3. POLICY-RELEVANT ASSESSMENT OF HEALTH EFFECTS EVIDENCE

3.1 INTRODUCTION

This chapter assesses key policy-relevant information on the known and potential health effects associated with exposure to ambient O_3, alone and in combination with other pollutants that are routinely present in ambient air. This assessment focuses specifically on the health effects evidence evaluated in Chapters 4 through 7 of the CD with particular emphasis on the integrative synthesis presented in Chapter 8. That integrative synthesis focuses on integrating newly available scientific information with that available from the last review, as well as integrating information from various disciplines, to address a set of issues central to the assessment of scientific information upon which this review of the O_3 NAAQS is based. This chapter also addresses key issues relevant to quantitative assessment of controlled-human exposure and epidemiological evidence, to provide a foundation for the quantitative human exposure and health risk assessments presented below in Chapters 4 and 5. Those quantitative assessments, together with this evidence-based assessment, provide the foundation for the development of staff conclusions and identification of options for consideration related to primary standards for O_3 presented below in Chapter 6.

The decision in the last review focused primarily on evidence from short-term and prolonged controlled-exposure studies reporting lung function decrements, respiratory symptoms, and respiratory inflammation in humans, as well as epidemiology studies reporting excess hospital admissions and emergency department (ED) visits for respiratory causes. The CD prepared for this review emphasizes a large number of epidemiological studies published since the last review with these and additional health endpoints, including acute and chronic health effects of O_3 for premature mortality, enhanced respiratory symptoms and lung function decrements in asthmatic individuals, school absences, and ED visits for respiratory causes. It also emphasizes important new information from toxicology, dosimetry, and controlled human exposure studies.

As discussed in more detail below (section 3.3), highlights of the new evidence include:

- New controlled human-exposure studies have examined whether lung function decrements are observed in healthy adults under moderate exertion for 6.6 hr exposures to levels as low as 0.04 ppm.
- New controlled human-exposure studies offer evidence of increased airway responsiveness to allergens in subjects with allergic asthma and allergic rhinitis exposed to O_3.

- Numerous controlled human-exposure studies have reported indicators of O_3-induced inflammatory response in both the upper respiratory tract (URT) and lower respiratory tract (LRT), while other studies have shown significant changes in host defense capability following O_3 exposure of healthy young adults.
- Animal toxicology studies provide new information regarding mechanisms of action, increased susceptibility to respiratory infection, and the biological plausibility of acute effects and chronic, irreversible respiratory damage.
- Numerous acute exposure epidemiological studies published during the past decade offer added evidence of ambient O_3-related lung function decrements and respiratory symptoms in exercising healthy subjects and asthmatic subjects, as well as evidence on new health endpoints, such as the relationships between ambient O_3 concentrations and school absenteeism and between ambient O_3 and cardiac physiologic endpoints.
- Several new studies have been published over the last decade examining the temporal associations between O_3 exposures and ED visits for respiratory diseases and on respiratory-related hospital admissions.
- Newly available, large multicity studies, designed specifically to examine the effects of acute exposure to PM and O_3 on mortality, provide much more robust and credible information than was available in the last review. The results from two key studies carried out in 95 U.S. communities (U.S. National Morbidity, Mortality Air Pollution Study [NMMAPS]) and in 23 European cities (Air Pollution and Health: European Approach [APHEA]) reported positive and significant O_3 effect estimates for all cause (nonaccidental) mortality.
- In a recent study, Bell et al. (2006) applied several statistical models to data on air pollution, weather, and mortality for the 98 NMMAPS communities to evaluate whether a threshold level exists for premature mortality. The results indicate that even low levels of tropospheric O_3 are associated with premature mortality.
- Three recent meta-analyses evaluated potential sources of heterogeneity in O_3-mortality associations, and these studies provide evidence of a robust association between ambient O_3 and mortality, especially for the warm O_3 season.

Section 3.2 provides an overview of mechanisms of toxicity, with more detailed discussion in Appendix 3A. Section 3.3 summarizes the nature of effects induced by O_3 exposure or associated with exposure to O_3, alone and in combination with other pollutants, drawing on information in Chapters 5-8 of the CD. Section 3.4 summarizes conclusions and judgments from the CD's integrative assessment of the epidemiological evidence regarding the extent to which causal inferences can be made about observed associations between health endpoints and exposure to O_3, and discusses key issues related to quantitative risk assessment based on such evidence. Section 3.5 discusses biological plausibility and coherence of evidence for O_3-related adverse health effects, including short-term respiratory effects, short-term cardiovascular effects, long-term health effects, and mortality-related health endpoint. Drawing from the CD's integrative synthesis, section 3.6 discusses factors that modify responsiveness to O_3; potentially susceptible and vulnerable populations groups; and public health impacts of exposure to ambient O_3. Finally, section 3.7, summarizes key policy-relevant conclusions from the CD about O_3-related health effects, in the context of a discussion of issues related to our confidence in and the utility of the underlying evidence.

3.2 MECHANISMS OF TOXICITY

Evidence is covered in Chapters 5 and 6 of the CD on possible mechanisms by which exposure to O_3 may result in acute and chronic health effects. While most of the available evidence addresses mechanisms for O_3, we recognize that O_3 serves as an indicator for the total photochemical oxidant mixture found in the ambient air, which includes various reactive oxidant species (ROS). Some effects may be caused by one or more components in the overall pollutant mix, either separately or in combination with O_3. Evidence from dosimetry, toxicology, and human exposure studies has contributed to an understanding of the mechanisms that help to explain the biological plausibility and coherence of evidence for O_3-induced respiratory health effects reported in epidemiological studies. In the past, however, little information was available to help explain potential biological mechanisms which linked O_3 exposure to premature mortality or cardiovascular effects. More recently, however, an emerging body of animal toxicology evidence is beginning to suggest mechanisms that may mediate acute O_3 cardiovascular effects.

Scientific evidence discussed in the CD (section 5.2) indicates that reactions with lipids and antioxidants are the initial step in mediating deleterious health effects of O_3. There is subsequent activation of a cascade of events starting with inflammation, altered permeability of the epithelial barrier, impaired clearance mechanisms (including host defense), and pulmonary structural alterations can potentially exacerbate a preexisting disease status. According to the CD, the scientific evidence is still lacking for clearly establishing a role for one or a group of mechanistic pathways underlying O_3 health effects observed in epidemiological studies. Appendix 3A provides a further discussion of mechanisms of toxicity.

3.3 NATURE OF EFFECTS

The CD provides new evidence that notably enhances our understanding of short-term exposure effects, including effects on lung function, symptom, and inflammatory effects reported in controlled exposure studies. These studies support and extend the findings of the previous CD. There is also a significant body of new epidemiological evidence of associations between short-term exposure to O_3 and effects such as premature mortality, hospital admissions and ED visits for respiratory (e.g., asthma) causes. Key epidemiological and human controlled exposure studies are summarized in Appendices 3B and 3C, respectively.

The following discussions of O_3-related health effects are based on scientific evidence critically reviewed in chapters 5, 6, and 7 of the CD, as well as the CD's integration of scientific evidence contained in Chapter 8. In addition, these health effects discussions rely on the more detailed information and tables presented in the CD's annexes AX5, AX6, and AX7. Conclusions drawn about O_3-related health effects depend on the full body of evidence from controlled-exposure human, epidemiological and toxicological data contained in the CD. Section 3.3.1 focuses on a broad array of morbidity effects, including both acute and chronic exposures. Section 3.3.2 focuses on the expanded body of evidence on associations between acute O_3 exposure and mortality, as well as the more limited evidence on chronic O_3 exposures and mortality.

3.3.1 Morbidity

This section summarizes scientific information contained in the CD on respiratory and cardiovascular effects associated with exposure to O_3. Evidence of the effects of short-term and long-term exposure to O_3 on the respiratory system is discussed in sections 3.3.1.1 and 3.3.1.2, and evidence of O_3-related cardiovascular effects in section 3.3.1.3.

3.3.1.1 Effects on the Respiratory System from Short-term Exposures

Short-term exposures to O_3 have been reported to induce a wide variety of respiratory health effects. These effects include a range of effects, such as morphological changes in the respiratory tract, pulmonary function decrements, respiratory symptoms, respiratory inflammation, increased airway responsiveness, changes in host defense capability, acute morphological effects, increased ED visits and hospital admissions, and effects on exercise performance. Short-term O_3 exposure has also been associated with increases in restricted activity days and school absences but evidence is limited for these effects.

3.3.1.1.1 Pulmonary Function Decrements, Respiratory Symptoms, and Asthma Medication Use

A very large literature base of studies published prior to 1996, which investigated the health effects on the respiratory system from short-term O_3 exposures, was reviewed in the 1986 and 1996 CDs (U.S. Environmental Protection Agency, 1986, 1996). In the last review, the lowest O_3 concentration at which statistically significant reductions in forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) had been reported in sedentary subjects was 0.5 ppm (CD, p 6-3). During exercise, spirometric and symptomatic responses were observed at much lower O_3 exposures. When minute ventilation was considerably increased by continuous exercise (CE) during O_3 exposures lasting 2 hr or less at $\geq$ 0.12 ppm, healthy subjects generally experienced decreases in FEV_1, FVC, total lung capacity (TLC), inspiratory capacity (IC), mean forced expiratory flow from 25% to 75% of FVC (FEF_{25-75}), and tidal volume (V_T);

increases in specific airway resistance (sRaw), breathing frequency (f_B), and airway responsiveness; and symptoms such as cough, pain on deep inspiration, shortness of breath, throat irritation, and wheezing. When exposures were increased to 4- to 8-hr in duration, statistically significant spirometric and symptom responses were reported at O_3 concentrations as low as 0.08 ppm and at lower minute ventilation (i.e., moderate rather than high level exercise) than the shorter duration studies (CD. p. 6-6).

The most important observations drawn from studies reviewed in the 1996 CD were that: (1) young healthy adults exposed to O_3 concentrations $\geq$ 0.08 ppm develop significant, reversible, transient decrements in pulmonary function if minute ventilation or duration of exposure is increased sufficiently, (2) children experience similar spirometric responses but lesser symptoms from O_3 exposure relative to young adults, (3) O_3-induced spirometric responses are decreased in the elderly relative to young adults, (4) there is a large degree of intersubject variability in physiologic and symptomatic responses to O_3 but responses tend to be reproducible within a given individual over a period of several months, (5) subjects exposed repeatedly to O_3 for several days show an attenuation of response upon successive exposures; this attenuation is lost after about a week without exposure; and (6) acute O_3 exposure initiates an inflammatory response which may persist for at least 18 to 24 hr post exposure (CD, p. 6-2).

Since 1996, there have been a number of studies published investigating spirometric and symptomatic responses, and they generally support the observations previously drawn. Recent studies for acute exposures of 1 to 2 hr and 6 to 8 hr in duration are summarized in Tables AX6-1 and AX6-2 of the CD (p. AX6-5 to AX 6-7 and p. AX6-11 to AX6-12) and reproduced as Tables 3C-1 and 3C-2 in Appendix 3C. Among the more important of the recent studies was McDonnell et al. (1997) which examined reported changes in FEV_1 in 485 white males (ages 18-36) exposed for 2 hr to O_3 concentrations from as low as 0.08 ppm up to 0.40 ppm, at rest or with intermittent exercise (IE). Decrements in FEV_1 were modeled by sigmoid-shaped curve as a function of subject age, O_3 concentration, minute ventilation, and duration of exposure. In another study, Ultman et al. (2004) found that exposing 60 young, healthy subjects to 0.25 ppm O_3 for 1 hr with continuous exercise produced considerable intersubject variability in FEV_1 decrements ranging from 4% improvement to a 56% decrement, which was consistent with findings in the 1996 CD. One third of subjects had FEV_1 decrements > 15% and 7% had decrements > 40%. Foster et al. (1993, 1997) examined the effects of O_3 on ventilation distribution and reported results suggesting a prolonged O_3 effect on the small airways and ventilation distribution (CD, p. 6-5).

For prolonged exposures (4 to 8 hr) in the range of 0.08 to 0.16 ppm O_3 using moderate quasi-continuous exercise (QCE; 50 min exercise [minute ventilation of 35 to 40 L/min] and 10 min rest per hr), several pre- and post-1996 studies (Folinsbee et al., 1988,1994; Horstman et al., 1990; Adams, 2002, 2003a, 2006) have reported statistically significant spirometric responses and increased symptoms in healthy adults with increasing duration of exposure, O_3 concentration, and minute ventilation. Based on review of several prolonged exposure studies, the CD (p. 6-6) concluded that FEV_1 decrements are a function of minute ventilation in 6.6 hr exposure studies and that data from recent studies do not support the contention that minute ventilation should be normalized to BSA for adults. Triangular exposure studies (Hazucha et al., 1992; Adams 2003a, 2006) suggest that, depending upon the profile of the exposure, the triangular exposure, which may reflect the pattern of ambient exposures in some locations, can potentially lead to greater FEV_1 decrements than square wave exposures when the overall O_3 doses are equal (CD, p. 6-10), suggesting that peak exposures are important in terms of O_3 toxicology.

