in same regression, TSP (200) only pollutant associated with COPD; high correlation between OX (10), TSP (200), and SO$_2$ (hours more than 4 pphm). Improved exposure assessment over previous paper; however, no clear statement possible about effects of oxidants due to colinearity with TSP and SO$_2$. | Euler et al. (1988) |
| Not reported | | O$_3$ | Same as Abbey et al. (1991a) but analysis applied to COPD severity and a "multi-pollutant" analysis performed; also evaluated effect of using data for different time periods of ambient air monitoring. | Cumulative incidence of COPD symptoms when each pollutant entered separately, similar to above study; joint effects of OZ (10) and TSP (200) and mean concentrations of each pollutant evaluated only for cumulative asthma incidence; TSP (200) entered logistic regression in preference to OZ (10) but mean O$_3$ concentration entered in preference to mean TSP; change in asthma severity associated with mean O$_3$ concentration (1977 to 1987) and with exceedance frequency for OZ (10), OZ (12), and TSP (200) considered separately; findings for asthma severity similar to cumulative incidence when TSP and O$_3$ evaluated together; in no analysis did TSP and O$_3$ both remain jointly significant, nor were there any interactions; data unable to unequivocally disentangle effects of individual pollutants. | Abbey et al. (1993) |

[a]See Appendix A for acronyms and abbreviations.

The basic population for these studies represents California-resident, Seventh-Day Adventists aged □25 years of age who had lived 11 years or longer (as of August 1976) in either a high-oxidant-polluted area (South Coast Air Basin [Los Angeles and vicinity] and a portion of the nearby Southeast Desert Air Basin) or a low-pollution area (San Francisco or San Diego). This sample was supplemented by an additional group of subjects who met the 11-year residence requirement but who came from low-exposure rural areas in California. The total, baseline sample (March 1977) comprised 8,572 individuals, of whom 7,267 enrolled. From this group, 109 current smokers and 492 subjects who had lived outside of the designated areas for a portion of the previous 11 years were excluded. Detailed respiratory illness and occupational histories were obtained. In these studies, "COPD" refers to "definite chronic bronchitis", "definite emphysema", and "definite asthma" as defined by the study questionnaire. Measures of pulmonary function are not included.

Air monitoring data were obtained from the California ARB monitoring system. Ninety-nine percent of the subjects (excluding the rural supplement) lived at a distance from the nearest ARB monitoring site that was considered to provide relatively reliable concentration estimates for the outdoor, ambient environment at their residence. Concentrations at the monitors were interpolated to the centroid of each residential zip code from the three nearest monitoring sites with the use of a $1/R^2$ interpolation. Subsequent development of exposure indices took account of the improvements in ARB data after 1973. Data were available for total oxidants, $O_3$, TSP, $SO_2$, $NO_2$, CO, and $SO_4$ (excluding 1973 to 1975).

The initial report from this study was summarized in the 1986 criteria document (U.S. Environmental Protection Agency, 1986). Based upon a multiple logistic regression that adjusted for smoking, occupation, race, sex, age, and education, it was estimated that residence in the South Coast Air Basin conferred a 15% increase in risk for prevalent COPD. No estimates of exposure were provided, and the data were considered to be of limited utility.

In their 1988 publication, Euler et al. provided exposure estimates based on the cumulative number of hours, over 11 years prior to the baseline, that individuals lived in environments at various oxidant thresholds, beginning at 10 pphm [OX (10)] (196 □g/m³) and the total dosage to which they would be exposed. The estimates in this report did not correct for time spent indoors. When the OX (10) was the only pollutant considered, each 750 h/year increment in exposure was associated with a 20% increase in risk for COPD in a multiple logistic regression analysis that adjusted for effects of occupation, passive exposure to tobacco smoke, personal smoking, sex, age, race, and education (baseline data only). Moreover, the data were compatible with a threshold effect at 10 pphm. However, when hours above a TSP concentration of 200 □g/m³ [TSP (200)] and $SO_2$ concentration of 4 pphm were included in the logistic regression model, only TSP (200) was associated with the occurrence of COPD. No significant interactions were found between the various pollutant thresholds. The authors noted that their failure to control for time spent indoors may have led to an underestimation of the oxidant effect. Moreover, the fact that 74% of the variance of OX (10) was explained by the other pollutants certainly reduced the power of this study to detect an independent effect of oxidants on the occurrence of COPD. The authors also noted the limitations imposed by the cross-sectional nature of the data that were used in this analysis. Thus, on the basis of this study, no clear statement could be made about the chronic respiratory system effects of oxidant exposure.

A major improvement in the methods for assessment of exposure was presented in Abbey et al (1991a).  Previous exposure estimates were refined by the computation of "excess concentrations" (concentration minus cutoff, summed over all relevant time periods and corrected for missing data).  Exposures also were corrected for time spent at work and time away from residence, with estimates provided for the environments where work occurred and for geographic areas away from residence.  The quality of the interpolations (in terms of distance of monitor from residence zip codes) also was evaluated and incorporated into the estimates.  Adjustments were made for the time spent indoors by individuals.  New indices were developed that were based on $O_3$, rather than on total oxidants.  The investigators demonstrated correlation coefficients of 0.98 between monthly mean total oxidants and $O_3$ at concentrations ☐12 pphm.  (It should be noted that a more appropriate comparison would have been between the mean and the differences of the two measurements.)

The above estimates were applied to data that included 6 years of follow-up of the study population (Abbey et al., 1991b).  This analysis focused on incident occurrence of obstructive airways disease (AOD—same definition as for COPD above).  Incident symptoms of AOD were significantly associated with hours above several TSP thresholds, but not with hours above any $O_3$ threshold.  There was a suggestion of an association between hours above 10 pphm $O_3$ [OZ (10)] and the 6-year cumulative incidence of asthma [RR for 500 h/year above OZ (10) = 1.40 (95% CL = 0.90 to 2.34)] and definite bronchitis (RR = 1.20 [95% CL = 0.97 to 1.53]).  Approximately 43% of the study population experienced at least 500 h in excess of the OZ (10) criterion.  Cumulative incidence estimates were adjusted with the use of Cox proportional hazard models for the same variables noted in the original publication of Hodgkin et al. (1984), as well as the presence of possible symptoms in 1977 and childhood respiratory illness history.  None of the analyses included both $O_3$ and TSP thresholds.  No data were provided on the details of the subjects available for the prospective analysis and their representativeness versus the entire base population.  Therefore, assuming no bias due to selective loss to follow-up, these data are consistent with a small $O_3$ effect and are limited by the same considerations of colinearity and subsequent reduction of power noted above.

Another analysis by Abbey et al. (1993) evaluated changes in respiratory symptom severity with the TSP and $O_3$ thresholds noted above.  In this analysis, logistic regression, rather than Cox proportional hazard modeling, was used to assess cumulative incidence of components of the COPD/AOD complex; and multiple, linear regression was used to evaluate changes in symptom severity.  When $O_3$ was considered by itself, there was a trend toward an increased risk of asthma for a 1,000-h average annual increment in the OZ (10) criterion (RR = 2.07, 95% CL = 0.98 to 4.89).  In this analysis, there was a suggestion that recent ambient $O_3$ concentrations were more related to cumulative incidence than past concentrations.  Change in asthma severity score was associated significantly with the 1977 to 1987 average annual exceedance frequency for $O_3$ thresholds of 10 and 12 pphm.  No significant effects were found for COPD or bronchitis alone.  In contrast to the above study of cumulative incidence, the investigators carried out an analysis in which TSP (200) and OZ (10) were allowed to compete for entry into a model to evaluate asthma cumulative incidence and changes in severity.  In the cumulative incidence model that employed exceedance frequencies (number of hours above threshold), TSP (200) entered before OZ (10); when average annual mean concentrations were used, $O_3$ entered before TSP.  From this, the authors concluded that both TSP and $O_3$ were relevant to asthma cumulative incidence.  In no case did both pollutants remain significant

simultaneously in the same regression. No interactions were observed between TSP and $O_3$ for either metric. A similar result was observed for change in asthma severity. As in previous analyses, there was a high correlation between TSP (200) and OZ (10) exceedance frequencies (0.72) and their respective average annual mean concentrations (0.74).

The AHSMOG study represents the most extensive effort to date to provide realistic exposure estimates within the constraints of a large, population-based study. Moreover, the exposure estimates for photochemical oxidants have been tied to current $O_3$ levels and have taken into account many of the sources of inaccuracy and imprecision in the assignment of exposures to individuals (short of detailed personal monitoring). As such, they do represent a considerable improvement over all other studies to date. Nonetheless, it is not possible from these data to determine if there is an effect of $O_3$ on the outcomes that were studied. This largely is due to the difficulty of partitioning effects between $O_3$ and particles.

*Other Studies*. Subsequent to the publication of the 1986 criteria document, two additional publications have emerged from the UCLA study (Detels et al., 1987, 1991). The data presented are derived from the same population bases that were used in previous publications; and, therefore, they are subject to the same limitations that were cited in the introduction to this section.

In 1987, Detels et al. reported a 5-year follow-up study of white, non-Hispanic subjects from the Lancaster and Glendora study areas. The 12- and 3-mo mean peak hourly total oxidant values from 1972 to 1982 for Lancaster and Glendora were 7 and 10 pphm and 11 and 20 pphm, respectively. Only 47 and 58% of subjects, respectively, were retested with both the questionnaire and measures of lung function. Effects of air pollution on the days of testing were evaluated by comparing lung function test results in a subgroup of individuals who were tested three times at 3- to 4-mo intervals. No effect was observed, but the power to find differences was low. Over the follow-up period, there were no changes in reported respiratory symptoms for either community. In adults ($\geq$19 years of age) who never smoked, all spirometric and nitrogen-washout results showed more rapid deterioration in Glendora. Differences were significant only for mid-expiratory flows and for slope of Phase III from the nitrogen-washout curve. The effects were greater in females, in whom changes in $FEV_1$ also were significant. In subjects less than 19 years of age, only changes in slope of Phase III were significant, although FVC in Glendora females was lower than that observed in Lancaster.

The results of this study remain limited by the lack of adequate exposure data and the failure to control for the possible effects of other ambient pollutant differences between the communities. Problems with loss to follow-up represent a significant issue, especially for the pulmonary function measurements, given that approximately 50% of the original subjects were not available for repeated testing. Baseline comparability is also of concern because subjects who were retested in Lancaster had a better slope of Phase III than those not retested. Because this measure most consistently differed between the two study communities, the possibility of selection bias is very real. Overall, these results do not strengthen the usefulness of this study for the attribution of an effect of oxidant exposure on respiratory health.

The 1991 report from the UCLA group compared Lancaster with Long Beach, the latter area with relatively high levels of $SO_2$, sulfates, $NO_x$, and hydrocarbons, as well as increased total oxidant levels (mean 1-h daily peak values, 1972 to 1982, 30 pphm versus 110 pphm, respectively) (Detels et al., 1991). As above, the analysis was restricted to non-Hispanic whites who never smoked cigarettes and with 5 years of follow-up. Only 47% of the Lancaster cohort and 44% of the Long Beach cohort had pulmonary function retested on two

occasions. Over the age range of 25 through 59 years, changes in slope of Phase III of the nitrogen-washout curve and most spirometric indices were significantly worse in Long Beach, compared to Lancaster. In subjects under 25 years of age, there were significant differences in slope of Phase III, especially in subjects 7 to 10 years of age.

All of the limitations identified for the 1989 report apply to this report as well. Moreover, comparison between the two communities of the interlaboratory differences (mobile laboratory versus UCLA reference laboratory; 3% sample) indicated that average annual decrements in $FEV_1$ were exaggerated by ⬜13 mL/year (standard error $\pm7$ mL/year) in Long Beach versus ⬜2 mL/year ($\pm7$ mL/year) in Lancaster. Application of this difference to the data in their Table 6A would suggest that the "significant" difference in $FEV_1$ for both males and females may be largely, if not entirely, due to bias. Thus, all of the functional differences reported in this study are suspect on this basis alone. This, of course, ignores any additional biases that may have been due to the large losses to follow-up in both communities.

A number of additional studies have addressed data relevant to the chronic effects of $O_3$ on respiratory health (see Table 7-26).

Schwartz (1989) evaluated the effect of air pollution on children and young adults ages 6 to 24 years with the use of data derived from NHANES II (Second National Health and Nutrition Examination Survey, February 1976 to 1980). All individuals in each census tract were assigned average pollutant values derived from monitors located within 10 miles of the centroid of the census tract. Average hourly values for the 365 days preceding spirometry were used, and an annual average was created for $O_3$ (EPA Storage and Retrieval of Aerometric Data [SAROAD] database). For $O_3$ (chemiluminescence and ultraviolet [UV] spectroscopy), six of the seven hourly readings between 11:00 a.m. and 5:00 p.m. were required to include a day's data. Only 1,005 of the 3,922 (25.6%) of the subjects lived close enough to a monitor to have $O_3$ exposures assigned to them. Data for TSP, $NO_2$, and $SO_2$ were assigned to 47.1, 13.6, and 21.2% of the subjects, respectively. Analyses were restricted to consideration of single pollutants, because the author reported that there was insufficient overlap between the locations where data were available for all or any combination of pollutants. Data for a variety of relevant personal and demographic covariates were available. Statistical analyses appropriate to the correlation structure of the data (induced by the sampling design of NHANES) were utilized. There was a nonlinear relationship between the annual hourly average $O_3$ concentration and FVC, $FEV_1$, and PEFR. A threshold of effect around 0.04 ppm was observed, above which there appeared to be a linear decline in FVC (only data shown graphically). The effect persisted after control for sex, race, age, family income, educational level, chronic respiratory symptoms, and smoking history. Results were little affected by region or use of a 2-year averaging time. Ozone levels above the threshold were significantly associated with an FVC $<70\%$, a result not seen for TSP but observed for $NO_2$.

The major limitation of the Schwartz (1989) analysis is the inability to distinguish between the effects of $O_3$, TSP, and $NO_2$ and the choice of only a single metric for $O_3$ (hourly average). Support for the former concern can be seen in the similarity of the effects of $NO_2$ and $O_3$ in the logistic regression analyses, which suggests that the results could reflect the joint effect of a number of species in a complex oxidant environment. The operating assumption that near-term (1- to 2-year) exposure reasonably reflects a "lifetime" of exposure is highly suspect in the mobile U.S. population. In fact, restriction of the analysis to subjects who still resided in the state in which they were born led to slight reductions of $O_3$ effect, especially for $FEV_1$ and PEFR. Despite these limitations, the data do suggest that, for children and young

adults, if there is a chronic $O_3$ effect (or, more accurately for these data, a subchronic effect) on lung function, it could occur at levels at or below 120 ppb. However, the particular pattern of exposure (peaks, season, etc.) that may be relevant cannot be discerned from these data.

In 1989, Stern et al. reported a cross-sectional study, conducted in 1983 and 1984, of the relationship between respiratory health effects of second- through sixth-grade children in two Canadian communities (one in southern Ontario and one in southern Manitoba). The Ontario region was characterized by low levels of gaseous pollutants ($SO_2$ and $NO_2$) and moderately elevated levels of particulate sulfate, FPs, and $O_3$. Frequent episodes of elevated sulfate and $O_3$ concentrations occurred in the summer and early fall. The Manitoba community was not subject to the same pattern of air pollutants. Gases and $O_3$ (measured by chemiluminescence) were sampled continuously, and TSP, sulfates, and total nitrates were sampled every sixth day. Fixed monitoring stations were established at the center of each community, and monitoring was carried out from October 1983 to April 1984. Ozone measurements in Ontario were derived from sites between 35 to 45 km from the study area. Average annual maximum $O_3$ concentrations were similar in the two communities (0.136 and 0.130 ppm in Ontario and Manitoba, respectively), but the frequency of elevated $O_3$ events (>0.080 ppm, Canadian standard for 1-h maximum) was more frequent in Ontario (30 days) than in Manitoba (3 days) in 1983. Ninety-two percent of the subjects (n = 1,317) provided data from detailed questionnaires, but only 70% (1,010) provided spirometric data (tested in fall and winter months). There were no meaningful differences in the prevalence of all of the respiratory health outcomes studied after adjustment for parental smoking, gas cooking, sex, length of residence, parental education, and past respiratory illness history. Ontario children had a 2% lower FVC (adjusted for age, sex, height, and parental smoking) and a 1.7% lower $FEV_1$; both differences were statistically significant. The differences were somewhat greater when children with underlying respiratory illness or symptoms were excluded from the analyses. These data are very difficult to interpret in relation to $O_3$ due to the marked colinearity between the $O_3$ and sulfate levels in Ontario. Moreover, the differences observed in lung function are very small (an average of 50 mL and 40 mL for FVC and $FEV_1$, respectively) and of questionable importance without further follow-up data on the subjects. Such follow-up data would need to attempt to identify whether the small decrements observed are "across the board" with respect to the overall population or the result of decrements in a susceptible subset of the population, particularly a set of children at the lower end of the pulmonary function distribution. In these children, small decrements might be associated with adverse respiratory effects as a result of their already lowered (absolute or relative) levels of lung function.

Stern et al. (1994) extended the 1983 and 1984 (Stern et al., 1989) study to 10 rural Canadian communities. Five towns in southwestern Ontario and five towns in Saskatchewan were selected and studied between September 1985 and March 1986. Children 7 to 11 years of age were studied (n = 3,945) with techniques similar to the previous study. In 1986, $SO_2$, $NO_2$, and $O_3$ were monitored continuously through a 10-site network (one site in each town). Particles were sampled every 3 days for 24 h in Saskatchewan and every 6 days in Ontario. Annual mean 1-h maximum $O_3$ concentrations were slightly higher in Ontario, but the 90th and 99th percentile values were much greater (90th: 80 ppb versus 47 ppb; 99th: 115 ppb versus 57 ppb). This was particularly true for the months of June to August. The levels of $PM_1$ and nitrate did not vary between the areas and were well within the Canadian Ambient Air Quality

Objectives.  Annual mean $SO_4$ levels were three to four times greater in Ontario communities ($6.6 \ \mu g/m^3$ versus $1.9 \ \mu g/m^3$).