McDonnell (1996) and Adams (2002, 2006) used data from a series of studies to investigate the frequency distributions of FEV_1 decrements following 6.6 hr exposures and found that average FEV_1 responses were relatively small (between 5 and 10 %) at 0.08 ppm O_3 (CD, p. 8-17). However, about 18% of the exposed subjects had moderate functional decrements (10 to 20%), and about 8% experienced large decrements (>20%). Figure 3-1A,B,C (CD, Figures 8-1A,B and 8-2, pp. 8-17 and 8-19) demonstrates that while average responses may appear small and insignificant, some individuals can experience much more significant and severe effects that may be clinically significant. The FEV_1 responses illustrated in this figure were not corrected for the effect of exercise in clear air. When that is done for the Adams (2002, 2006) data, the percentage of subjects experiencing $\geq$10% FEV_1 decrements changes to 7%, 7% and 23% at O_3 concentrations of 0.04, 0.06 and 0.08 ppm, respectively in a set of studies conducted in southern California (CD, p. 8-18). The development of these effects is time-dependent during both exposure and recovery periods, with great overlap for development and disappearance of the effects. In healthy human subjects exposed to typical ambient O_3 levels near 0.12 ppm, spirometric responses largely resolve within 4 to 6 hr postexposure, but cellular effects persist for about 24 hr. In these healthy subjects, small residual lung function effects are almost completely gone within 24 hr, while in hyperresponsive subjects, recovery can take as much as 48 hr to return to baseline. The majority of these responses are attenuated after repeated exposure, but such attenuation to O_3 is lost one week postexposure (CD, p. 8-19).

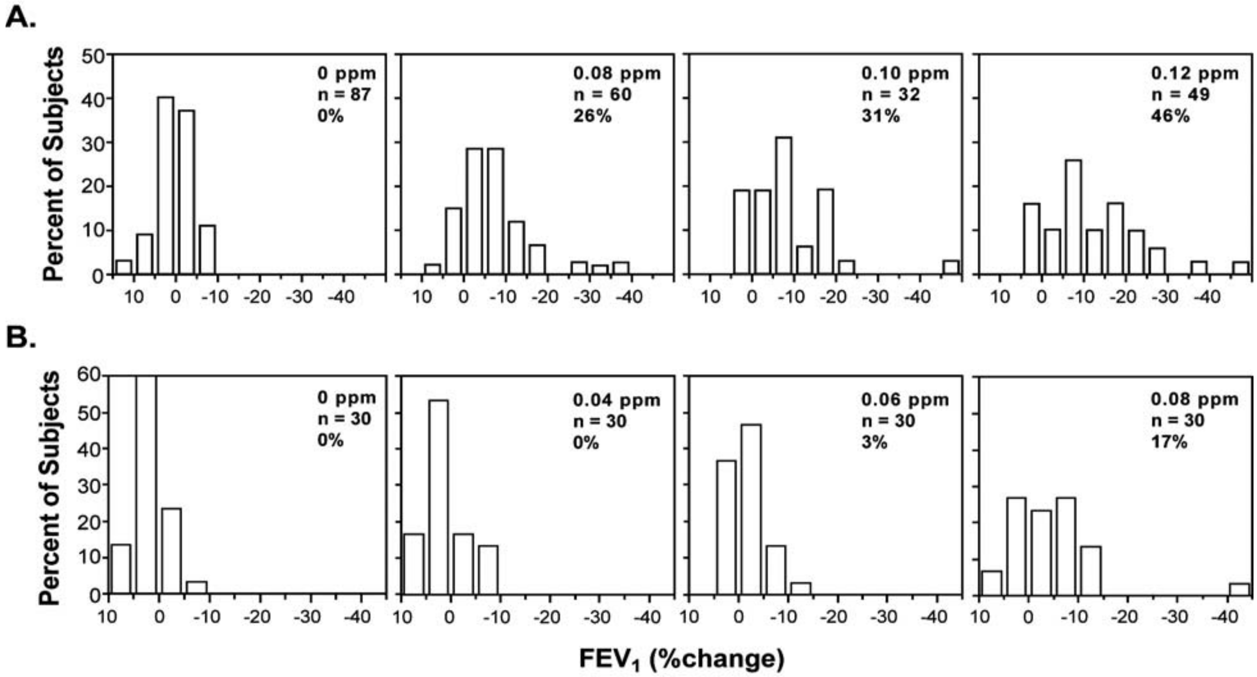


Figure 3-1A and B. Frequency distributions of FEV_1 changes following 6.6-h exposures to a constant concentration of O_3 or filtered air. Note that the percentage in each panel indicates the portion of subjects tested having FEV_1 decrements in excess of 10%.

Source:Panel A, McDonnell (1996); Panel B, Adams (2002, 2006), pre- and post-FEV_1 data for each subject provided by author.

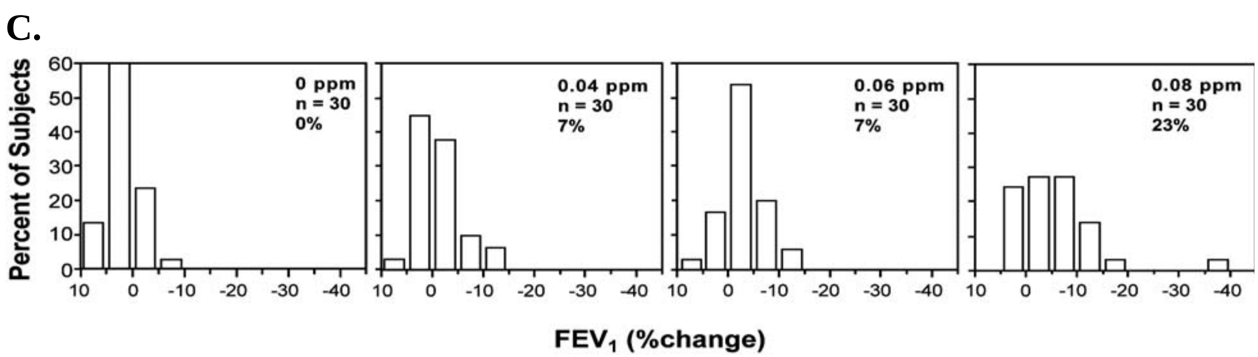


Figure 3-1C. Frequency distributions of FEV_1 changes following 6.6-h exposures to a constant concentration of O_3 or filtered air. The FEV_1 changes following O_3 exposures have been corrected for filtered air responses, i.e., they are O_3-induced FEV_1 changes. Note that the percentage in each panel indicates the portion of subjects tested having FEV_1 decrements in excess of 10%.

Source: Adams (2002, 2006), pre- and post- FEV_1 data for each subject provided by author.

A relatively large number of field studies investigating the effects of ambient O_3 concentrations, in combination with other air pollutants, on lung function decrements and respiratory symptoms have been published since 1996 (see CD, sections 7.2.3, 7.2.4, and 8.4.4.1). These newer studies support the major findings of the 1996 CD that lung function changes, as measured by decrements in FEV_1 or peak expiratory flow (PEF), and respiratory symptoms in healthy adults and asthmatic children are closely correlated to ambient O_3 concentrations. Pre-1996 field studies focused primarily on children attending summer camps and found O_3-related impacts on measures of lung function, but not respiratory symptoms, in healthy children. The newer studies have expanded into looking at O_3-related effects on outdoor workers, athletes, the elderly, hikers, school children, and asthmatics. Collectively, these studies confirm and extend clinical observations that prolonged exposure periods, combined with elevated levels of exertion or exercise, may magnify the effect of O_3 on lung function. The most representative data come from the hiker study (Korrick et al., 1998), which provided outcome measures stratified by several factors (e.g., gender, age, smoking status, presence of asthma) within a population capable of more than normal exertion. In this study, lung function was measured before and after hiking, and both ambient and personal O_3 exposure measurements were made. Decreased lung function was associated with O_3 exposure, with the greatest effect estimates reported for the subgroup that reported having asthma or wheezing, and for those who hiked for longer periods of time, thus increasing the exposure period (CD, p. 7-36).

Asthma panel studies, conducted both in the U.S. and in other countries, have reported that decrements in PEF are associated with O_3 exposures among asthmatic and healthy persons (CD, sections 7.2.3.2 and 8.4.4.1). One large U.S. multicity study (Mortimer et al., 2002) examined O_3-related changes in PEF in 846 asthmatic children from 8 urban areas and reported that the incidence of $\geq$ 10% decrements in morning PEF are associated with a 30 ppb increase in 8-hr average O_3 for a 5-day cumulative lag, suggesting that O_3 exposure may be associated with clinically significant changes in PEF in asthmatic children; however, no associations were reported with evening PEF (CD, p. 7-43). The authors also reported that the associations reported with morning PEF remained statistically significant when days with 8-hr O_3 concentrations above 80 ppb were excluded (CD, p. 7-46). Two studies (Romieu et al., 1996, 1997) carried out simultaneously in northern and southwestern Mexico City with mildly asthmatic school children reported statistically significant O_3-related reductions in PEF, with variations in effect depending on lag time and time of day. While several studies (Gielen et al., 1997; Jalaludin et al., 2000; Ross et al., 2002; Thurston et al., 1997) report statistically significant associations between O_3 exposure and reduced PEF in asthmatics, other studies (Hiltermann et al., 1998; Delfino et al., 1997a) did not, possibly due to very low levels of O_3.

Collectively, however, these studies indicate that O_3 may be associated with declines in lung function in asthmatic individuals (CD, p. 7-40 to 7-46).

Mortimer et al. (2002) discussed biological mechanisms for delayed effects on pulmonary function, which included increased bronchial reactivity secondary to airway inflammation associated with irritant exposure (CD, p. 7-43). Animal toxicological and human chamber studies (CD, Chapters 5 and 6) provide supporting evidence that exposure to O_3 may augment cellular infiltration and cellular activation, enhance release of cytotoxic inflammatory mediators, and alter membrane permeability (CD, p.7-44). In most laboratory animals studied, biochemical markers of lung injury and associated morphological changes were not found to be attenuated, even though at similar exposures pulmonary function changes might be attenuated.

Most of the panel studies which have investigated associations between O_3 exposure and respiratory symptoms or increased use of asthma medication are focused on asthmatic children (CD, sections 7.2.4 and 8.4.4.1). Two large U.S. studies (Mortimer et al., 2002; Gent et al., 2003), as well as several smaller U.S. (Delfino et al., 2003; Just et al., 2002; Newhouse et al., 2004; Romieu et al., 1996, 1997; Ross et al., 2002; Thurston et al., 1997) and international studies (Hilterman et al., 1998; Desqueyroux et al., 2002a,b), have reported fairly robust associations between ambient O_3 concentrations and daily symptoms/asthma medication use, even after adjustment for copollutants.

The National Cooperative Inner-City Asthma Study (NCICAS) reported morning symptoms in 846 asthmatic children from 8 U.S. urban areas to be most strongly associated with a cumulative 1- to 4-day lag of O_3 concentrations (Mortimer et al., 2002). The NCICAS used standard protocols that included instructing caretakers of the subjects to record symptoms in the daily diary by observing or asking the child (Mitchell et al., 1997). Symptoms reported included cough, chest tightness, and wheeze. In the analysis pooling individual subject data from all eight cities, the odds ratio for the incidence of symptoms was 1.35 (95% CI: 1.04, 1.69) per 30 ppb increase in 8-hr avg O_3 (10 a.m.-6 p.m.). The mean 8-hr avg O_3 was 48 ppb across the 8 cities. Excluding days when 8-hr avg O_3 was greater than 80 ppb (less than 5% of days), the odds ratio was 1.37 (95% CI: 1.02, 1.82) for incidence of morning symptoms

Gent and colleagues (2003) followed 271 asthmatic children under age 12 and living in southern New England for 6 months (April through September) in a diary study of daily symptoms in relation to O_3 and $PM_{2.5}$. Mean 1-hr max O_3 and 8-hr max O_3 concentrations were 58.6 ppb (SD 19.0) and 51.3 ppb (SD 15.5), respectively. The data were analyzed for two separate groups of subjects, 130 who used maintenance asthma medications during the follow-up period and 141 who did not. The need for regular medication was considered to be a proxy for more severe asthma. Not taking any medication on a regular basis and not needing to use a bronchodilator would suggest the presence of very mild asthma. Effects of 1-day lag O_3 were observed on a variety of respiratory symptoms only in the medication user group. Both daily 1-hr max and 8-hr max O_3 concentrations were similarly related to symptoms such as chest tightness and shortness of breath. Effects of O_3, but not $PM_{2.5}$, remained significant and even increased in magnitude in two-pollutant models. Some of the associations were noted at 1-hr max O_3 levels below 60 ppb. In contrast, no effects were observed among asthmatics not using maintenance medication. In terms of person days of follow-up, this is one of the larger studies currently available that address symptom outcomes in relation to O_3, and provides supportive evidence for effects of O_3 independent of $PM_{2.5}$. Study limitations include limited control for meteorological factors and the post-hoc nature of the population stratification by medication use (CD, p. 7-53).

The multicities study by Mortimer et al. (2002), which provides an asthmatic population most representative of the United States, and several single-city studies indicate a robust association of O_3 concentrations with respiratory symptoms and increased medication use in asthmatics. While there are a number of well-conducted, albeit relatively smaller, studies which showed only limited or a lack of evidence for symptom increases associated with O_3 exposure, these studies had less statistical power and/or were conducted in areas with relatively low O_3 levels (CD, p. 7-54). The CD (p. 7-55) concludes that the asthma panel studies, as a group, and the NCICAS in particular, indicate a positive association between ambient concentrations and respiratory symptoms and increased medication use in asthmatics. The evidence has continued to expand since 1996 and now is considered to be much stronger than in the previous review of the O_3 primary standard.