The adjusted (age, sex, parental education, gas cooking, and parental smoking) prevalence of respiratory symptoms did not differ among the 10 communities.  Adjusted (height, weight, plus the above adjustment factors) FVC and $FEV_1$ averaged 1.7 and 1.3% less, respectively, in the five Ontario towns.  No differences were observed for PEFR, $FEF_{25\ 75\%}$, or $\dot{V}_{max5\ \%}$.  The results did not change when the analysis was restricted to life-long residents or to children without respiratory symptoms.  Although not statistically significant, Ontario children with doctor-diagnosed current asthma had $FEF_{25\ 75\%}$ and $\dot{V}_{max5\ \%}$ levels that were 6.6 and 6.5%, respectively, lower than similar children in Saskatchewan.  Overall, the prevalence of asthma was 4% for the entire sample.

These results are consistent, in terms of the magnitude of the $FEV_1$ and FVC effects, with those of the previous Stern study (Stern et al., 1989).  In addition, these data provide suggestive evidence of enhanced effects for children with current asthma.  The two major limitations of the study are recognized by the authors:  (1) the effects observed cannot be attributed to $O_3$ or to $SO_4$ (or acid) aerosols and could be due to either part of the pollutant mixture or attributed to the combination of the component, and (2) the differences in the mean values reported do not take into account the variability in the pulmonary function distribution and the variability of responses across the distribution (see above).

Portney and Mullahy (1990) used the 1979 U.S. National Health Interview Survey and SAROAD data to explore the relationship between $O_3$ and TSP and chronic respiratory disease.  Average hourly $O_3$ concentrations from 1974 to 1979 were used; data from 1974 to 1979 and data from 1979 alone were evaluated.  Individuals were matched to the nearest centroid of the census tract in which they lived in 1979.  Individuals were excluded if they lived >20 miles from the nearest monitor.  Only 29.3% of the 4,500 adults surveyed who participated in the smoking and respiratory disease supplemental interview and for whom residential data were available could be included.  Seven different model specifications (probit analysis) evaluated cumulative (5-year) and 1-year effects of $O_3$ on various respiratory diseases.  Hourly average $O_3$ concentrations, but not TSP concentrations, over 1974 to 1979 were significantly associated with the report of sinusitis and hay fever after control for smoking, sex, income, race, education, temperature, and stability of residence.  In contrast, neither $O_3$ nor TSP were associated with reported asthma and emphysema.  An enormous amount of data reduction, the lack of individual exposure data, lack of specification of the age and sex distribution of the study population, lack of data on occupational exposures, the use of a single $O_3$ metric, and the restricted formulation of the particulate data all severely limited the usefulness of these data.

Kilburn et al. (1992) studied the effect of "air pollution" on expiratory flows and vital capacity in Mexican-American children in Los Angeles.  In 1984, 556 second- and fifth-grade students were studied, and 251 of these were studied again in 1987.  The analytical strategy, the losses to follow-up, and the lack of reasonable exposure data make the data from this study virtually uninterpretable.

A study by Castillejos et al. (1992) evaluated the effects of acute exposures to ambient $O_3$ concentrations on pulmonary function and respiratory symptoms.  One-hundred and forty-eight 9-year-old children in the southwest part of Mexico City were studied between January and June 1988.  Weekly spirometric measurements were made over 10 weeks.  Ambient air data were obtained from the monitoring system maintained by the Mexican

government and included hourly values for temperature, RH, and $O_3$ concentration. Ozone concentration exceeded 120 ppb on 74% of days and "frequently" exceeded 240 ppb. No data are presented for $SO_2$ or particles. All subjects had to live within 5 km of a monitoring station. The study demonstrated that levels of $FEV_1$ and $FEF_{25\,75\%}$ were associated with mean hourly $O_3$ levels in the preceding 24, 48, and 168 h. The authors interpreted their data as consistent with a subchronic effect of $O_3$ on measures derived from spirometry that may be due to an "inflammatory process". However, this interpretation seems at odds with the statement in the paper that the initial $FEV_1$ measurements for the group did not differ from those observed in a comparable age group in the Harvard Six Cities Study who were not exposed to $O_3$ concentrations as high as those reported in this study. If the overall level of pulmonary function of this group does not differ from those children who live in ambient environments with far lower $O_3$ concentrations, the data would suggest that the subchronic effects observed are not translated into persistent abnormalities, at least as can be observed with spirometry.

Austrian investigators (Schmitzberger et al., 1992) described a cross-sectional study of the effects of $O_3$ on the respiratory health of 1,156 children, ages 6 to 15 years. Pulmonary function in two different areas with differing "annual" $O_3$ concentrations (actual metric on which "annual" based not given) were compared (52 ppb versus 26 ppb). No differences were observed for FVC. All flow measures ($FEV_1$, $FEF_{5\,\%}$, and $FEF_{75\%}$) were significantly lower in the children in the "high"-$O_3$ area. These data are of limited value for a variety of reasons, the most important being lack of individual exposure data, lack of data on other pollutants, the uninterpretable specification of "annual" $O_3$ concentration, lack of data on chronic respiratory illness (especially asthma), and the lack of data on smoking for the teenage members of the subject group.

Schmitzberger et al. (1993), following up on their preliminary data (Schmitzberger et al., 1992), studied additional subjects in the Austrian Tyrolian Alps. Three zones were identified based upon ambient air conditions: (1) Zone 1 was characterized by annual mean $SO_2$ (UV fluorescence) of 20 $\mu g/m^3$, monthly mean $NO_2$ (Palmes tubes) of 17 ppb, and annual mean $O_3$ (chemiluminescence) of 15 ppb (maximum half-hour mean = 102 ppb); (2) Zone 2 was characterized by values of 14 $\mu g/m^3$, 13 ppb, and 26 ppb (112 ppb), respectively; and (3) Zone 3 was characterized by 12 $\mu g/m^3$, 8 ppb, and 52 ppb (146 ppb), respectively. Children ages 6 to 15 years who lived in the study areas for $\geq$3 years were enrolled. Respiratory health questionnaire data and forced expiratory flows were obtained. Full data were available from 81% of the enrolled subjects. Adjusted (age, sex, environmental tobacco smoke, socioeconomic status, and home heating) levels of FVC and forced flows did not follow the gradient in $O_3$ concentrations. Although Zone 3 differed significantly from Zone 2 on several measures, there were no meaningful differences with Zone 1. Adjusted asthma prevalence was highest in Zone 3 (6.4% versus 4.8 and 2.7% for Zones 1 and 2, respectively). There were no differences for other respiratory symptoms. Although the authors conclude that "residence in the area of elevated $O_3$ increases the risk...of low small airway-related lung function," careful inspection of the data does not support this conclusion. This conclusion is based on the supposed increased frequency of $FEV_1$ of less than 70% in Zone 3 relative to the other zones, although the specific data are not provided. Moreover, the mean levels for all functional measurements are lowest in Zone 1, the zone with the lowest $O_3$ concentrations and the highest $SO_2$ and $NO_2$ concentrations. This report is handicapped by the lack of any information that could be used to access individual exposures. Moreover, only a single monitoring station was employed that was placed at the center of Zone 1, which itself was at

the center of the study area (1,200 km$^2$).  No information is provided as to how the concentrations of the various pollutants were estimated for Zones 2 and 3.  Therefore, these data virtually are of no quantitative value.

### *Other Chronic Disease Morbidity and Mortality*
Only AHSMOG study has provided any data on possible O$_3$-related health effects other than those related to the respiratory system or malignant disease of the respiratory system (Abbey et al., 1991b; Mills et al., 1991) (see Table 7-27).  The population studied and the assignment of exposures has been presented previously (Hodgkin et al., 1984; Euler et al., 1988; Abbey et al., 1991a).

In their initial study based on 6 years of follow-up, Mills et al. (1991) found that for 500 h in excess of the OZ (10) threshold, there was a relative risk of 2.24 for respiratory cancer incidence after adjustment for a number of factors listed previously.  When the TSP (200) and OZ (10) thresholds were allowed to compete for entry into a Cox proportional hazards model for respiratory cancer incidence, the O$_3$ threshold entered in  preference to TSP.  Ozone exposure was not associated with excess respiratory cancer mortality or incidence of nonrespiratory cancer over the 6-year follow-up period.

A second chronic disease study from the AHSMOG population extended the above observations to include myocardial infarction and all-cause mortality (Abbey et al., 1993).  Incident chronic respiratory disease also was included in this analysis.  Ambient levels of O$_3$ were not associated with incidence of myocardial infarction at any of the threshold indices that were tested.  Neither the mean concentration of O$_3$ nor any of the thresholds were associated with incidence of chronic respiratory diseases, as previously defined.  However, there was a trend toward an association between 6-year cumulative incidence of asthma and 500-h exceedance of the OZ (10) threshold (RR = 1.40, 95% CL = 0.99 to 2.34).