The association between school absenteeism and ambient O_3 concentrations was assessed in three relatively large field studies (CD, section 7.2.6). Chen et al. (2000) examined daily school absenteeism in 27,793 elementary school students in Nevada over a 2-year period (after adjusting for PM_{10} and CO concentrations) found that ambient O_3 concentrations were associated with 10.41% excess rate of school absences per 40 ppb increase in 1-hr max O_3. Gilliland et al. (2001) studied O_3-related absences among 1,933 4th grade students in 12 southern California communities and found significant associations between 30-day distributed lag of 8-hr average O_3 concentrations and all absence categories, particularly for respiratory causes. Neither PM_{10} nor NO_2 were associated with any respiratory or nonrespiratory illness-related absences in single pollutant models. The CD concludes that these studies of school absences suggest that ambient O_3 concentrations, accumulated over two to four weeks, may be associated with school absenteeism, particularly illness-related absences, but further replication is needed before firm conclusions can be reached regarding the effect of O_3 on school absences (CD, p. 7-60).

3.3.1.1.2 Airway Responsiveness

Airway hyperresponsiveness (AHR), also know as bronchial hyperreactivity, refers to a condition in which the propensity for the airways to bronchoconstrict due to a variety of stimuli (e.g., exposure to cold air, allergens, or exercise) becomes augmented (CD, section 6.8). This condition is typically quantified by measuring the decrement in pulmonary function (e.g., spirometry or plethysmography) after inhalation exposure to specific (e.g., antigen, allergen) or nonspecific (e.g., methacholine, histamine) bronchoconstrictor stimuli. Exposure to O_3 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 SRaw. 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 various stimuli, such as specific allergens, cold air or SO_2 (CD, p. 8-21). Significant, clinically relevant decreases in pulmonary function have been observed in early phase allergen response in subjects with rhinitis after consecutive (4-day) exposure to 0.125 ppm O_3 (Holz et al., 2002). Similar increased airway responsiveness in asthmatics to house dust mite antigen 16 to 18 hrs after exposure to a single dose of O_3 (0.16 ppm for 7.6 hrs) was observed. These observations suggest that O_3 exposure may be a clinically important factor that can exacerbate the response to ambient bronchoconstrictor substances in individuals with preexisting allergic asthma and that O_3's influence may have an immediate impact on asthmatics as well as contribute to effects that persist for longer periods (CD, p. 8-21).

An important aspect of increased airway responsiveness after O_3 exposure is that it represents a plausible link between O_3 exposure and increased hospital admissions. Kreit et al. (1989) found that O_3 can induce increased airway responsiveness in asthmatic subjects to O_3, who typically have increased airway responsiveness at baseline. A subsequent study (Jorres et al., 1996) suggested an increase in specific (i.e., allergen-induced) airway reactivity in subjects with allergic asthma, and to a lesser extent in subjects with allergic rhinitis after exposure to 0.25 ppm O_3 for 3 hrs; other studies (Molfino et al., 1991; Kehrl et al., 1999) reported similar results. According to one study (Folinsbee and Hazucha, 2000), changes in airway responsiveness after O_3 exposure resolve more slowly than changes in FEV_1 or respiratory symptoms. Other studies of repeated exposure to O_3 suggest that changes in airway responsiveness tend to be somewhat less affected by attenuation with consecutive exposures than changes in FEV_1 (Dimeo et al., 1981; Folinsbee et al., 1994; Gong et al., 1997a; Kulle et al., 1982) (CD, p. 6-31).

An extensive laboratory animal data base exploring the effects of acute, long-term, and repeated exposure to O_3 indicates that induction of AHR occurs at relatively high ($\geq$1ppm) O_3 concentrations (p. 8-21). These studies provide clues to the roles of physiological and biochemical components involved in this process, but caution should be exercised in interpreting these results, as different mechanisms may be involved in mediating high- and low-dose responses. As observed in humans, the acute changes in AHR do not persist after long-term exposure of animals exposed to near-ambient concentrations of O_3, and attenuation has been reported. In addition, dosimetric adjustments potentially could be made to allow better estimation of levels that would be relevant to human exposure effect levels.

The CD concludes that O_3 exposure is linked with increased AHR (CD, section 6.8). Both human and animal studies indicate that airway responses are not associated with inflammation, but they do suggest a likely role for neuronal involvement (CD, p. 8-21). Increases in AHR do not appear to be strongly associated with decrements in lung function or increases in symptoms (CD, p. 6-31).

3.3.1.1.3 Respiratory Inflammation and Permeability

Based on evidence from the previous review, acute inflammatory responses in the lung have been observed subsequent to 6.6 hr O_3 exposures to the lowest tested level of 0.08 ppm in healthy adults. Some studies suggest that inflammatory responses may be detected in some individuals following O_3 exposures in the absence of O_3-induced pulmonary decrements in those subjects. Short-term exposures to O_3 also can cause increased permeability in the lungs of humans and experimental animals (CD, sections 5.2.3, 6.9, 7.2.5 and 8.4.3). Not only are the newer findings consistent with the previous review, but also there is better evidence about the physiological mechanisms by which O_3 causes these effects.

Lung inflammation and increased permeability, which are distinct events controlled by different mechanisms, are two well characterized effects of O_3 exposure observed in all species studied. Disruption of the lung barrier leads to leakage of serum proteins, influx of polymorphonuclear leukocytes (PMNs), release of bioactive mediators, and movement of compounds from the airspaces into the blood.

In the animal toxicological studies discussed in the CD (Chapter 5), the lowest O_3 concentration that induced inflammation in the mouse lung was 0.11 ppm for 24 hr exposures. Shorter exposures of 8 hours required concentrations of 0.26 ppm to induce epithelial permeability though there was no effect on inflammation. The lowest O_3 concentration that affected epithelial permeability or inflammation in the rat was 0.5 ppm for a 3 hr exposure or 0.12 ppm for 6 hr (CD, p. 8-23). After acute exposures, the influence of the duration of exposure increases as the concentration of O_3 increases; however, dosimetric adjustments would need to be done before one can compare levels. The exact role of inflammation in causation of lung disease is not known; nor is the relationship between inflammation and lung function (CD, p. 5-23).

A number of human O_3-exposure studies have analyzed bronchoalveolar lavage (BAL) and nasal lavage (NL) fluids and cells for markers of inflammation and lung damage. These studies are summarized in the CD (Annex AX6, Tables AX6-12 and AX6-13). Increased lung inflammation is demonstrated by the presence of neutrophils (PMNs) found in BAL fluid in the lungs, which has long been accepted as a hallmark of inflammation. It is apparent, however, that inflammation within airway tissues may persist beyond the point that inflammatory cells are found in the BAL fluid. Soluble mediators of inflammation, such as cytokines and arachidonic acid metabolites have been measured 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 responsiveness following O_3 exposure (CD, p. 6-31, p. 8-22). An in vitro study of epithelial cells from nonatopic and atopic asthmatics exposed to 0.01 to 0.10 ppm O_3 showed significantly increased permeability compared to cells from normal persons. This indicates a potentially inherent susceptibility of cells from asthmatic individuals for O_3-induced permeability.

In the 1996 CD, assessment of human exposure studies indicated that a single, acute (1 to 4 hr) O_3 exposure ($\geq$ 0.08 to 0.1 ppm) of subjects engaged in moderate to heavy exercise could induce a number of cellular and biochemical changes suggestive of pulmonary inflammation and lung permeability (CD, p. 8-22). These changes persisted for at least 18 hrs. Graham and Koren (1990) compared inflammatory mediators present in NL and BAL fluids of humans exposed to 0.4 ppm O_3 for 2 hrs and found similar increases in PMNs in both fluids, suggesting a qualitative correlation between inflammatory changes in the lower airways (BAL) and upper respiratory tract (NL). Acute airway inflammation was shown in Devlin et al. (1990) to occur among adults exposed to 0.08 ppm O_3 for 6.6 hr with exercise, and McBride et al. (1994) reported that asthmatic subjects were more sensitive than non-asthmatics to upper airway inflammation for O_3 exposures (0.24 ppm, 1.5 hr, with light IE) that did not affect pulmonary function (CD, p. 6-33).

Since 1996, a substantial number of human exposure studies have been published which have provided important new information on lung inflammation and epithelial permeability. Mudway and Kelly (2004) examined O_3-induced inflammatory responses and epithelial permeability with a meta-analysis of 21 controlled human exposure studies and showed that PMN influx in healthy subjects is associated with total O_3 dose (product of O_3 concentration, exposure duration, and minute ventilation) (CD, p. 6-34). Results of the analysis suggest that the time course for inflammatory responses (including recruitment of neutrophils and other soluble mediators) is not clearly established, but differential attenuation profiles for many of these parameters are evident (CD, p. 8-22).

A number of studies (Peden et al., 1997; Scannell et al., 1996; Hiltermann et al., 1999; Bosson et al., 2003) have provided evidence suggesting that asthmatics show greater inflammatory response than healthy subjects when exposed to similar O_3 levels (CD, section 6.9). Markers from BAL fluid following both 2-hr (Devlin et al., 1997) and 4-hr (Christian et al., 1998; Jorres et al., 2000) O_3 exposures repeated up to 5 days indicate that there is ongoing cellular damage irrespective of attenuation of some cellular inflammatory responses of the airways, pulmonary function, and symptom responses (CD, p. 8-22).

The CD (p. 8-24) concludes that interaction of O_3 with lipid constituents of epithelial lining fluid (ELF) and cell membranes and the induction of oxidative stress is implicated in injury and inflammation. Alterations in the expression of cytokines, chemokines, and adhesion molecules, indicative of an ongoing oxidative stress response, as well as injury repair and regeneration processes, have been reported in animal toxicology and human in vitro studies evaluating biochemical mediators implicated in injury and inflammation. While antioxidants in ELF confer some protection, O_3 reactivity is not eliminated at environmentally relevant exposures. Further, antioxidant reactivity with O_3 is both species-specific and dose-dependent (CD, p. 8-24).

3.3.1.1.4 Changes in Host Defense Capability

As discussed in the CD (sections 5.2.2, 6.9.6, and 8.4.2), short-term exposures to O_3 have been shown to impair host defense capabilities in both humans and experimental animals by depressing alveolar macrophage (AM) functions and by altering the mucociliary clearance of inhaled particles and microbes. Short-term O_3 exposures also interfere with the clearance process by accelerating clearance for low doses and slowing clearance for high doses. Animal toxicological studies have reported that acute O_3 exposures suppress alveolar phagocytes and immune functions. Dysfunction of host defenses and subsequent increased susceptibility to bacterial lung infection in laboratory animals has been induced by short-term exposures to O_3 levels as low as 0.08 ppm (CD, p. 8-26).

Changes in antibacterial defenses are dependent on exposure regimens, species and strain of lab animals, species of bacteria, and age of the animals used. Acute O_3-induced suppression of alveolar phagocytosis and immune function in experimental animals appeared to be transient and attenuated with continuous or repeated exposures. Ozone exposure has also been shown to interfere with AM-mediated clearance in the respiratory region of the lung and with mucociliary clearance of the tracheobronchial airways. These interferences with clearance are dose dependent, with low doses accelerating clearance and high doses slowing the process (CD, p. 8-26).

A single controlled human exposure study (Devlin et al., 1991) reviewed in the 1996 CD reported that exposure to 0.08 to 0.10 ppm O_3 for 6.6 hrs (with moderate exercise) induced decrements in the ability of AMs to phagocytose microorganisms (CD, p. 8-26). Integrating the recent study results with evidence available in the 1996 CD, the CD concludes that available evidence indicates that short-term O_3 exposures have the potential to impair host defenses, primarily by interfering with AM function. Any impairment in AM function may lead to decreased clearance of microorganisms or nonviable particles. Compromised AM functions in asthmatics may increase their susceptibility to other O_3 effects, the effects of particles, and respiratory infections (CD, p. 8-26).

3.3.1.1.5 Morphological Effects

The 1996 CD found that short-term O_3 exposures cause similar alterations in lung morphology in all laboratory animal species studied, including primates. Cells in the centriacinar region (CAR) of the lung (the segment between the last conducting airway and the gas exchange region) have been recognized as a primary target of O_3-induced damage (epithelial cell necrosis and remodeling of respiratory bronchioles), possibly because epithelium in this region receives the greatest dose of O_3 delivered to the lower respiratory tract. Following chronic O_3 exposure, structural changes have been observed in the CAR, the region typically affected in most chronic airway diseases of the human lung (CD, p. 8-24).

Ciliated cells in the nasal cavity and airways, as well as Type I cells in the gas-exchange region, are also identified as targets. While short-term O_3 exposures can cause structural changes such as fibrosis in the CAR, these changes appear to be transient with recovery time after exposure, depending on species and O_3 dose. The potential impacts of repeated short-term and chronic morphological effects of O_3 exposure are discussed later in section 3.3.1.2.5.

Recent studies continue to show that short-term and sub-chronic exposures to O_3 cause similar alterations in lung structure in a variety of experimental animal species, at concentrations of 0.15 ppm in rats and even lower concentrations in primates (CD, section 5.2.4.). Recent work has shown that a topical anti-inflammatory corticosteroid can prevent these effects in nasal epithelia, while exposure to bacterial endotoxin can potentiate effects. Ozone-induced fibrotic changes in the CAR are maximal at 3 days of exposure and recover 3 days post-exposure with exposures of 0.2 ppm O_3 in rodents. One study has demonstrated variability of local O_3 dose and subsequent injury in the respiratory tract due to depletion of glutathione (GSH). The proximal respiratory bronchiole receives the most acute epithelial injury from exposures $\leq$ 1 ppm, while metabolic effects were greatest in the distal bronchioles and minor daughter airways (CD, p. 5-38).

Based on evidence from animal toxicological studies, short-term and sub-chronic exposures to O_3 can cause morphological changes in the respiratory systems, particularly in the CAR, of a number of laboratory animal species (CD, section 5.2.4).

3.3.1.1.6 Emergency Department Visits/Hospital Admissions for Respiratory Causes

The 1996 CD evaluated ED visits and hospital admissions as possible outcomes following exposure to O_3 (CD, section 7.3). The evidence was limited for ED visits, but results of several studies generally indicated that short-term exposures to O_3 were associated with respiratory ED visits. The strongest and most consistent evidence, both below and above 0.12

ppm 1-hr max O_3, was found in the group of studies which investigated summertime daily hospital admissions for respiratory causes in different eastern North American cities. These studies were consistent in demonstrating that ambient O_3 levels were associated with increased hospital admissions and accounted for about one to three excess respiratory hospital admissions per million persons with each 100 ppb increase in 1-hr max O_3, with adjustment for possible confounding effects of temperature and copollutants. Overall, the 1996 CD concluded that there was strong evidence that ambient O_3 exposures can cause significant exacerbations of preexisting respiratory disease in the general public (CD, p. 7-66). Excess respiratory-related hospital admissions associated with O_3 exposures for the New York City area (based on Thurston et al., 1992) were included in the quantitative risk assessment in the prior review and are included in the current assessment along with estimates for respiratory-related hospital admissions in Cleveland, Detroit, and Los Angeles based on more recent studies (see Chapter 5). Significant uncertainties and the difficulty of obtaining reliable baseline incidence numbers resulted in ED visits not being used in the quantitative risk assessment conducted in the last O_3 NAAQS review.

In the past decade, a number of studies have examined the temporal associations between O_3 exposures and ED visits for respiratory causes (CD, section 7.3.2). These studies are summarized in the CD (Table AX7-3, Chapter 7 Annex). Respiratory causes for ED visits include asthma, bronchitis, emphysema, pneumonia, and other upper and lower respiratory infections, such as influenza, but asthma visits typically dominate the daily incidence counts. Among studies with adequate controls for seasonal patterns, many reported at least one significant positive association involving O_3. These studies examined ED visits for total respiratory complaints (Delfino et al., 1997b, 1998b; Hernandez-Garduno et al., 1997; Ilabaca et al., 1999; Lin et al., 1999), asthma (Friedman et al., 2001; Jaffe et al., 2003; Stieb et al., 1996; Tenias et al., 1998; Tobias et al., 1999 ; Tolbert et al., 2000 ; Weisel et al., 2002), and COPD (Tenias et al., 2002).

Figure 7-8 (CD, p. 7-68) provides effect estimates for associations between ED visits for asthma and short-term O_3 exposures. In general, O_3 effect estimates from summer only analyses tended to be positive and larger compared to results from cool season or all year analyses (CD, p. 7-67). Several of the studies reported significant associations between O_3 concentrations and ED visits for respiratory causes. However, inconsistencies were observed which were at least partially attributable to differences in model specifications and analysis approach among various studies. For example, ambient O_3 concentrations, length of the study period, and statistical methods used to control confounding by seasonal patterns and copollutants appear to affect the observed O_3 effect on ED visits. Thus, the CD (p. 7-71) has concluded that stratified analyses by season generally supported a positive association between O_3 concentrations and ED visits for asthma in the warm season.

Unscheduled hospital admissions occur in response to unanticipated disease exacerbations and are more likely to be affected by environmental factors, such as high O_3 levels. Thus, hospital admissions studies focus specifically on unscheduled admissions. Results of a fairly large number of these studies published during the past decade are summarized in Table AX7-4 (CD, Chapter 7 Annex). As a group, these hospital admissions studies tend to be larger geographically and temporally than the ED visit studies and provide results that are generally more consistent. The largest and most significant associations of respiratory hospital admissions with O_3 concentrations were observed using short lag periods, in particular for a 0-day lag (same day exposure) and a 1-day lag (previous day exposure). Most studies in the United States and Canada indicated positive, statistically significant associations between ambient O_3 concentrations and respiratory hospital admissions in the warm season, including studies with 98th percentile 8-hr maximum O_3 levels as low as about 50 ppb. However, not all studies found a statistically significant relationship with O_3, possibly because of insufficient power and/or very low ambient O_3 levels. Analyses for confounding using multipollutant regression models suggest that copollutants generally do not confound the association between O_3 and respiratory hospitalizations. Ozone effect estimates were robust to PM adjustment in all-year and warm-season only data.

Overall, the CD concludes that positive and robust associations were found between ambient O_3 concentrations and various respiratory disease hospitalization outcomes, when focusing particularly on results of warm-season analyses. Recent studies also generally supported a positive association between O_3 concentrations and ED visits for asthma during the warm season (CD, p. 7-175). These observations are strongly supported by the human clinical, animal toxicologic, and epidemiologic evidence for lung function decrements, increased respiratory symptoms, airway inflammation, and increased airway responsiveness. Taken together, the overall evidence supports a causal relationship between acute ambient O_3 exposures and increased respiratory morbidity outcomes resulting in increased ED visits and hospitalizations during the warm season (CD, p. 8-77).

3.3.1.1.7 Effects on Exercise Performance

The effects of O_3 exposure on exercise performance of healthy individuals have been investigated in a number of controlled exposure studies (CD, section 6.7). Several studies discussed in the 1996 CD reported that endurance exercise performance and VO_{2max} may be limited by acute exposure to O_3. Other studies found that significant reductions in maximal endurance exercise performance may occur in well-conditioned athletes while they perform CE ($V_E > 80$ L/min) for 1 hr at O_3 concentrations ≥ 0.18 ppm. There are no new studies available in the CD. Thus, as in the 1996 CD, the CD concludes that reports from studies of O_3 exposure during high-intensity exercise indicate that breathing discomfort associated with maximal ventilation may be an important factor in limiting exercise performance in some, but not all, subjects (CD, p. 6-30).

3.3.1.2 Effects on the Respiratory System from Long-term Exposures

The 1996 CD concluded that there was insufficient evidence from the limited number of studies to determine whether long-term O_3 exposures resulted in chronic health effects at ambient levels observed in the U.S. However, the aggregate evidence suggested that O_3 exposure, along with other environmental factors, could be responsible for health effects in exposed populations (CD, section 7.5). Animal toxicological studies carried out in the 1980's and 1990's demonstrated that long-term exposures can result in a variety of morphological effects, including permanent changes in the small airways of the lungs, including remodeling of the distal airways and CAR and deposition of collagen, possibly representing fibrotic changes. These changes result from the damage and repair processes that occur with repeated exposure. Fibrotic changes were also found to persist after months of exposure providing a potential pathophysiologic basis for changes in airway function observed in children in some recent epidemiological studies. It appears that variable seasonal ambient patterns of exposure may be of greater concern than continuous daily exposures.

This section reviews studies published since 1996 in which health effects were assessed for O_3 exposures lasting from weeks to several years. Summaries of recent morphological effects studies of subchronic and chronic exposures are listed in Table AX5-10 (CD, Annex AX5). Summaries of recent morbidity effects epidemiological studies of long-term exposure are listed in Table AX7-6 (CD, Annex AX7).

3.3.1.2.1 Seasonal Ozone Effects on Lung Function

It is well documented in controlled human exposure and field studies that daily multi-hour exposures to O_3 produce transient declines in lung function; however, lung function effects of repeated exposures to O_3 over extended periods are far less studied. Several studies published since 1996 have investigated lung function changes over seasonal time periods (CD, section 7.5.3). One large, three-year study (Frischer et al., 1999) collected repeated lung function measurements in 1,150 young, Austrian school children and reported that there was an association between growth-related increases in lung function over the summer season and seasonal mean O_3 levels. Mean summertime 24-hr avg O_3 concentrations ranged from 32.5 to 37.3 ppb during the three summers. Growth-related increases in lung function over the summer season were reduced in relation to seasonal mean O_3. It was cautioned that it was difficult to attribute the reported effects to O_3 alone independently of copollutants (CD, p. 7-113). A one-year extension of this study by Horak et al. (2002a,b) confirmed the results that seasonal mean O_3 levels are associated with a negative effect on increases in lung function in children. A study

(Kopp et al., 2000) of 797 children in Austria and southwestern Germany reported smaller increases in lung function in children exposed to higher levels of ambient O_3 (mean O_3 concentration of 44 to 52 ppb) compared to children living in areas with lower ambient O_3 levels (25 to 33 ppb). Another Austrian study (Ihorst et al., 2000) of 2,153 young children found significantly lower FVC and FEV_1 increases associated with higher O_3 exposures in the summer but not in the winter. A pilot study (Kinney and Lippmann, 2000) of 72 young adult, military academy students provided results that are consistent with a seasonal decline in lung function that may be due, in part, to O_3 exposures. According to the CD (p. 7-114), these studies collectively indicate that seasonal O_3 exposure is associated with smaller growth-related increases in lung function in children than they would have experienced living in clean air and that there is some limited evidence that seasonal O_3 also may affect lung function in young adults, although uncertainty about the role of copollutants makes it difficult to attribute the effects to O_3 alone.

3.3.1.2.2 Reduced Baseline Lung Function and Respiratory Symptoms

Lung capacity grows during childhood and adolescence as body size increases, reaches a maximum during the twenties, and then begins to decline steadily and progressively with age. Long-term exposure to air pollution has long been thought to contribute to slower growth in lung capacity, diminished maximally attained capacity, and/or more rapid decline in lung capacity with age (CD, section 7.5.4). Toxicological findings evaluated in the 1996 CD demonstrated that repeated daily exposure of rats to an episodic profile of O_3 caused small, but significant, decrements in growth-related lung function that were consistent with early indicators of focal fibrogenesis in the proximal alveolar region, without overt fibrosis (CD, section 5.2.5.2). Because O_3 is a strong respiratory irritant and has been shown to cause inflammation and restructuring of the respiratory airways, it is plausible that long-term O_3 exposures might have a negative impact on baseline lung function, particularly during childhood when these exposures might have long-term risks. As noted in the current CD, however, no recent toxicological studies have been published on effects of chronic O_3 exposure.

Several epidemiological studies published since 1996 have examined the relationship between growth-related lung function and long-term O_3 exposure. The most extensive and robust study of respiratory effects in relation to long-term air pollution exposures among children in the U.S. is the Children's Health Study carried out in 12 communities of southern California starting in 1993 (Avol et al., 2001; Gauderman et al., 2000, 2002, 2004a,b; Peters et al., 1999a,b). One study (Peters et al., 1999a) examined the relationship between long-term O_3 exposures and self reports of respiratory symptoms and asthma in a cross sectional analysis and found a limited relationship between outcomes of current asthma, bronchitis, cough and wheeze and a 40 ppb increase in 1-hr max O_3 (CD, p. 7-115). Another analysis (Peters et al., 1999b) examined the relationship between growth-related lung function at baseline and levels of air pollution in the community and reported evidence that annual mean O_3 levels were associated with decreases in FVC, FEV_1, PEF and FEF_{25-75} (the latter two being statistically significant) among females but not males (CD, p. 7-116). In a separate study (Gauderman et al., 2000) of 4th, 7th, and 10th grade students, a longitudinal analysis of growth-related lung function over four years found no association with O_3 exposure. Subsequent studies by the same group (Gauderman et al., 2002, 2004a,b) led the authors to conclude that results provide little evidence that ambient O_3 at current levels is associated with chronic deficits in the rate of increase in growth-related lung function in children (CD, p. 7-116 to 7-118). Avol et al. (2001) examined children who had moved from participating communities in southern California to other states with improved air quality and found, with the exception of FEV_1, the O_3 effect estimates for all other spirometric parameters were negative, but the associations were not as strong as those observed for PM_{10} (CD, p. 7-116). Collectively, the results of these reports from the children's health cohorts provide little evidence for impact of long-term O_3 exposures on smaller increases in growth-related lung function (CD, p. 7-122).

Evidence for a significant relationship between long-term O_3 exposures and decrements in maximally attained lung function was reported in a nationwide study of first year Yale students (CD, p. 7-120). Males had much larger effect estimates than females, which might reflect higher outdoor activity levels and correspondingly higher O_3 exposures during childhood. A similar study (Kunzli et al., 1997; Tager et al., 1998) of college freshmen at University of California at Berkeley also reported significant effects of long-term O_3 exposures on lung function (CD, p. 7-121). In a comparison of students whose city of origin was either Los Angeles or San Francisco, long-term O_3 exposures were associated with significant changes in mid- and end-expiratory flow measures, which could be considered early indicators for pathologic changes that might progress to COPD.