### 7.4.2.3  Conclusions
The body of data that has accumulated since publication of the previous air quality criteria document for O$_3$ (U.S. Environmental Protection Agency, 1986) provides only suggestive evidence for health effects of chronic O$_3$ exposure.  Most of the studies suffer from one or another of the following limitations:  (1) simplistic assignment of exposure in terms of choice of O$_3$ metrics or adequate adjustment for relevant covariates and (2) lack of ability to isolate effects related to O$_3$ from those of other pollutants, especially the particulate fraction.  The AHSMOG study has made substantive progress in the problem of the assignment of individual exposures (Abbey et al., 1991a).  Unfortunately, the results from this study cannot disentangle the effects of chronic  O$_3$ exposure from those due to chronic exposure to the particulate fraction of ambient pollution.  The study also lacks sufficient power to evaluate the possibility of interactions   between O$_3$ and particulate pollution in relation to health effects.  Thus, the overall data are not conclusive, but current evidence is suggestive of possible health effects from chronic exposure to O$_3$.

**Table 7-27.  Effects of Chronic Ozone Exposure on the Incidence of Cardiovascular and Malignant Diseases[a]**

| Concentrations(s) | | Pollutants and Environmental | | | |
|---|---|---|---|---|---|
| ppm | $\square$g/m | Variables | Study Description | Results and Comments | Reference |
| Not reported | | Hodgkin et al. (1984) | Hodgkin et al. (1984) and Abbey et al. (1991a); analysis based upon exceedance frequencies, 1973 to 1977, and cancer cumulative incidence, 1977 to 1982. | Exceedance of OZ (10) threshold borderline associated with respiratory cancer; no association with mean concentration; multipollutant analysis with TSP (200) and OZ (10), only OZ (10) entered the logistic regression for respiratory malignancy; TSP (200) was significant for females for all malignancy; no association between $O_3$ and any measure of cancer mortality; overall results suggestive of $O_3$ effect on respiratory cancer morbidity at level of exposure within range experienced by large percentage of study population. | Mills et al. (1991) |
| Not reported | | See above | See above | No association between any O threshold and all-cause mortality or incidence of myocardial infarction. | Abbey et al. (1991b) |

[a]See Appendix A for acronyms and abbreviations.

# 7.5  Summary and Conclusions
## 7.5.1  Controlled Human Studies of Ozone Exposure
### 7.5.1.1  Effects on Pulmonary Function

Controlled human $O_3$ exposure studies have provided the strongest and most quantifiable exposure-response data on the health effects of $O_3$.  This chapter reviews the results of studies involving subjects exposed to $O_3$ concentrations ranging from 0.08 to 0.75 ppm $O_3$ while at rest or during CE or IE of varying intensity for periods of up to 8 h.  In many of these studies, small sample size and suboptimal experimental design limit the ability to generalize to the larger population.  Of particular concern in considering studies with small sample sizes is the risk of making a beta (Type II) error:  the incorrect conclusion that no difference exists between treatments when comparisons are not significantly different.  The likelihood of making a Type II error greatly limits the ability to determine the minimum $O_3$ concentration that results in a significant pulmonary response in the larger population.  As a result, the conclusions drawn from many of the studies cited in this chapter may underestimate the presence of responses at low $O_3$ concentrations in healthy, young adults.

### *Healthy Subjects*

Results from studies of at-rest exposures to $O_3$ for 2 h in healthy adult subjects have demonstrated decrements in forced expiratory volumes and flows occurring at and above 0.5 ppm $O_3$ (Folinsbee et al., 1978; Horvath et al., 1979).  Airway resistance is not clearly affected during at-rest exposure to these $O_3$ concentrations.

With moderate IE for 2 h, eliciting a $\dot{V}_E$ of 30 to 50 L/min, decrements in forced expiratory volumes and flows, secondary to decreases in IC, have been observed in healthy adult subjects at and above 0.3 ppm $O_3$ (Folinsbee et al., 1978; Seal et al., 1993).  With IE ($\dot{V}_E$ $\square$ 65 L/min), pulmonary symptoms and decrements in forced expiratory volumes and flows are present following 2-h exposures to 0.12 ppm $O_3$ (McDonnell et al., 1983).  Symptoms are present and decrements in forced expiratory volumes and flows occur at 0.16 to 0.24 ppm $O_3$ following 1 h of continuous heavy exercise ($\dot{V}_E$ $\square$ 55 to 90 L/min) (Adams and Schelegle, 1983; Folinsbee et al., 1984; Avol et al., 1984; Gong et al., 1986) and following 2 h of intermittent heavy exercise ($\dot{V}_E$ $\square$ 65 to 68 L/min) (McDonnell et al., 1983; Kulle et al., 1985; Linn et al., 1986).  With longer exposures of 4- to 8-h duration, responses have been observed at lower $O_3$ concentrations and lower ventilation rates.  In the range of concentrations between 0.08 and 0.16 ppm, a number of studies using moderate IE and durations between 4 and 8 h have shown significant responses under the following conditions:  0.16 ppm for 4 h of IE at $\dot{V}_E$ $\square$ 40 L/min (Folinsbee et al., 1994), 0.08 to 0.12 ppm for 6.6 h of IE at $\dot{V}_E$ $\square$ 35 to 40 L/min (Folinsbee et al., 1988; Horstman et al., 1990), and 0.12 ppm for 8 h of IE at $\dot{V}_E$ $\square$ 40 L/min (Hazucha et al., 1992).  Symptom and spirometry responses were increased, with increased duration of exposure, $O_3$ concentration, and total ventilation.  Airway resistance is only modestly affected with moderate or even heavy exercise combined with $O_3$ exposure to concentrations as high as 0.5 ppm $O_3$ (Folinsbee et al., 1978; McDonnell et al., 1983; Seal et al., 1993).  Increased breathing frequency (f) and decreased $V_T$, while maintaining $\dot{V}_E$, occur with exposure to 0.20 to 0.24 ppm $O_3$ when combined with heavy exercise for 1 to 2.5 h (McDonnell et al., 1983; Adams and Schelegle, 1983).  Differences in response to a given $O_3$ concentration among individuals have been shown to be reproducible (Gliner et al., 1983; McDonnell et al., 1985b), indicating some individuals are consistently more responsive to $O_3$ than others.

Group mean decrements in pulmonary function can be estimated roughly when expressed as a nonlinear function of effective (i.e., exposure) dose of $O_3$, the simple product of $O_3$ concentration, mean ventilation, and exposure duration (Silverman et al., 1976; Folinsbee et al., 1978; Adams et al., 1981). The $O_3$ concentration appears to make a greater impact on the pulmonary function response than does $\dot{V}_E$ or exposure duration (Folinsbee et al., 1978; Adams et al., 1981), and, indeed, Larsen et al. (1991) suggest an exponent of approximately 4/3 for the $O_3$ concentration. Another way of expressing this relationship is that doubling the $O_3$ concentration under any given exposure scenario will have a greater impact on spirometry responses than doubling either $\dot{V}_E$ or exposure duration. However, at any given $O_3$ concentration, the major external determinants of response are $\dot{V}_E$ and exposure duration. Because of the broad range of intersubject variability, and the inability to identify characteristics that influence this variability (other than age), efforts to estimate or model individual responses have so far been fruitless (McDonnell et al., 1993). Nevertheless, prediction of group mean $FEV_1$ responses using the variables of the $O_3$ concentration, $\dot{V}_E$, and exposure duration can be successful (Adams et al., 1981; Folinsbee et al., 1978, 1988; Hazucha, 1987; Hazucha et al., 1992; Larsen et al., 1991; McDonnell et al., 1993).

In acute $O_3$ exposure studies of 3 h or less in duration, the responses observed during and following acute exposure to $O_3$ at concentrations between 0.12 and 0.50 ppm in normal, healthy human subjects include decreases in TLC, IC, FVC, $FEV_1$, $FEF_{25\,75\%}$, and $V_T$ and increases in $SR_{aw}$, f, and airway responsiveness. Ozone exposure also has been shown to result in the symptoms of cough, PDI, SB, throat irritation, and wheezing. Similar responses are seen with 4- to 8-h exposures in the $O_3$ concentration range between 0.08 and 0.16 ppm.

When viewed collectively, these physiological and symptom responses may be separated into four general categories, including (1) symptoms, (2) changes in lung volume or spirometry, (3) changes in $R_{aw}$, and (4) changes in airway responsiveness. These categories are based on the absence of correlation between spirometry responses and change in $R_{aw}$ or airway responsiveness. The attenuation by atropine of $R_{aw}$ but not spirometry responses supports the notion of independent mechanisms. The attenuation by indomethacin or ibuprofen of spirometry responses, but not changes in $R_{aw}$ or airway responsiveness, also supports this categorization. A bronchodilator, albuterol, given to healthy subjects prior to $O_3$ exposure did not prevent changes in spirometry, symptoms, or airway responsiveness. Symptoms ratings represent reflex responses (e.g., cough) or a perceptual evaluation of consciously appreciated afferent information (e.g., chest tightness, PDI), and it is therefore somewhat difficult to separate these responses from the more objective physiological responses. However, cough and pain on deep inspiration are related temporally to spirometry and breathing pattern responses (i.e., volume-related changes). In repeated exposure studies, changes in spirometry and breathing pattern become attenuated with the same time course as the changes in symptom responses.