In summary, recent publications from the southern California children's cohort study provide no evidence for an association between long-term O_3 exposure and lung function in children (CD, p. 7-118), while limited evidence available from studies of adults and college students suggest that long-term O_3 exposure may affect lung function or respiratory symptoms (CD, pp. 7-120, 7-121). Overall, the CD concluded that this body of evidence was inconclusive for effects of long-term O_3 exposure on respiratory symptoms or lung function (CD, p. 7-175).

3.3.1.2.3 Long-term O_3 Exposure and Respiratory Inflammation

As noted above in section 3.3.1.1.3 and in the CD (Chapter 6), chamber studies of exercising humans exposed to O_3 for 2 to 6.6 hrs have demonstrated inflammation in the lungs, including the alveolar region where gas exchange takes place. The potential long-term significance of short-term exposures to O_3 is that they can result in the release of reactive substances from inflammatory cells that can damage the sensitive cells lining the lungs. Over time repeated inflammation can lead to permanent lung damage and restructuring of the small airways and alveoli. Also, since inflammation is a hallmark characteristic of asthma, there is the possibility that O_3-induced inflammation may exacerbate existing asthma or contribute to the development of asthma in genetically predisposed individuals (CD, section 7.5.5).

For subchronic exposures of animals, permeability changes are transient (and species-dependent) and return to control levels even with continuing exposure. For long-term O_3 exposures, persistent O_3-induced inflammation plays an important role in alterations of lung structure and function. Significant remodeling of the epithelium and underlying connective tissues in distal airways have been reported in rats exposed to 0.25 ppm O_3 (12 hr/day for 6 weeks) and in monkeys exposed to 0.2 ppm O_3 (8 hr/day for 90 days)(CD, p. 8-23).

In one epidemiological field study (Kinney et al., 1996), BAL fluids were taken in the summer and winter from a group of joggers in New York and were compared for evidence of acute inflammation and of enhanced cell damage (CD, p. 7-122). The mean 1-hr max concentrations for a 3-month period were 58 ppb (max 110 ppb) in the summer and 32 ppb (max 64 ppb) in the winter. There was little evidence of acute inflammation in the summer BAL fluids compared to winter, but there was evidence of enhanced cell damage. This suggests that even though inflammation may diminish over the summer, cell damage may be continuing. A cross-sectional cohort study (Calderon-Garciduenas et al., 1995) conducted in Mexico City provides evidence of inflammation and genetic damage to cells in the nasal passages of children chronically exposed to O_3 and other air pollutants (CD, p. 7-123). In Mexico City, the 1-hr avg O_3 concentrations exceeded 120 ppb for 4.4 hr/day. Significantly higher DNA damage was reported in children living in Mexico City compared to nonurban children and in older compared to younger children. Another marker of inflammation, urinary eosinophils, was analyzed in an Austrian school children study (Frischer et al., 2001), and it was reported that O_3 exposure (mean 30 day avg O_3 concentration before sample collection was 31.6 ppb) was significantly associated with eosinophil inflammation (CD, p. 7-122).

In assessing these studies, the CD (p. 7-123) concluded that specific attribution of these adverse respiratory and genotoxic effects to O_3 is difficult given the complex mixture in ambient air, although inflammatory changes like eosinophil levels observed in the Austrian study would be consistent with known effects of O_3.

3.3.1.2.4 Risk of Asthma Development

There have been a few studies investigating associations between long-term O_3 exposures and the onset of new cases of asthma (CD, section 7.5.6). The Adventist Health and Smog (AHSMOG) study cohort of 3,914 was drawn from nonsmoking, non-Hispanic white adult Seventh Day Adventists living in California (Greer et al., 1993; McDonnell et al., 1999).

Subjects were surveyed in 1977, 1987, and 1992. During the ten-year follow-up in 1987, it was reported that the incidence of new asthma was 2.1% for males and 2.2% for females (Greer et al., 1993). A statistically significant relative risk of 3.12 (95% CI: 1.16, 5.85) per 10 ppb increase in annual mean O_3 was observed in males, compared to a nonsignificant relative risk of 0.94 (95% CI: 0.65, 1.34) in females. In the 15-year follow-up in 1992, it was reported that 3.2% of eligible males and 4.3% of eligible females had developed adult asthma (McDonnell et al., 1999). For males, the relative risk of developing asthma was 2.27 (95% CI: 1.03, 4.87) per 30 ppb increase in 8-hr average O_3, but there was no evidence of an association in females. The lack of an association in females does not necessarily mean there is no effect but may be due to differences in time-activity patterns in males and females, which could lead to greater misclassification of exposure in females. Consistency of results in the two studies with different follow-up times provides supportive evidence of an association between long-term O_3 exposure and asthma incidence in adult males; however, representativeness of this cohort to the general U.S. population may be limited (CD, p. 7-125).

In a similar study (McConnell et al., 2002) of incident asthma among children (ages 9 to 16 at enrollment), annual surveys of 3,535 children initially without asthma were used to identify new-onset asthma cases as part of the Children's Health Study. Six high-O_3 (75.4 ppb mean 1-hr max over four years) and six low-O_3 (50.1 ppb, mean 1-hr max) communities were identified where the children resided. There were 265 children who reported new-onset asthma during the follow-up period. Although asthma risk was no higher for all residents of the six high-O_3 versus six low-O_3 communities, asthma risk was 3.3 times greater for children who played three or more sports as compared with children who played no sports within the high-O_3 communities. This association was absent in the communities with lower O_3 concentrations. No other pollutants were found to be associated with new-onset asthma (CD, p. 7-125).

Playing sports may result in extended outdoor activity and exposure occurring during periods when O_3 levels are higher. The sports activities would cause an increased ventilation rate, thus resulting in increased O_3 dose. It should be noted, however, that the results of the Children's Health Study (McConnell et al., 2002) were based on a small number (20 in high-O_3 areas and 9 in low- O_3 areas) of new-onset asthma cases among children who played three or more sports (CD, p. 7-125). Future replication of these findings in other cohorts would help determine whether a causal interpretation is appropriate.

3.3.1.2.5 Morphological Effects

In animal toxicology studies, the progression of morphological effects reported during and after a chronic exposure in the range of 0.5 to 1.0 ppm O_3 is complex, with inflammation peaking over the first few days of exposure, then dropping, then plateauing, and finally, largely disappearing (CD, section 5.2.4.4). By contrast, fibrotic changes in the tissue increase very slowly over months of exposure, and, after exposure ceases, the changes sometimes persist or increase. Epithelial hyperplasia peaks soon after the inflammatory response but is usually maintained in both the nose and lungs with continuous exposure. Epithelial hyperplasia/metaplasia also does not repair after the end of exposure. Patterns of exposure in this same concentration range determine effects, with 18 months of daily exposure, causing less morphologic damage than exposures on alternating months. This is important as environmental O_3 exposure is typically seasonal. Long-term studies of Plopper and colleagues (Evans et al., 2003; Schelegle et al., 2003; Chen et al., 2003; Plopper and Fanucchi, 2000) investigated infant rhesus monkeys exposed to simulated, seasonal O_3 (0.5 ppm, 8 hrs/day for 5 days, every 14 days for 11 episodes) and demonstrated: 1) remodeling in the distal airways, 2) abnormalities in tracheal basement membrane; 3) eosinophil accumulation in conducting airways; and 4) decrements in airway innervation (CD, p. 5-45). As with other effects, these findings advance earlier information regarding possible injury-repair processes occurring with long-term O_3 exposures suggesting that these processes are only partially reversible and may progress following cessation of O_3 exposure and may lead to nonreversible structural damage to lung tissue; however, there is still too much uncertainty to quantitatively extrapolate these levels to human effect levels at this time (CD, p. 8-25).

3.3.1.2.6 Summary

In the past decade, important new longitudinal studies have examined the effect of chronic O_3 exposure on respiratory health outcomes. Evidence from recent long-term morbidity studies have suggested in some cases that chronic exposure to O_3 may be associated with seasonal declines in lung function, increases in inflammation, and development of asthma in children and adults. Seasonal decrements or smaller increases in lung function measures have been reported in several studies; however, it remains uncertain to what extent these changes are transient. While there is supportive evidence from animal studies involving chronic exposures, large uncertainties still remain as to whether current ambient levels and exposure patterns might cause these same effects in human populations. The CD also concludes that epidemiological studies of new asthma development and longer-term lung function declines remain inconclusive at present (CD, p. 7-134).

3.3.1.3 Effects on the Cardiovascular System

At the time of the 1997 review, the possibility of O_3-induced cardiovascular effects was a largely unrecognized issue. Since then, evidence has emerged that provides plausibility for how O_3 exposures could exert cardiovascular system effects. This includes direct effects such as O_3-induced release from lung epithelial cells of platelet activating factor (PAF) that may contribute to blood clot formation that would increase the risk of serious cardiovascular outcomes (e.g., heart attack, stroke, mortality). Also, interactions of O_3 with surfactant components in epithelial lining fluid of the lung results in production of oxysterols and reactive oxygen species that may exhibit PAF-like activity contributing to clotting and also may exert cytotoxic effects on lung and heart muscle cells. Other possible mechanisms may involve O_3-induced secretions of vasoconstrictive substances and/or effects on neuronal reflexes that may result in increased arterial blood pressure and/or altered electrophysiologic control of heart rate or rhythm. Some animal toxicology studies have shown O_3-induced decreases in heart rate, mean arterial pressure, and core temperature. The only controlled human exposure study that evaluated effects of O_3 exposure on cardiovascular health outcomes found no significant O_3-induced differences in ECG, heart rate, or blood pressure in healthy or hypertensive subjects, but did observe a significant O_3-induced increase the alveolar-to-arterial PO_2 gradient in both groups resulting in an overall increase in myocardial work and impairment in pulmonary gas exchange.

Epidemiologic panel and field studies that examined associations between O_3 and various cardiac physiologic endpoints have yielded limited evidence suggestive of a potential association between acute O_3 exposure and altered heart rate variability, ventricular arrhythmias, and incidence of heart attacks. A number of epidemiological studies have also reported associations between short-term exposures and hospitalization for cardiovascular diseases. As shown in Figure 7-13 of the CD, many of the studies reported negative or inconsistent associations. Some other studies, especially those that examined the relationship when O_3 exposures were higher, have found robust positive associations between O_3 and cardiovascular hospital admissions (CD, p. 7-82). For example, one study reported a positive association between O_3 and cardiovascular hospital admissions in Toronto, Canada in a summer-only analysis (mean 1-hr max O_3 of 41.2 ppb). The results were robust to adjustment for various PM indices, whereas the PM effects diminished when adjusting for gaseous pollutants. Other studies stratified their analysis by temperature, i.e., by warms days (≥20 °C) versus cool days (<20 °C). Several analyses using warms days consistently produced positive associations.

The epidemiologic evidence for cardiovascular morbidity is much more mixed than for respiratory morbidity, with only one of several U.S./Canadian studies showing statistically significant positive associations of cardiovascular hospitalizations with warm-season O_3 concentrations. Most of the available European and Australian studies (all of which conducted all-year O_3 analyses) did not find an association between short-term O_3 concentrations and cardiovascular hospitalizations. Overall, the currently available evidence is inconclusive regarding an association between cardiovascular hospital admissions and ambient O_3 exposure (CD, p. 7-83)

Based on the evidence from animal toxicology, human controlled exposure, and epidemiologic studies, the CD concludes that this generally limited body of evidence is highly suggestive that O_3 can directly and/or indirectly contribute to cardiovascular-related morbidity, but that much needs to be done to more fully substantiate links between ambient O_3 exposures and adverse cardiovascular outcomes (CD, p. 8-77).

3.3.2 Premature Mortality

There were only a limited number of studies which examined the relationship between O_3 and mortality available for review in the 1996 CD. Some studies suggested that mortality was associated with short-term exposure to O_3, but conclusions could not be drawn regarding such associations (CD, p. 7-84). Numerous recent studies have provided new and more substantial evidence supporting such an association, as discussed below in section 3.3.2.1.

At the time of the last review, little epidemiological evidence was available on potential associations between long-term exposure to O_3 and mortality. Among the recent studies are some that have evaluated this relationship, and these newer studies still provide limited, if any, evidence for an association between chronic O_3 exposure and mortality, as described in section 3.3.2.2.

3.3.2.1 Mortality and Short-term O_3 Exposure

The 1996 CD concluded that an association between daily mortality and O_3 concentration for areas with high O_3 levels (e.g., Los Angeles) was suggested. However, due to a very limited number of studies available at that time, there was insufficient evidence to conclude that the observed association was likely causal, and thus the possibility that O_3 exposure may be associated with mortality was not relied upon in the 1997 decision on the O_3 primary standard.

The 2006 CD includes results from numerous epidemiological analyses of the relationship between O_3 and mortality. Key findings are available from multi-city time-series studies that report associations between O_3 and mortality. These studies include analyses using data from 90 U.S. cities in the National Mortality, Morbidity and Air Pollution (NMMAPS) study and from 95 U.S. cities in an extension to the NMMAPS analyses (Samet et al., 2000, reanalyzed in Dominici, 2003) and further analyses (Bell et al., 2004) using a subset of 19 U.S. cities and focusing on cause-specific mortality associations (Huang et al., 2005). An additional study (Schwartz, 2005)used case-crossover design and data from 14 U.S. cities to further investigate the influence of adjustment for weather variables in the O_3-mortality relationship (CD, p. 8-38). Finally, results are available from a European study, Air Pollution and Health: a European Approach (APHEA), an analysis using data from 23 cities (Gryparis et al., 2004) and 4 cities (Toulomi et al., 1997) (CD, p. 7-93).

The original 90-city NMMAPS analysis, with data from 1987 to 1994, was primarily focused on investigating effects of PM_{10} on mortality. A significant association was reported between mortality and 24-hr average O_3 concentrations during the warm season, but the association was not significant in analyses for the full year (Samet et al., 2000) (CD, Figure 7-21; p. 7-98). This is because the estimate using all available data was about half that for the summer-only data at a lag of 1-day. The extended NMMAPS analysis included data from 95 U.S. cities and included an additional 6 years of data, from 1987-2000 (Bell et al., 2004), and significant associations were reported between O_3 and mortality. The effect estimate for increased mortality was 0.5% per 24-hr average O_3 measured on the same day (20 ppb change; 95% PI: 0.24, 0.78), and 1.04% per 24-hr average O_3 in a 7-day distributed lag model (20 ppb change; 95% PI: 0.54, 1.55) (CD, p. 7-88). In analyses using only data from the warm season, the results were not significantly different from the full-year results; the effect estimate for increased mortality was 0.44% per 24-hr average O_3 measured on the same day (20 ppb change; 95% PI: 0.14, 0.74), and 0.78% per 24-hr average O_3 in a 7-day distributed lag model (20 ppb change; 95% PI: 0.26, 1.30). The authors also report that O_3-mortality associations were robust to adjustment for PM (CD, p. 7-100).

Using a subset of the NMMAPS data set, another study focused on associations between cardiopulmonary mortality and O_3 exposure (24-hr avg) during the summer season only. The authors report a 1.47% increase per 20 ppb change in O_3 concentration measured on the same day (95% PI: 0.54, 2.39) and a 2.52% increase per 20 ppb change in O_3 concentration using a 7-day distributed lag model (95% PI: 0.94, 4.10)(CD, p. 7-92). These findings suggest that the effect of O_3 on mortality is immediate but also persists for several days.

As discussed below in section 3.4, Huang et al. (2005) assessed confounding by weather, especially temperature, is complicated by the fact that higher temperatures are associated with the increased photochemical activities that are important for O_3 formation. Using a case-crossover study design, Schwartz (2005) assessed associations between daily maximum concentrations and mortality, matching case and control periods by temperature, and using data only from the warm season. The reported effect estimate of 0.92% change in mortality per 40 ppb O_3 (1-hr max, 95% PI: 0.06, 1.80) was similar to time-series analysis results with adjustment for temperature (0.76% per 40 ppb O_3, 95% PI, 0.13, 1.40), suggesting that associations between O_3 and mortality are not sensitive to the adjustment methods for temperature (CD, p. 7-93).

An initial publication from APHEA, a European multi-city study, reported statistically significant associations between daily maximum O_3 concentrations and mortality, with an effect estimate of a 4.5% increase in mortality per 40 ppb O_3 (95% CI: 1.6, 7.7) in four cities (Toulomi et al., 1997). An extended analysis was done using data from 23 cities throughout Europe (Gryparis et al., 2004). In this report, a positive but not statistically significant association was found between mortality and 1-hr daily maximum O_3 in a full year analysis (CD, p. 7-93). Gryparis et al. (2004) noted that there was a considerable seasonal difference in the O_3 effect on mortality; thus, the small effect for the all-year data might be attributable to inadequate adjustment for confounding by seasonality. Focusing on analyses using summer measurements, the authors report statistically significant associations with total mortality [1.8% increase per 30 ppb 8-hr O_3 (95% CI: 0.8, 2.9)], cardiovascular mortality [2.7% increase per 30 ppb 8-hr O_3 (95% CI: 1.2, 4.3)] and with respiratory mortality (6.8% increase per 30 ppb 8-hr O_3, 95% CI: 4.5, 9.2) (CD, p. 7-93, 7-99).

Two of the recent multi-city mortality studies (Bell et al., 2004; Gryparis et al., 2004) have also reported associations for multiple averaging times (CD, p. 8-38). Bell and colleagues (2004) reported associations between mortality and 1-hr daily max, 8-hr daily max and 24-hr avg O_3 concentrations. Effect estimates for associations with 1-hr O_3 was slightly larger than that reported for 8-hr O_3 concentrations, and both were distinctly larger than the association with 24-hr avg O_3, but the effect estimates did not differ statistically. The APHEA study (Gryparis et al., 2004) also reported effect estimates that were slightly larger with 1-hr than with 8-hr O_3 concentrations, but not significantly so.

Numerous single-city analyses have also reported associations between mortality and short-term O_3 exposure, especially for those analyses using warm season data. As shown in Figure 7-21 of the CD, the results of recent publications show a pattern of positive, often statistically significant associations between short-term O_3 exposure and mortality during the warm season (CD, p. 7-97). For example, statistically significant associations were reported in southern California (Ostro, 1995), Philadelphia (Moolgavkar et al., 1995), Dallas (Gamble et al., 1998), and Vancouver (Vedal et al., 2003), as well as numerous studies conducted in other countries. However, no evidence of an association was seen in a study conducted in Pittsburgh (Chock et al., 2000). In considering results from year-round analyses, there remains a pattern of positive results but the findings are less consistent. For example, statistically significant associations were reported in Philadelphia (Moolgavkar et al., 1995) and Dallas (Gamble et al., 1998), while positive but not statistically significant associations were reported in Detroit (Lippmann et al., 2000, reanalyzed in Ito, 2003), San Jose (Fairley, 1999, reanalyzed Fairley, 2003), and Atlanta (Klemm et al., 2004). No evidence for associations was reported in Los Angeles (Kinney et al., 1995), Coachella Valley (Ostro et al., 2003), and St. Louis and Eastern Tennessee (Dockery et al., 1992). In most single-city analyses, effect estimates were not substantially changed with adjustment for PM (CD Figure 7-22, p. 7-101).

In addition, several meta-analyses have been conducted on the relationship between O_3 and mortality. As described in section 7.4.4 of the CD, these analyses reported fairly consistent and positive combined effect estimates ranging from 1.5 to 2.5% increase in mortality for a standardized change in O_3 (CD, Figure 7-20, p. 7-95). Three recent meta-analyses evaluated potential sources of heterogeneity in O_3-mortality associations (Bell et al., 2005; Ito et al., 2005; Levy et al., 2005). The CD (p. 7-96) observes common findings across all three analyses, in that all reported that effect estimates were larger in warm season analyses, reanalysis of results using default GAM criteria did not change the effect estimates, and there was no strong evidence of confounding by PM (CD, p. 7-97). Bell et al. (2005) and Ito et al. (2005) both provided suggestive evidence of publication bias, but O_3-mortality associations remained after accounting for that potential bias. The CD (7-97) concludes that the "positive O_3 effects estimates, along with the sensitivity analyses in these three meta-analyses, provide evidence of a robust association between ambient O_3 and mortality."

Most of the single-pollutant model estimates from single-city studies range from 0.5 to 5% excess deaths per standardized increments. Corresponding summary estimates in large U.S. multi-city studies ranged between 0.5 to 1% with some studies noting heterogeneity across cities and studies (CD, p. 7-110).

In the CD (p. 7-101), Figure 7-22 shows the O_3 risk estimates with and without adjustment for PM indices using all-year data in studies that conducted two-pollutant analyses. Approximately half of the O_3 risk estimates increased slightly, whereas the other half decreased slightly with the inclusion of PM in the models. In general, the O_3-mortality risk estimates were robust to adjustment for PM in the models, with the exception of Los Angeles, CA data with PM_{10} (Kinney et al., 1995) and Mexico City data with TSP (Borja-Aburto et al., 1997). The U.S. 95 communities study (Bell et al., 2004) examined the sensitivity of acute O_3-mortality effects to potential confounding by PM_{10} (CD, 7-100). Restricting analysis to days when both O_3 and PM_{10} data were available, the community-specific O_3-mortality effect estimates as well as the national average results indicated that O_3 was robust to adjustment for PM_{10} (Bell et al., 2004).

Several O_3-mortality studies examined the effect of confounding by PM indices in different seasons (CD, p. 7-102, Figure 7-23). In analyses using all-year data and warm-season only data, O_3 effect estimates were once again fairly robust to adjustment for PM indices, with values showing both slight increases and decreases with the inclusion of PM in the model. In the analyses using cool season data only, the O_3 effect estimates all increased slightly with the adjustment of PM indices, although none reached statistical significance.

The three recent meta-analyses (Bell et al., 2005; Ito et al., 2005; Levy et al., 2005) all examined the influence of PM on O_3 risk estimates. No substantial influence was observed in any of these studies. In the analysis by Bell et al. (2005), the combined estimate without PM adjustment was 1.7% (95% PI: 1.10, 2.37) from 41 estimates, and the combined estimate with PM adjustment was 1.95% (95% PI: 1.06, 4.00) from 11 estimates per 20 ppb increase in 24-hr avg O_3. In the meta-analysis of 15 cities (Ito et al., 2005), the combined estimate was 1.6% (95% PI: 1.1, 2.2) and 1.5% (95% PI: 0.8, 2.2) per 20 ppb in 24-hr avg O_3 without and with PM adjustment, respectively (CD, p. 7-103). The additional time-series analysis of six cities by Ito et al. (2005) found that the influence of PM by season varied across alternative weather models but was never substantial. Levy et al. (2005) examined the regression relationships between O_3 and PM indices (PM_{10} and $PM_{2.5}$) with O_3-mortality effect estimates for all year and by season. Positive slopes, which might indicate potential confounding, were observed for $PM_{2.5}$ on O_3 effect estimates in the summer and all-year periods, but the relationships were weak. The effect of one causal variable (i.e., O_3) is expected to be overestimated when a second causal variable (e.g., PM) is excluded from the analysis, if the two variables are positively correlated and act in the same direction. However, the results from these meta-analyses, as well as several single- and multiple-city studies, indicate that copollutants generally do not appear to substantially confound the association between O_3 and mortality (CD, p. 7-103).

Finally, from those studies that included assessment of associations with specific causes of death, it appears that effect estimates for associations with cardiovascular mortality are larger than those for total mortality; effect estimates for respiratory mortality are less consistent in size, possibly due to reduced statistical power in this subcategory of mortality (CD, p. 7-108). In addition to all-cause mortality, several studies examined broad underlying causes of mortality, such as cardiovascular and respiratory causes. The U.S. 95 communities study (1987-2000) analyzed O_3 effect estimates from cardiovascular and respiratory mortality. The analysis by Bell et al. (2005) used all available data, which included all-year data from 55 communities and warm-season only data from 40 communities. The national average estimate from the constrained distributed lag model was slightly greater for cardiopulmonary deaths than deaths from all causes, with an excess risk of 1.28% (95% PI: 0.62, 1.97) compared to1.04% (95% PI: 0.54, 1.55) per 20 ppb increase in 24-hr avg O_3 in the preceding week.

A related study (Huang et al., 2005) examined O_3 effects on cardiopulmonary mortality during the summers (June to September) of 1987 to 1994 in 19 large U.S. cities from the NMMAPS database. Figure 7-24 in the CD (p. 7-104), presents the Bayesian city-specific and overall average O_3 effect estimates for cardiopulmonary mortality per 20 ppb increase in 24-hr avg O_3 from a constrained 7-day distributed lag model. The O_3 effect estimate was 2.52% (95% PI: 0.94, 4.10) excess risk in cardiopulmonary mortality per 20 ppb increase in 24-hr avg O_3 in the preceding week for the combined analysis of all cities. For analyses of summer data, confounding of the O_3 effect by PM is of concern as daily variations in O_3 may be correlated to PM during the summer months. Huang et al. (2005) observed that when PM_{10} was included in the model, the O_3 effect estimate, on average, remained positive and significant. As PM_{10} measurements were available only every 1 to 6 days, only single-day lags were examined. At a 0-day lag, O_3 was associated with a 1.47% (95% PI: 0.54, 2.39) excess risk versus a 1.49% (95% PI: 0.66, 3.47) excess risk in cardiopulmonary mortality in the O_3-only model and after adjustment for PM_{10}, respectively. The slight sensitivity of the O_3 health effects to the inclusion of PM_{10} in the model may indicate a true confounding effect. However, as only the days with

PM_{10} data available were included in the analysis, the lack of significance is likely attributable to higher statistical uncertainty due to the lack of daily PM_{10} measurements (CD, p. 7-105).