Recent multihour $O_3$ exposure studies indicate that spirometry and symptom responses to concentrations as low as 0.08 ppm occur in healthy subjects with exposures lasting 6 to 8 h. Prolonged exposures (8 h) at lower $O_3$ concentrations (0.12 ppm) also indicate that there is a plateau of response to $O_3$ (Hazucha et al., 1992). Although suggested in previous studies (Gliner et al., 1983), such a plateau is difficult to verify with the typical duration of less than 2 h and the large responses seen with higher concentrations. The level of the response plateau (i.e., the spirometry decrement at which the response no longer changes) must be dependent on the dose rate of exposure (i.e., the product of the $O_3$ concentration and

$\dot{V}_E$) because the magnitude of response at a higher dose rate may greatly exceed the response plateau seen at a lower dose rate. Prolonged exposure studies also suggest that $O_3$-induced spirometry responses depend on the immediate exposure history. With relatively low dose rates (e.g., Hazucha et al., 1992), responses to exposure that occurred 2 to 4 h previously may influence the current response. The cumulative effect of exposures has not been studied at higher dose rates, but greater persistence of effects may be expected based on the longer recovery period at higher doses rates.

Recovery from $O_3$ exposure has not been systematically investigated in a large group of subjects, but available information indicates that an initial phase of recovery proceeds relatively rapidly, and some 40 to 65% of the acute response appears to be recovered within about 2 h (Folinsbee and Hazucha, 1989). However, there is some indication that the spirometric responses, at least to higher $O_3$ concentrations, are not fully recovered within 24 h (Folinsbee and Horvath, 1986; Folinsbee et al., 1994). Collectively, these observations suggest that there is a rapid recovery of $O_3$-induced spirometry and symptom responses, which may occur during resting exposure to $O_3$ (Folinsbee et al., 1977) or as $O_3$ concentration is reduced during exposure (Hazucha et al., 1992), and a slower phase, which, in some cases, may take at least 24 h to complete. Repeated exposure studies at higher concentrations typically show that the response to $O_3$ is enhanced on the second of several days of exposure. This enhanced response suggests a residual effect of the previous exposure, about 22 h earlier, even though the preexposure spirometry may be the same as on the previous day. The absence of the enhanced response with repeated exposure at lower $O_3$ concentrations may be the result of a more complete recovery or less damage to pulmonary tissues.

Studies of repeated daily exposure to $O_3$ have shown that $O_3$-induced changes in spirometry, symptoms, $R_{aw}$, airway responsiveness, and airway inflammation are attenuated with repetitive exposure. At higher dose rates, symptom and spirometry responses may be enhanced on the second exposure. Attenuation of response within 3 to 5 days is a consistent finding in repeated exposure studies, regardless of $O_3$ exposure dose rate, although attenuation of response occurs after fewer exposures at the lower dose rates. The attenuation of response appears to occur more rapidly in less responsive individuals (Horvath et al., 1981) or in responsive subjects exposed to lower $O_3$ dose rates (Folinsbee et al., 1978, 1994). Loss of attenuation is relatively rapid, with $O_3$ responsiveness being partially restored within 4 to 7 days (Kulle et al., 1982; Linn et al., 1982b), and normal responsiveness restored within 1 to 2 weeks after a series of 4 or 5 daily $O_3$ exposures. The attenuation of airway responsiveness may occur somewhat more slowly than that of symptom and spirometry responses. Airway inflammation also appears to attenuate, but less completely than the spirometry responses and with a more gradual recovery (Devlin et al., 1995; Folinsbee et al., 1995). Some markers of inflammation (e.g., LDH and elastase) have not demonstrated attenuation.

The mechanisms leading to the observed pulmonary responses induced by $O_3$ are beginning to be better understood. The available descriptive data suggest several possible mechanisms, some leading to alterations in lung volumes, symptoms, and exercise breathing patterns, and others leading to increases in central and peripheral $R_{aw}$. These mechanisms appear to involve (1) $O_3$ reactions with the airway lining fluid and epithelial cell membranes; (2) local tissue responses, including injury and inflammation; and (3) stimulation of neural afferents (bronchial C fibers) and the resulting reflex responses and symptoms. Much remains to be understood in order to determine how each event in this cascade contributes to the pulmonary responses induced by acute $O_3$ inhalation in human subjects.

### Subjects with Preexisting Disease

Of the subpopulations studied, those with preexisting impediments in pulmonary function and exercise capacity are of primary concern in evaluating the health effects of $O_3$ because even a small change in function is likely to have more impact on a person with reduced reserve. Inherent in these studies are several limitations that, at present, hamper the ability to make definitive conclusions regarding the relative $O_3$ responsiveness of the various groups of subjects studied. Furthermore, it is ultimately necessary to determine whether their responses are representative of the larger population with preexisting disease. These limitations include subject selection (in controlled studies, typically only people with milder disease are selected or volunteer for study), standardized methods for the characterization of some responses, and limited range of exposure doses utilized to examine some endpoints.

These limitations are evident in studies on subjects with COPD, chronic bronchitis, and ischemic heart disease. For patients with COPD performing light to moderate IE, no decrements in pulmonary function were observed after 1- and 2-h exposures to ◻0.30 ppm $O_3$ (Linn et al., 1982a, 1983a; Solic et al., 1982; Kehrl et al., 1985) and only small decreases in forced expiratory volume were observed for 3-h exposures of chronic bronchitics to 0.41 ppm $O_3$ (Kulle et al., 1984). Small decreases in arterial blood oxygen saturation also have been observed in some of these studies, but the interpretation of these results and their clinical significance is uncertain.

Similar limitations also apply to the early studies examining $O_3$ effects in adult and adolescent asthmatics. Decrements in pulmonary function were not observed for adult asthmatics exposed for 2 h at rest (Silverman, 1979) or with intermittent light exercise (Linn et al., 1978) to $O_3$ concentrations of 0.25 ppm and less. Similarly, no significant changes in pulmonary function or symptoms were found in adolescent asthmatics exposed for 1 h at rest to 0.12 ppm $O_3$ (Koenig et al., 1985) and in adolescent asthmatics and nonasthmatics exposed to 0.12 and 0.18 ppm $O_3$ with intermittent moderate exercise up to 1 h (Koenig et al., 1987, 1988), although a small decrease in forced expiratory flow at 50% of FVC was observed in asthmatics after exposure to 0.12 ppm $O_3$. More recent observations by Kreit et al. (1989), Eschenbacher et al. (1989), and Linn et al. (1994) suggest that mild to moderate asthmatics are at least as sensitive to the acute effects of $O_3$ inhalation as healthy subjects when the asthmatics are exposed to $O_3$ under conditions that elicit a significant response in healthy subjects. Kreit et al. (1989) and Eschenbacher et al. (1989) exposed adult asthmatic and nonasthmatic subjects to 0.4 ppm $O_3$ with intermittent moderate exercise for 2 h and observed a greater response in $R_{aw}$, $FEV_1$, and $FEF_{25-75\%}$ in the asthmatic subjects, although changes in FVC and symptoms were similar in both groups. Ozone exposure also resulted in a marked increase in airway responsiveness to methacholine in both the asthmatic and nonasthmatic subjects. These responses take on greater importance when it is considered that the observed $O_3$-induced pulmonary effects were superimposed on preexisting impairment of pulmonary function and airway responsiveness. In addition, the observations of Koenig et al. (1990) and Molfino et al. (1991) suggest the possibility that acute exposure to $O_3$ at doses that do not produce measurable pulmonary function decrements may increase the responsiveness of asthmatics to inhaled $SO_2$ or antigens.