Figure 7-25 in the CD (p., 7-106), presents effect estimates for associations between O_3 and cardiovascular mortality for all-year and warm-season analyses. All studies, with the exception of Ponka et al. (1998), showed positive associations between O_3 and cardiovascular mortality (CD, p. 7-105). As with all-cause mortality, there appears to be heterogeneity in the effect estimates across studies. The cardiovascular mortality estimate from one meta-analysis appears to be close to the mode of the effect estimates from the various studies, as shown in Figure 7-25, in the CD (p. 7-106). This is expected, given that many of these studies were also included in the meta-analysis. This study observed that the posterior mean estimate for cardiovascular causes (2.23% excess risk per 20 ppb increase in 24-hr avg O_3 from 25 estimates) was slightly larger than that for total mortality (1.75% excess risk from 41 estimates). However, since cardiovascular deaths account for the largest fraction (over 40%) of total deaths, it is not surprising that the risk estimates for cardiovascular mortality are somewhat similar to those from all-cause mortality. Overall, the cardiovascular mortality risk estimates in the current literature show consistently positive associations with some heterogeneity (most estimates fall within the range of 1 to 8% per 40 ppb increase in 1-hr avg O_3 (CD, p. 7-107).

Several studies observed that the risk estimates for the respiratory category were larger than the cardiovascular and total nonaccidental categories (Anderson et al., 1996; Gouveia and Fletcher, 2000; Gryparis et al., 2004; Zmirou et al., 1998). The apparent inconsistencies across studies may be due in part to the differences in model specifications, but they may also reflect the lower statistical power associated with the smaller daily counts of the respiratory category (usually accounting for less than 10% of total deaths) compared to the larger daily counts for the cardiovascular category (approximately 40 to 50% of total deaths). Thus, an examination of the differences in risk estimates across specific causes requires a large population and/or a long period of data collection. In one meta-analysis (Bell et al., 2005), which combined 23 estimates from 17 studies for respiratory mortality, the effect estimate for respiratory causes was smaller (0.94% excess risk per 20 ppb increase in 24-hr avg O_3) compared to the estimates for total mortality (1.75% excess risk) and cardiovascular mortality (2.23% excess risk) (CD, p. 7-107).

In summary, several single-city studies observed positive associations between ambient O_3 concentrations and cardiovascular mortality. In addition, a meta-analysis that examined specific causes of mortality found that the cardiovascular mortality risk estimates were higher than those for total mortality. The findings regarding the effect size for respiratory mortality have been less consistent, possibly because of lower statistical power in this subcategory of mortality. The CD finds that the results from U.S. multi-city time-series studies provide the strongest evidence to date for O_3 effects on acute mortality. Recent meta-analyses also indicate positive risk estimates that are unlikely to be confounded by PM; however, future work is needed to better understand the influence of model specifications on the risk coefficient (CD, p. 7-175). For cardiovascular mortality, the CD (Figure 7-25, p. 7-106) suggests that effect estimates are consistently positive and more likely to be larger and statistically significant in warm season analyses. The CD (p. 8-78) concludes that these findings are highly suggestive that short-term O_3 exposure directly or indirectly contribute to non-accidental and cardiopulmonary-related mortality, but additional research is needed to more fully establish underlying mechanisms by which such effects occur.

3.3.2.2 Mortality and Long-term O_3 Exposure

Little evidence was available in the last review on the potential for associations between mortality and long-term exposure to O_3. In the Harvard Six City prospective cohort analysis, the authors report that mortality was not associated with long-term exposure to O_3 (Dockery et al., 1993). The authors note that the range of O_3 concentrations across the six cities was small (19.7 to 28.0 ppb in average 24-hr concentrations over the 7-year study period), which may have limited the power of the study to detect associations between mortality and O_3 levels (CD, p. 7-127).

As discussed in section 7.5.8 of the CD, in this review there are results available from three prospective cohort studies: the American Cancer Society (ACS) study, the Adventist Health and Smog (AHSMOG) study, and the U.S. Veterans Cohort study. In addition, a major reanalysis report includes evaluation of data from the Harvard Six City cohort study (Krewski et al., 2000). This reanalysis also includes additional evaluation of data from the initial ACS cohort study report that had only reported results of associations between mortality and long-term exposure to fine particles and sulfates (Pope et al., 1995).[1]

In this reanalysis of data from the previous Harvard Six City prospective cohort study, the investigators replicated and validated the findings of the original studies, and the report included additional quantitative results beyond those available in the original report (Krewski et al., 2000). In the reanalysis of data from the Harvard Six Cities study, the effect estimate for the association between long-term O_3 concentrations (8.3 ppb between the highest and lowest concentrations in the cities) and mortality was negative and nearly statistically significant (relative risk = 0.87, 95% CI: 0.76, 1.00).

The ACS study is based on health data from a large prospective cohort of approximately 500,000 adults and air quality data from about 150 U.S. cities. The initial report (Pope et al., 1995) focused on associations with fine particles and sulfates, for which significant associations

[1] This reanalysis report and the original prospective cohort study findings are discussed in more detail in section 8.2.3 in *Air Quality Criteria for Particulate Matter* (EPA, 2004).

had been reported in the earlier Harvard Six Cities study (Dockery et al., 1993). As part of the major reanalysis of these data, results for associations with other air pollutants were also reported, and the authors report that no significant associations were found with O_3. However, results of seasonal analyses show a small positive association between long-term O_3 concentrations in the warm months (April-September) with a relative risk of 1.02 for all-cause mortality (95% CI: 0.96-1.07) and a stronger association was reported for cardiopulmonary mortality (relative risk=1.08, 95% CI: 1.01, 1.16) (Krewski et al., 2000, p. 174). For some specifications of O_3 exposure in the ACS study, there was an effect in the warm quarter, as there was in the reanalysis of the Harvard Six Cities study.

The ACS II study (Pope et al., 2002) reported results of associations with an extended data base; the mortality records for the cohort had been updated to include 16 years of follow-up (compared with 8 years in the first report) and more recent air quality data were included in the analyses. Results are presented for full-year analyses, and show no evidence for a significant association between long-term exposure to O_3 and mortality. As shown in Figure 7-27 of the CD, the effect estimates are near zero and sometimes negative (though not statistically significant) for associations between long-term O_3 exposure and all-cause, cardiopulmonary, and lung cancer mortality (CD, p. 7-128).

The Adventist Health and Smog (AHSMOG) cohort includes about 6,000 adults living in California. In two studies from this cohort, a significant association has been reported between long-term O_3 exposure and increased risk of lung cancer mortality among males only (Beeson et al., 1998; Abbey et al., 1999). No significant associations were reported between long-term O_3 exposure and mortality from all causes or cardiopulmonary causes. Due to the small numbers of lung cancer deaths (12 for males, 18 for females) and the precision of the effect estimate (i.e., the wide confidence intervals), the CD raised concerns about the plausibility of the reported association with lung cancer (CD, p. 7-130).

The U.S. Veterans Cohort study (Lipfert et al., 2000b, 2003) of approximately 50,000 middle-aged males diagnosed with hypertension, reported some positive associations between mortality and peak O_3 exposures (95^{th} percentile level for several years of data). The analysis included numerous analyses using subsets of exposure and mortality follow-up periods which spanned the years 1960 to 1996. In the results of analyses using deaths and O_3 exposure estimates concurrently across the study period, there were positive, statistically significant associations between peak O_3 and mortality, with a 9.4% excess risk (95% CI: 0.4, 18.4) per mean 95% percentile O_3 (CD, p. 7-129).

Thus, the results from all-year analyses in the Harvard Six Cities and ACS cohorts provide no evidence for associations between long-term O_3 exposure and mortality, though the warm-season results in the reanalysis of the ACS cohort study suggest a potential association.

Imprecise and inconclusive associations were reported in analyses for the AHSMOG cohort study. Significant associations between long-term O_3 exposure and mortality were only reported for the Veterans cohort study; while this study used an indicator of peak O_3 concentrations, the cohort is also a rather specific subgroup of the U.S. population. Overall, the CD concludes that consistent associations have not been reported between long-term O_3 exposure and all-cause, cardiopulmonary or lung cancer mortality (CD, p. 7-130).

3.3.3 Ozone Effects on UV-B Flux

The CD (Chapter 10) provides a thorough analysis of the current understanding of the relationship between reducing tropospheric O_3 concentrations and the potential impact these reductions might have on increasing UV-B surface fluxes and indirectly contributing to increased UV-B related health effects. It is clear that there are many factors that influence UV-B radiation penetration to the earth's surface, including cloud cover, surface albedo, PM concentration and composition, and gas phase pollution. A risk assessment of UV-B related health effects would need to take into account human habits, such as outdoor activities, dress and skin care. However, little is known about the impact of these factors on individual exposure to UV-B, and detailed information does not exist regarding type (e.g., peak or cumulative) and time period (e.g., childhood, lifetime, current) of exposure, wavelength dependency of biological responses, and interindividual variability in UV-B resistance. In fact there have been recent reports indicating the necessity of UV-B in producing vitamin D, suggesting that increased risks of human disease due to slight excess UV-B exposure may be offset by the benefits of enhanced vitamin D production. However, as with other impacts of UV-B on human health, this beneficial effect of UV-B radiation has not been studied in sufficient detail to allow for a credible health benefits or risk assessment. The CD (p. 10-38) concluded that the effects of changes in surface-level O_3 concentrations on UV-induced health effects cannot be critically assessed given the significant uncertainties summarized above.

3.3.4 Summary

The CD (Chapters 4-8) summarizes and assesses substantial new evidence which builds upon what was previously known about the health effects of O_3. The new information supports previous findings that short-term O_3 is associated with lung function decrements and respiratory symptoms, as well as numerous more subtle effects on the respiratory system such as morphological changes and altered host defense mechanisms. Short-term O_3 exposure has also been associated with hospital admissions for respiratory causes in numerous new studies that further confirm the findings evaluated in the 1996 CD. The CD reports that warm-season studies show evidence for positive and robust associations between ambient O_3 concentrations and respiratory hospital admissions, respiratory symptoms and lung function effects in asthmatic children, and positive but less conclusive evidence for associations with respiratory ED visits (CD, p. 7-175).

Some new studies have suggested associations between increased incidence of asthma or reduced lung function and long-term exposure to elevated ambient O_3 levels. The findings of this small group of studies are inconsistent, however, and the CD concludes that the evidence for this group of associations is inconclusive (CD, p. 7-175).

A new body of studies has suggested associations between short-term O_3 exposure and effects on the cardiovascular system, including changes in heart rate variability, cardiac arrhythmia, incidence of MI and hospitalization for cardiovascular diseases. The CD finds this body of evidence to be limited but supportive of potential effects of O_3 on the cardiovascular system (CD, p. 8-77).

A major area where new information presented in the CD has significantly expanded our knowledge on health effects is evidence of an elevated risk of mortality associated with acute exposure to O_3, especially in the summer or warm season when O_3 levels are typically high. Results from recent large U.S. multicity time-series studies and meta-analyses provide the strongest evidence for associations between short-term O_3 exposure and mortality (CD, p. 7-175). The risk estimates shown are consistent across studies and robust to control for potential confounders. This overall body of evidence is highly suggestive that O_3 directly or indirectly contributes to nonaccidental and cardiopulmonary-related mortality, but additional research is needed to more fully establish underlying mechanisms by which such effects occur (CD, p. 8-78).

3.4 ASSESSMENT OF EVIDENCE FROM EPIDEMIOLOGICAL STUDIES

In Chapter 8, the CD assesses the new health evidence, integrating findings from experimental (e.g., toxicological, dosimetric and controlled human exposure) and epidemiological studies, to make judgments about the extent to which causal inferences can be made about observed associations between health endpoints and exposure to O_3. Section 8.4.4.3 of the CD indicates that *strength* of epidemiologic evidence (including the magnitude and precision of reported O_3 effect estimates and their statistical significance), *consistency* of effects associations (looking across results of multiple- and single-city studies conducted by different investigators in different places and times), and *robustness* of epidemiological associations (i.e., stability in the effect estimates after considering a number of factors) are all important in forming judgments as to the likely causal significance of observed associations (CD, p. 8-40).

In evaluating the evidence from epidemiological studies in sections 7.1.3 and 8.4.4.3, the CD focuses on well-recognized criteria, including: (1) the *strength* of reported associations, including the magnitude and precision of reported effect estimates and their statistical significance; (2) the *robustness* of reported associations, or stability in the effect estimates after considering factors such as alternative models and model specification, potential confounding by co-pollutants, as issues related to the consequences of exposure measurement error; and (3) the *consistency* of the effects associations as observed by looking across results of multiple- and single-city studies conducted by different investigators in different places and times (CD, p. 8-40). Integrating more broadly across epidemiological and experimental evidence, the CD also focuses on the *coherence* and *plausibility* of observed O_3-related health effects to reach judgments about causality (CD, section 8.6).

Subsequent to the final CD being published, CASAC sent a letter to the Administrator (Henderson, 2006) providing additional advice on some key issues in order to inform specifically the preparation of this draft Staff Paper specifically and the review of the O_3 NAAQS in general. The issues related to assessment of epidemiological studies are addressed in this section and more generally in section 3.5, and include the general issue of the utility of time-series epidemiological studies in assessing the risks from exposure to O_3 and other criteria pollutants, as well as related issues about exposure measurement error in O_3 mortality time-series studies and O_3 as a surrogate for the broader mix of photochemical oxidant pollution in time-series studies. Implications of these issues for staff conclusions about the adequacy of the current O_3 NAAQS and the identification of options for consideration will be considered below in Chapter 6.

The following discussion summarizes the conclusions and judgments from the CD's summary of epidemiologic evidence and integrative assessment, focusing in particular on discussions of strength, robustness, and consistency in the epidemiological evidence; judgments in the CD about coherence and plausibility are summarized below in section 3.5. This section also addresses issues related to lag periods between O_3 ambient exposure levels and health outcomes, the nature of O_3-health effect concentration-response relationships, and the assessment of air pollutant mixtures containing O_3 in time-series epidemiological studies.