### 7.5.1.2 Symptom Responses to Ozone

Following exposure to $O_3$ many subjects report respiratory symptoms, the most common of which are cough, shortness of breath, and PDI. There is a broad range of severity in rating symptom responses among subjects in these studies. A number of 2-h $O_3$ exposure studies that have examined the exposure dose-pulmonary function and symptom response relationships have included a semiquantitative analysis of symptom responses (Avol et al., 1983; Kulle et al., 1985; McDonnell et al., 1983; Seal et al., 1993). In each of these studies, as $O_3$ concentration increased, the pulmonary function response became more negative (a decrease in $FEV_1$), and the level of the respiratory symptoms (cough, shortness of breath, PDI) increased. The mean decrement in $FEV_1$ in each of these studies was highly correlated (r > 0.98 in all cases) with the mean change in symptom rating or symptom score (the determination of symptoms varied between studies). This high correlation results primarily because each of these variables is highly correlated with $O_3$ concentration. Correlation of individual changes in symptoms and changes in pulmonary function seldom exceed r = 0.6 (Horstman et al., 1990). Contributing to this low individual correlation is the fact that symptoms scores have lower test-retest reliability than tests of lung function. For example, McDonnell et al. (1985b) report test-retest coefficients of about 0.9 for spirometry responses but only about 0.8 for symptoms. Thus individual symptom responses are not good predictors of individual pulmonary function responses. However, group mean symptom responses still provide a good marker of the average $FEV_1$ response to $O_3$ exposure. In two of the very heavy exercise studies (McDonnell et al., 1983; Avol et al., 1983) symptoms of cough or total respiratory symptom scores were increased significantly at 0.12 and 0.16 ppm $O_3$, respectively. In the heavy exercise study (Seal et al., 1993), cough symptoms increased significantly at 0.18 ppm $O_3$. Other studies that support this relationship of symptoms and pulmonary function have been conducted with various exposure durations and exercise intensities (Gong et al., 1986; Horstman et al., 1990) ranging from 1 h of severe exercise to 6.6 h of moderate exercise at $O_3$ concentrations from 0.08 to 0.20 ppm.

In comparing the spirometry and symptom responses of older adults and young adults exposed to $O_3$ under the same conditions, Drechsler-Parks et al. (1989) found significantly lower spirometry responses (□19% versus □6% $FEV_1$) in the older adults. In addition, the incidence of respiratory symptom responses for the three symptoms most commonly reported with $O_3$ exposure were almost twice as high in the young adults, whereas the incidence of symptoms unrelated to $O_3$ exposure (e.g., eye irritation, muscle soreness) typically was greater in the older adults. The comparable or greater incidence of nonrespiratory symptoms in the older adults clearly indicates that they felt less respiratory discomfort in conjunction with their smaller spirometry responses. Asthmatics, when compared with nonasthmatics, tend to have greater changes in $R_{aw}$ and expiratory flow with $O_3$ exposure (Kreit et al., 1989; Horstman et al., 1995) but similar changes in lung volume (i.e., FVC). Asthmatics also have similar symptom responses for cough, PDI, and shortness of breath, although, in one study (Horstman et al., 1995), asthmatics reported a higher incidence of wheezing.

In repeated exposure studies (Folinsbee et al., 1994; Linn et al., 1982b), the changes in symptoms track the changes in spirometry. With repeated exposure to high $O_3$ concentrations, the change in $FEV_1$ is typically greatest on the second exposure day. Correspondingly, symptoms are increased on the second exposure day and diminish to near baseline levels by the fourth or fifth exposure when the spirometry responses become negligible. With repeated exposure to lower $O_3$ concentrations, the largest spirometry

response is seen on the first day and attenuates by the third or fourth day. Symptom responses also are largest on the first day and are attenuated with the same time course. In a single 2-h study in which symptom and spirometry responses were measured during exposure and recovery, the mean changes in symptoms and spirometry responses followed similar time courses (McDonnell et al., 1987).

Intervention studies examining the effects of various drug treatments on the responses to $O_3$ also report parallel changes in symptoms and spirometry. Although atropine blocked the increase in $R_{aw}$ in response to $O_3$ exposure, it did not alter the spirometry or symptom responses (Beckett et al., 1985). Similarly, albuterol and salbutamol, which had no effect on $O_3$-induced changes in spirometry, also had no effect of symptom responses (McKenzie et al., 1987; Gong et al., 1988). The anti-inflammatory medications indomethacin and ibuprofen, which partially inhibit the spirometry responses to $O_3$ exposure, also cause a reduction in respiratory symptoms (Schelegle et al., 1987; Hazucha et al., 1994).

The individual correlations between symptoms and spirometry responses are relatively low ($<0.6$) and are of little predictive value. However, the group mean responses have similar exposure-response characteristics and follow a similar time course of response to exposure and recovery. Symptom and spirometry responses also follow a similar time course of attenuation to repeated exposure and they are affected similarly by a number of medication interventions.

### 7.5.1.3 Effects on Exercise Performance

Endurance exercise performance and $\dot{V}O_{2max}$ may be limited by acute exposure to $O_3$ (Adams and Schelegle, 1983; Schelegle and Adams, 1986; Gong et al., 1986; Foxcroft and Adams, 1986; Folinsbee et al., 1977; Linder et al., 1988). Gong et al. (1986) and Schelegle and Adams (1986) found that significant reductions in maximal endurance exercise performance may occur in well-conditioned athletes while they perform CE ($\dot{V}_E > 80$ L/min) for 1 h at $O_3$ concentrations $\Box 0.18$ ppm. Data from Linder et al. (1988) suggest that small decrements in maximal exercise performance may occur at $O_3$ concentrations less than 0.18 ppm. The mechanisms that lead to these responses and the minimum $O_3$ concentration at which these effects occur have not yet been defined clearly. Reports from studies of exposure to $O_3$ during high-intensity exercise indicate that breathing discomfort associated with maximal ventilation may be an important factor in limiting exercise performance. However, these studies do not exclude the possibility that some as yet undefined physiological mechanism may limit exercise performance.

### 7.5.1.4 Effects on Airway Responsiveness

Ozone exposure causes an increase in nonspecific airway responsiveness as indicated by a reduction in the concentration of methacholine or histamine required to produce a given reduction in $FEV_1$ or increase in $SR_{aw}$. Increased airway responsiveness is an important consequence of exposure to $O_3$ because its presence means that the airways are predisposed to narrowing on inhalation of a variety of stimuli (e.g., specific allergens, $SO_2$, cold air). Markedly increased airway responsiveness is a classical feature of asthma and also may be present with other respiratory diseases (e.g., chronic bronchitis, acute viral infections) and even in a sizeable percentage of the healthy asymptomatic population. Many studies have demonstrated $O_3$-induced increases in nonspecific airway responsiveness in healthy subjects after a 1- to 2-h exposure with exercise to concentrations in the range of 0.20 to 0.60 ppm

(Golden et al., 1978; Holtzman et al., 1979; König et al., 1980; Dimeo et al., 1981; Gong et al., 1986; Folinsbee and Hazucha, 1989) and after 6.6 h of exposure to concentrations in the range of 0.08 to 0.12 ppm (Folinsbee et al., 1988; Horstman et al., 1990). Ozone-induced increases in airway responsiveness tend to resolve within 24 h after exposure but may persist in selected individuals for longer periods (Golden et al., 1978).

Ozone exposure of asthmatic subjects, who characteristically have increased airway responsiveness at baseline, can cause further increases in responsiveness (Kreit et al., 1989). The difference in baseline airway responsiveness between healthy and mild asthmatic subjects may be as much as 100-fold, whereas the changes in airway responsiveness induced by $O_3$ are typically two- to fourfold. Similar relative changes in airway responsiveness are seen in asthmatics exposed to $O_3$ despite their markedly different baseline airway responsiveness. One study (Molfino et al., 1991) has been published suggesting an increase in specific (i.e., allergen-induced) airway reactivity. This response was observed after a 1-h resting exposure of atopic asthmatics to 0.12 ppm $O_3$. One of the important aspects of this observation of increased airway responsiveness after $O_3$ exposure is that this represents a plausible link between ambient $O_3$ exposure and increased hospital admissions for asthma. However, experimental design flaws preclude the use of this study in the determination of a lowest-observed-effect level.

Changes in airway responsiveness after $O_3$ exposure appear to be resolved more slowly than changes in $FEV_1$ or respiratory symptoms. Furthermore, in studies of repeated exposure to $O_3$, changes in airway responsiveness tend to be somewhat less susceptible to attenuation with consecutive exposures than changes in $FEV_1$ (Dimeo et al., 1981; Kulle et al., 1982; Folinsbee et al., 1994). The question of whether chronic $O_3$ exposure can induce a persistent increase (or decrease) in airways responsiveness has not been studied adequately.

Increases in airway responsiveness do not appear to be strongly associated with decrements in lung function or increases in symptoms. This conclusion is based on studies in healthy subjects; however, asthmatics who have widely different baseline airway responsiveness exhibit $FEV_1$ changes after $O_3$ exposure that are similar to those seen in healthy subjects (Kreit et al., 1989).

The mechanism of $O_3$-induced increases in airway responsiveness is only partially understood, but it appears to be associated with a number of cellular and biochemical changes in airway tissue. Airway inflammation may be temporally associated with the presence of increased airway responsiveness (Holtzman et al., 1983; O'Byrne et al., 1984; Seltzer et al., 1986), but many animal models of induced neutrophilia report a conflicting role of these cells in eliciting nonspecific bronchial hyperresponsiveness. Several animal species, for example, have shown an increased airway responsiveness induced by $O_3$ exposure in the absence of an influx of PMNs into the airway mucosa (Evans et al., 1988; Okazawa et al., 1989; Li et al., 1992). In one human study (Ying et al., 1990), preexposure treatment with the anti-inflammatory drug indomethacin blocked the effect of $O_3$ on $FEV_1$ and FVC but not on airway responsiveness; however, cyclooxygenase inhibitors have not been effective at blocking the $O_3$-induced influx of PMNs into BAL fluid (Hazucha et al., 1996; Kleeberger and Hudak, 1992). Therefore, $O_3$-induced airway responsiveness may not be due to the presence of PMNs in the airway or to the release of arachidonic acid metabolites. Rather, it seems likely that the mechanism for this response is multifactorial, possibly involving the presence of cytokines, prostanoids, or neuropeptides; activation of macrophages, eosinophils, or mast cells; and

epithelial damage that increases direct access of mediators to the smooth muscle or receptors in the airways that are responsible for reflex bronchoconstriction.

### 7.5.1.5 Inflammation and Host Defense Effects

A number of studies clearly show that a single acute exposure (1 to 4 h) of humans to moderate concentrations of $O_3$ (0.2 to 0.6 ppm) while exercising at moderate to heavy levels results in a number of cellular and biochemical changes in the lung, as assessed by measurement of BAL constituents (Seltzer et al., 1986; Kehrl et al., 1987; Koren et al., 1989a,b, 1991; Schelegle et al., 1991; McGee et al., 1990; Aris et al., 1993a; Devlin et al., 1995). These exposures result in an inflammatory response characterized by increased numbers of PMNs, increased permeability of the epithelial cells lining the respiratory tract, cell damage, and production of proinflammatory cytokines and prostaglandins. This response can be detected as early as 1 h after exposure (Koren et al., 1991; Schelegle et al., 1991) and persists for at least 18 h (Koren et al., 1989a; Aris et al., 1993a). The response profile of these mediators is not defined adequately, although it is clear that the time course of response varies for different mediators and cells (Schelegle et al., 1991, Koren et al., 1989a, 1991).

A single study (Devlin et al., 1991) provides evidence that many of these changes also occur in humans exposed to 0.08 and 0.10 ppm $O_3$ with moderate exercise for 6.6 h. Decrements in the ability of AMs to phagocytose microorganisms also were reported in this study.

Ozone also causes inflammatory changes in the nose, as indicated by increased levels of PMNs and albumin, a marker for increased epithelial cell permeability. Increases in tryptase levels immediately after $O_3$ exposure suggested the release of mast cell products.

There appears to be no strong correlation between any of the measured cellular and biochemical changes and changes in lung function measurements, suggesting that different mechanisms may be responsible for these processes. Alternatively, the absence of a correlation may reflect either the temporal misalignment of these measurements, the fact that changes detected in the lavage fluid do not quantitatively reflect events occurring in tissues where functional or symptomatic events originate, or that BAL fluid may not be collected from the same lung region primarily implicated in pulmonary function responses. The idea of different mechanisms is supported by a study in which ibuprofen, a cyclooxygenase inhibitor, blunted the $O_3$-induced decrements in lung function without altering the $O_3$-induced increase in PMNs or epithelial cell permeability, although ibuprofen did change the concentration of a number of mediators, some of which may be related to changes in function (Hazucha et al., 1994).

In vitro studies suggest that epithelial cells are the primary target of $O_3$ in the lung and that $O_3$ induces them to produce many of the mediators found in the BAL fluid of humans exposed to $O_3$. Although $O_3$ does not induce AMs to produce these compounds in large quantities, it does directly impair the ability of AMs to phagocytose and kill microorganisms.

### 7.5.1.6 Factors Modifying Responsiveness to Ozone

Many variables that at least have potential for influencing response to $O_3$ remain inadequately addressed in the available clinical data. Factors such as smoking status, age, gender, race or ethnic group, season, and mode of breathing during exposure have been evaluated inadequately for their potential influence on responses to $O_3$ exposure.

Information derived from $O_3$ exposure of smokers is limited. Some degree of attenuation appears to occur in active smokers and may be reversed following smoking cessation (Emmons and Foster, 1991), but available results should be interpreted with caution. The possibility of age-related differences in response to $O_3$ has been explored to some extent since the publication of the previous $O_3$ criteria document (U.S. Environmental Protection Agency, 1986). Young adults historically have provided the subject population for air pollutant exposure studies. Pulmonary function responsiveness appears to decrease with age, although symptom rates remain similar to those of young adults (Drechsler-Parks et al., 1987b, 1989, 1990; Bedi et al., 1988; Reisenauer et al., 1988; McDonnell et al., 1993). The limited information available on the responses of children and adolescents to $O_3$ (McDonnell et al., 1985a; Avol et al., 1985a, 1987; Koenig et al., 1987, 1988) does not indicate that children and adolescents are either more or less responsive than young adults. Of the studies that have investigated gender differences in responsiveness to $O_3$, some (Lauritzen and Adams, 1985; Horvath et al., 1986; Adams et al., 1987; Drechsler-Parks et al., 1987a,b; Messineo and Adams, 1990) have suggested that women are more responsive to $O_3$ than men. However, the absence of consistent findings with respect to gender differences indicates that it cannot be concluded that men and women respond differently to $O_3$. Comparison of responses across gender, racial, ethnic, and age groups is complicated by the determination of equivalent exposures. For example, women and children have smaller lungs than adult men. Thus, with a given exposure concentration, duration, and ventilation, humans with smaller lungs will presumably receive a large relative intrapulmonary exposure. Some attempts have been made to normalize responses according to BSA or lung capacity (e.g., FVC). The only study in which this factor has been investigated systematically (Messineo and Adams, 1990) found no influence of lung size on the spirometry responses under identical exposure ($O_3$ concentration, $\dot{V}_E$, and T) conditions. Three studies (Fox et al., 1993; Seal et al., 1995; Weinmann et al. (1995) have compared pulmonary function responses of women during different phases of the menstrual cycle, but the results are conflicting. The responses of black and white young adults to various concentrations of $O_3$ have been compared in one study (Seal et al., 1993). The data suggested that black males experienced significant decrements in pulmonary function at a lower concentration of $O_3$ than white males, but that there were no differences among the responses of white males and black and white females. Thus, the question of ethnic or racial differences in responsiveness to $O_3$ is answered inadequately, and the available results should be interpreted with caution. No new studies are available on the effects of heat stress (i.e., increased temperature or RH) on $O_3$ responses. One study (Linn et al., 1988) suggests that sensitivity to $O_3$ may be related to seasonal variations in ambient $O_3$ concentrations; this finding needs to be confirmed. Two studies (Hynes et al., 1988; Adams et al., 1989) have reported that differences in the inhalation route (e.g., oral versus nasal or oronasal) appear to be of negligible importance in the responses of exercising adults to $O_3$ exposure. Studies of $O_3$ uptake in the upper airway (Gerrity et al., 1988) confirm the negligible differences between oral and nasal inhalation (also see Chapter 8). None of these potential influences on $O_3$ responsiveness (age, gender, race, hormonal fluctuations, smoking, seasonal variations in responsiveness, and ambient environmental factors) has been investigated thoroughly. However, the observation that healthy older adults appear to be less responsive to $O_3$ exposure than young adults has been confirmed to the point that it can be considered in risk assessment. Nevertheless, this does not address fully the question of age differences because children and adolescents remain inadequately studied.

### 7.5.1.7 Extrapulmonary Effects of Ozone

It still is believed that $O_3$ reacts immediately on contact with respiratory systems fluids and tissues and is not absorbed or transported to extrapulmonary sites to any significant degree. A number of laboratory animal studies reported in the previous chapter (Chapter 6) and early studies on human subjects reported in this chapter suggest that reaction products formed by the interaction of $O_3$ with respiratory system fluids or tissues may produce effects measured outside the respiratory tract—either in the blood, as changes in circulating blood lymphocytes, erythrocytes, or serum, or as changes in the structure or function of other organs, such as the parathyroid, the heart, the liver, and the central nervous system. No extrapulmonary effects have been reported to date in other organ systems of $O_3$-exposed human subjects, except for limited data indicating that acute (1- to 2-h) exposures with exercise at concentrations ☐0.35 ppm $O_3$ caused transient changes in blood cells and plasma. The interpretation of all these effects in regards to potential human health effects at ambient levels of exposure ($<0.35$ ppm $O_3$) is not clear. However, the demonstration in this chapter of an array of inflammatory mediators and immune modulators released at the airway surface in response to $O_3$ provides a possible mechanism for effects to occur outside of the lung. Additional studies are needed, therefore, in order to determine if there are any significant extrapulmonary effects of $O_3$ exposure and at what levels of exposure they might occur.

### 7.5.1.8 Effects of Ozone Mixed with Other Pollutants

No significant enhancement of respiratory effects (i.e., more than additive) has been consistently demonstrated for mixtures of $O_3$ with $SO_2$, $NO_2$, $H_2SO_4$, $HNO_3$, or particulate aerosols, or with multiple combinations of these pollutants. There is general agreement among studies of simultaneous exposure of healthy adults and asthmatic adolescents to mixtures of $O_3$ and $NO_2$, $SO_2$, $H_2SO_4$, or $HNO_3$ that pulmonary function responses are not significantly different from those following exposure to $O_3$ alone when compared to studies conducted at the same $O_3$ concentration. Exposure to high PAN concentrations (i.e., 0.3 ppm) combined with $O_3$ has been reported to induce greater pulmonary function responses than exposure to $O_3$ alone (Horvath et al., 1986), but when the PAN concentration is reduced to the ambient range, any additional effect of PAN in the mixture appears to be negligible (Drechsler-Parks et al., 1989).

In addition to simultaneous exposures to pollutant mixtures, studies of the responses to $O_3$ exposure either preceded or followed by another pollutant have been performed. To the extent that these exposure sequences mimic real ambient conditions, the results could be useful in the risk assessment process. Koenig et al. (1990) demonstrated that exposure of allergic (and probably asthmatic) adolescents to $O_3$ and then to $SO_2$ resulted in significant pulmonary function decrements not seen with an $O_3$-$O_3$ sequence or FA-$SO_2$ sequence. These results also can be interpreted in light of the fact that $O_3$ increases nonspecific bronchial responsiveness and that the increased $SO_2$ responses may simply reflect this increased responsiveness. Such responses would be unlikely in nonatopic healthy adolescents. Other studies (Aris et al., 1991; Hazucha et al., 1994; Linn et al., 1994; Utell et al., 1994) have assessed the responses to $O_3$ after previous exposure to another pollutant. Aris et al. (1991) found that preexposure to water or $HNO_3$ fog appeared to attenuate responses to $O_3$, whereas Hazucha et al. (1994) observed an increased airway responsiveness after $O_3$ exposure preceded by $NO_2$ exposure relative to $O_3$ exposure alone. Two studies of combined or sequential exposure to $H_2SO_4$ aerosol and $O_3$ suggest a possibly enhanced response to $O_3$ in asthmatics when the exposure is

combined with or preceded by exposure to $H_2SO_4$ aerosol (Linn et al., 1994; Utell et al., 1994). These findings are intriguing, but must be replicated before they can be useful for quantitative health assessment. Much is unknown about responses to air pollutant mixtures. Only a limited number of pollutant combinations and exposure protocols have been investigated, and subject groups are small and may not be representative of the general population. Few studies have included more than two pollutants, and most combinations have been evaluated in single studies. Furthermore, only rarely are endpoints other than pulmonary function and plethysmography measured.

## 7.5.2  Field and Epidemiology Studies of Ozone Exposure

Individual-level camp and exercise studies provide useful, quantitative information on the exposure-response relationships linking human lung function declines with $O_3$ exposure occurring in ambient air. Their utility derives largely from the reliability with which individual exposures can be estimated using outdoor measurements in studies of these kind. Although it usually has not been possible to isolate $O_3$ exposures from other copollutants (e.g., acid aerosols) and environmental factors (e.g., temperature) in the design of such studies, the available body of evidence now strongly supports a dominant role of $O_3$ in the observed lung function decrements.

The most extensive epidemiologic database on pulmonary function responses to ambient $O_3$ comes from camp studies. Six recent key studies from three separate research groups provide a combined database on individual exposure-response relationships for 616 children ranging in age from 7 to 17 years, each with at least six sequential measurements of $FEV_1$ and previous-hour $O_3$ exposures while attending summer camps (Avol et al., 1990; Higgins et al., 1990; Raizenne et al., 1987, 1989; Spektor et al., 1988a, 1991). When analyzed together using consistent methods, these data yielded an average relationship between $FEV_1$ and previous-hour $O_3$ concentration of ☐0.50 mL/ppb. The highest 1-h $O_3$ levels measured in five of the six studies ranged from 100 to 160 ppb, with one study reporting concentrations as high as 245 ppb. Minimum $O_3$ values ranged from 10 to 60 ppb. Although the regression results noted above were based on 1-h $O_3$ levels, exposure in camp studies usually extended for multiple hours. Because of the high level of correlation between single- and multiple-hour averages in the studies, these results may therefore, represent, to some extent, the influence of multihour exposures. In addition to the camp study results, two key studies involving lung function measurements before and after well-defined exercise events in adults have yielded exposure-response slopes of ☐0.40 and ☐1.35 mL/ppb (Spektor et al., 1988b; Selwyn et al., 1985). Ozone concentrations during exercise events of approximately 0.5 h duration ranged from 4 to 135 ppb in these studies. Consistent with chamber studies, there is no clear evidence from individual-level studies for a response threshold for the average population effects of $O_3$ on pulmonary function decline. However, as with chamber studies, there is evidence that responsivity varies across individuals. Thus, pulmonary function decline as a function of ambient $O_3$ exposure for an individual may be either greater than or less than the mean responses noted above.

Recent results of daily-life studies also support a consistent relationship between ambient $O_3$/oxidant exposure and acute respiratory morbidity in the population. Respiratory symptoms (or exacerbation of asthma) and decrements in PEFR occur with increasing ambient $O_3$, especially in asthmatic children (Lebowitz et al., 1991; Krzyzanowski et al., 1992; Thurston et al., 1995). Concurrent temperature, particles, $H^+$, aeroallergens, and asthma

severity or medication status also may contribute as independent or modifying factors. The aggregate results show greater responses in asthmatic individuals than in nonasthmatics (Lebowitz et al., 1991; Krzyzanowski et al., 1992), indicating that asthmatics constitute a sensitive group in epidemiologic studies of oxidant air pollution.

Recent aggregate population time series studies of $O_3$-related health effects provide relevant evidence of acute responses, even below a 1-h maximum of 0.12 ppm $O_3$. Emergency room visits, hospital admissions, and mortality all have been examined as possible outcomes of exposure to $O_3$. In the case of ER visits, the evidence is limited (e.g., Bates et al., 1990; Cody et al., 1992; White et al., 1994; Weisel et al., 1995), but results generally are consistent with an effect of $O_3$ on morbidity. Mortality studies vis-f-vis $O_3$ also are rather limited, but are more mixed in their results. One of two new, well-designed studies indicate a significant association between $O_3$ and total mortality in Los Angeles, CA, even after controlling for the potentially confounding effects of temperature and PM (Kinney and Ozkaynak, 1991). Los Angeles experienced peak 1-h maximum $O_3$ concentrations above 0.2 ppm during this study period. However, at lower concentrations, over a shorter time span, and with different statistical methods, a second study (Dockery et al., 1992) did not detect a significant $O_3$ association with mortality. The strongest and most consistent evidence of $O_3$ effects, both above and below 0.12 ppm $O_3$, then, is provided by the multiple studies that have been conducted over the last decade on summertime daily hospital admission for respiratory causes in various locales in eastern North America (Bates and Sizto, 1983, 1987, 1989; Thurston et al., 1992, 1994; Lipfert and Hammerstrom, 1992; Burnett et al., 1994). These studies consistently have shown that $O_3$ air pollution is associated with an increased incidence of admissions, accounting for roughly one to three excess respiratory hospital admissions per 100 ppb $O_3$ per million persons. This association has been shown to remain even after statistically controlling for the possible confounding effects of temperature and copollutants (e.g., $H^+$, $SO_4$, and $PM_1$ ), as well as when considering only days having 1-h maximum $O_3$ concentrations below 0.12 ppm. Furthermore, these results imply that $O_3$ air pollution can account for a substantial portion of summertime hospital admissions for respiratory causes on the most polluted days. Overall, the aggregate population time series studies considered in this chapter provide strong evidence that ambient exposures to $O_3$ can cause significant exacerbations of preexisting respiratory disease in the general public at concentrations below 0.12 ppm $O_3$.

Studies of chronic health effects that may relate to long-term exposure to ambient pollutants still have not provided enough data to determine if there are respiratory or other health effects that result directly from chronic $O_3$ exposure. However, the aggregate evidence to date suggests that chronic $O_3$ exposure, along with other environmental factors, could be responsible for health effects in exposed populations.

The most useful set of data has been provided by the AHSMOG studies (Hodgkin et al., 1984; Euler et al., 1987, 1988; Abbey et al., 1991a,b, 1993). These studies have provided the most refined measures of chronic exposure to date (including adjustment for quality of the monitoring data as determined by distance of monitoring sites from subject residences, topography, time spent indoors, and time spent at work). The most consistent effects that can be attributable, in part, to $O_3$ relate to an increase in 10-year cumulative incidence of asthma (RR = 2.07 for each 1,000 h above 10 pphm) and an increase in asthma severity. Unfortunately, for the entire set of studies, the colinearity between $O_3$ and TSP reduces the confidence that effects can be attributed to $O_3$ alone, $O_3$ in combination with the particulate fraction of ambient pollution, or the combination of the two. Some support for an

effect on persons with asthma also can be derived from a recent Canadian study (Stern et al., 1994) that demonstrated nonstatistically significant 6.6 and 6.5% reductions in $FEF_{25\ 75\%}$ and $\dot{V}_{max5\ \%}$ for people living in Ontario relative to those in Saskatchewan. Again, however, the effects of $O_3$ are impossible to disentangle from the other contributors such as the acid summer haze that characterizes the United States east of the Mississippi River.

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