3.4.1 Strength of Associations

The strength of associations most directly refers to the magnitude of the reported relative risk estimates. Taking a broader view, the CD draws upon the criteria summarized in a recent report from the U.S. Surgeon General, which define strength of an association as "the magnitude of the association and its statistical strength" which includes assessment of both effect estimate size and precision, which is related to the statistical power of the study (CDC, 2004). In general, when associations are strong in terms of yielding large relative risk estimates, it is less likely that the association could be completely accounted for by a potential confounder or some other source of bias (CDC, 2004). With associations that yield small relative risk estimates it is especially important to consider potential confounding and other factors in assessing causality.

Effect estimates between O_3 and many health outcomes are generally small in size and could thus be characterized as weak. For example, effect estimates for associations with mortality generally range from 0.5 to 5% increases per 40 ppb increase in 1-hr max O_3 or equivalent, whereas associations for hospitalization range up to 50% increases per standardized O_3 increment. The CD particularly notes that there are several multicity studies for associations between short-term O_3 exposure and mortality or morbidity that, although small in size, have great precision due to the statistical power of the studies, concluding that such associations are strong relative to the precision of the studies (CD, p.8-40). That is, the associations were strong enough to have been reliably measured by the studies such that many of the associations can be distinguished from the null hypothesis with statistical confidence.

3.4.2 Robustness of Associations

Factors considered in assessing *robustness* include impact of exposure error, potential confounding by copollutants, and alternative models and model specifications, as evaluated in the CD (sections 7.1.3 and 8.4.4.3) and discussed below.

3.4.2.1 Exposure Error

In time-series epidemiological studies, concentrations measured at ambient monitoring stations are generally used to represent a community's exposure to ambient O_3. For time-series studies, the emphasis is on the temporal (e.g., daily or hourly) changes in ambient O_3. In cohort or cross-sectional studies, air quality data averaged over a period of months to years are used as indicators of a community's long-term exposure to ambient O_3 and other pollutants. In both types of analyses, exposure error is an important consideration, as actual exposures to individuals in the population will vary across the community. As described in the CD, there are few sources of O_3 exposure for most people other than ambient air; potential indoor sources of O_3 include office equipment, air cleaners, and small electric motors (CD, p. 7-6). Exposure to ambient O_3 for individuals is influenced by factors related to the infiltration of O_3 into buildings, air exchange rate, indoor circulation rate, and O_3 removal processes, as well as the time spent out of doors by the individuals, particularly for those individuals who engage in exercise or other activities which induce increased respiration (e.g., sports, construction work).

In a study describing the relationships between panel studies and time-series studies, Sheppard (2005) noted that non-ambient exposures varied across individuals and were not likely to have strong temporal correlations, whereas ambient concentrations across individuals should be highly correlated. In the case of O_3, there are limited non-ambient sources, thus, the non-ambient sources are likely to be independent of the ambient sources. A related simulation study by Sheppard et al. (2005) examining non-reactive pollutants found no noticeable difference between effects estimates using either total personal exposure or ambient concentration data when non-ambient sources exposures were independent of ambient source exposures in times series studies. Since O_3 is a reactive pollutant, an additional assumption needs to be made in applying these conclusions to O_3, i.e., that its chemical reactivity does not induce strong temporal correlations.

The seasonal variation of personal behaviors and building ventilation practices can modify exposure, thereby obscuring the relationship between personal exposures and ambient concentrations. In addition, that relationship may be affected by temperature. For example, high temperatures may increase air conditioning use, which can reduce O_3 penetration indoors, further complicating the role of temperature as a confounder of O_3 health effects. It should be noted that the pattern of exposure misclassification error and the influence of confounders may differ across the outcomes of interest as well as in susceptible populations. Those who suffer from chronic cardiovascular or respiratory conditions may tend to protect themselves more from environmental threats by reducing their exposure to both O_3 and its confounders, such as high temperature and PM, than those who are healthy.

The CD discusses the potential influence of exposure error on epidemiological study results in section 7.1.3.1. Three components to exposure measurement error are outlined: (1) the use of average population rather than individual exposure data; (2) the difference between average personal ambient exposure and ambient concentrations at central monitoring sites; and (3) the difference between true and measured ambient concentrations (CD, p. 7-7). These components are expected to have different effects, with the first and third likely not causing bias in a particular direction ("nondifferential error") but increasing the standard error, while the second component may result in downward bias, or attenuation of the risk estimate (CD, pp. 7-7 to 7-8).

Some recent studies have evaluated the impact of exposure measurements error on O_3 effect estimates. Navidi et al. (1999) used data from a children's cohort study to compare effect estimates from a simulated "true" exposure level to results of analyses from O_3 exposures determined by several methods. The results indicated that the use of O_3 exposures from personal sampling or microenvironmental approaches is associated with nondifferential error in O_3 effect estimates, compared with effect estimates from "true" exposures. However, O_3 exposures based on the use of ambient monitoring data overestimates the individual's O_3 exposure and thus generally results in O_3 effect estimates that are biased downward (CD, p. 7-8). Similarly, Zidek (1997) noted that a statistical analysis must balance bias and imprecision (error variance). For example, in a reanalysis of a study by Burnett et al. (1994) on the acute respiratory effects of ambient air pollution, Zidek et al. (1998) noted that accounting for measurement error, as well as making a few additional changes to the analysis, resulted in qualitatively similar conclusions, but the effects estimates were considerably larger in magnitude (CD, p. 7-8).

In addition to overestimation of exposure and the resulting underestimation of effects, the use of ambient O_3 concentrations may obscure the presence of thresholds in epidemiologic studies (CD p. 7-9). Brauer et al. (2002) concluded that surrogate measures of exposure, such as those from centrally located ambient monitors, that were not highly correlated with personal exposures obscured the presence of thresholds in epidemiologic studies at the population level, even if a common threshold exists for individuals within the population.

As discussed in the CD Section 3.9, O_3 concentrations measured at central ambient monitoring sites may explain, at least partially, the variance in individual exposures; however, this relationship is influenced by other factors such as air exchange rates in housing and time spent outdoors which may vary from city to city. Other studies conducted in various cities observed that the daily averaged personal O_3 exposures from the population were well correlated with ambient O_3 concentrations, although substantial variability existed among the personal measurements. Thus, there is supportive evidence that ambient O_3 concentrations from central monitors may serve as valid surrogate measures for mean personal exposures experienced by the population, which is of the most relevance for time-series studies. This is especially true for respiratory hospital admission studies, for which much of the response is attributable to O_3 effects on people with asthma. Ambient monitors are more likely to correlate reasonably well with the personal exposures of children, who spend more time outdoors in the warm season and who are also more likely to have asthma than adults. Conversely, there is some concern about the extent to which ambient concentrations are representative of personal O_3 exposures of another particularly susceptible group of individuals, the debilitated elderly, and what impact that may have on mortality and hospitalization time-series studies. The correlation between ambient concentrations and personal exposure measurements has not been examined in this population. A better understanding of the relationship between ambient concentrations and personal exposures, as well as of the other factors that affect relationship will improve the interpretation of concentration-population health response associations observed with ambient O_3 concentrations.

Existing epidemiologic models may not fully take into consideration all of the biologically relevant exposure history or reflect the complexities of all of the underlying biological processes. As discussed in the CD, Section 3.9, using ambient concentrations to determine exposure generally overestimates true personal O_3 exposures by approximately 2- to 4-fold in available studies, resulting in biased descriptions of underlying concentration-response relationships and attenuated risk estimates. The implication is that the effects being estimated occur at fairly low exposures and the potency of O_3 is greater than these effects estimates indicate. As very few studies evaluating O_3 health effects with personal O_3 exposure measurements exist in the literature, effect estimates determined from ambient O_3 concentrations must be evaluated and used with caution to assess the health risks of O_3. Until more data on personal O_3 exposure becomes available, the use of routinely monitored ambient O_3 concentrations as a surrogate for personal exposures is not generally expected to change the principal conclusions from O_3 epidemiologic studies. Thus, the CD concludes that "there is supportive evidence that ambient O_3 concentrations from central monitors may serve as surrogate measures for mean personal O_3 exposures experienced by the population, which is of most relevance to time-series studies" (CD, p. 7-9). Therefore, population health risk estimates derived using ambient O_3 levels from currently available observational studies, with appropriate caveats about personal exposure considerations, remain useful.

In using epidemiological study results for quantification of health risks for certain health outcomes, staff recognizes that the risk estimates may be underestimating true public health risk. However, staff observes that the use of risk estimates for comparing relative risk reductions between alternative O_3 standards considered in the risk assessment is less likely to suffer from this concern. In addition, as discussed in Chapter 5, staff has conducted an exposure assessment in conjunction with a portion of the health risk assessment that incorporates estimated population exposures in developing risk estimates for health outcomes based on controlled human exposure studies.

3.4.2.2 Confounding by Copollutants

Confounding occurs when a health effect that is caused by one risk factor is attributed to another variable that is correlated with the causal risk factor; epidemiological analyses attempt to adjust or control for potential confounders. Copollutants (e.g., PM, CO, SO_2 and NO_2) can meet the criteria for potential confounding in O_3-health associations if they are potential risk factors for the health effect under study and are correlated with O_3. Effect modifiers include variables that may influence the health response to the pollutant exposure (e.g., co-pollutants, individual susceptibility, smoking or age). Both are important considerations for evaluating effects in a mixture of pollutants, but for confounding, the emphasis is on controlling or adjusting for potential confounders in estimating the effects of one pollutant, while the emphasis for effect modification is on identifying and assessing the level of effect modification.

The CD observes that O_3 is generally not highly correlated with other criteria pollutants (e.g., PM_{10}, CO, SO_2 and NO_2), but may be more highly correlated with secondary fine particles, especially during the summer months (CD, p. 7-148). In addition, the correlation between O_3 and other pollutants may vary across seasons, since O_3 concentrations are generally higher in the summer months. This may lead to negative correlations between O_3 and other pollutants during the cooler months, but positive associations between O_3 and pollutants such as fine particles during the warmer months (CD, p. 7-17). Thus, the CD pays particular attention to the results of season-specific analyses and studies that assess effects of PM in potential confounding of O_3-health relationships in its discussions in section 7.6.4.

Multipollutant models are commonly used to assess potential confounding in epidemiological studies. As discussed in the CD, the limitations to the use of multipollutant models include the difficulty in interpreting results where the copollutants are highly colinear, or where correlations between pollutants change by season (CD, p. 7-150). This is particularly the situation where O_3 and a copollutant, such as sulfates, are formed under the same atmospheric condition; in such cases multipollutant models would produce unstable and possibly misleading results (CD, p. 7-152).

For mortality, the results from numerous multi-city and single-city studies are shown in Figure 7-22 of the CD. These results indicate that O_3-mortality associations do not appear to be substantially changed in multipollutant models including PM_{10} or $PM_{2.5}$ (CD, p. 7-101). Focusing on results of warm season analyses, Figure 7-23 of the CD shows effect estimates for O_3-mortality associations that are fairly robust to adjustment for PM in multipollutant models (CD, p. 7-102). In general, based on results from several single- and multiple-city studies, and on recent meta-analyses, the CD (p. 7-103) concludes that "copollutants generally do not appear to substantially confound the association between O_3 and mortality."

Similarly, multipollutant models are presented for associations between short-term O_3 exposures and respiratory hospitalization in Figure 7-12 of the CD; the CD concludes that copollutants generally do not confound the relationship between O_3 and respiratory hospitalization (CD, p. 7-79 to 7-80). Multipollutant models were not used as commonly in studies of relationships between respiratory symptoms or lung function with O_3, but the CD reports that results of available analyses indicate that such associations generally were robust to adjustment for $PM_{2.5}$ (CD, p. 7-154). For various co-pollutant models, in a large multicity study of asthmatic children (Mortimer et al., 2002), the O_3 effect was attenuated, but there was still a positive association. In Gent et al. (2003), effects of O_3, but not $PM_{2.5}$, remained statistically significant and even increased in magnitude in two-pollutant models (CD, p. 7-53).

Considering this body of studies, the CD concludes: "Multipollultant regression analyses indicated that O_3 risk estimates, in general, were not sensitive to the inclusion of copollutants, including $PM_{2.5}$ and sulfate. These results suggest that the effects of O_3 on respiratory health outcomes appear to be robust and independent of the effects of other copollutants (CD, p. 7-154)." We use the results of single-pollutant model results in presentation of results in this chapter and in quantitative risk assessments conducted as part of this review (see Chapter 5) for purposes of comparing results from different studies. However, we also include the use of multipollutant model results in presenting risk estimates, when available, to more completely characterize the quantitative health risks associated with ambient O_3 levels.

3.4.2.3 Model Specification

The CD observes that one challenge of time-series epidemiological analysis is assessing the relationship between O_3 and health outcomes while avoiding bias due to confounding by other time-varying factors, particularly seasonal trends and weather variables (CD, p. 7-14). These variables are of particular interest because O_3 concentrations have a well-characterized seasonal pattern (see Chapter 2) and are also highly correlated with changes in temperature. Thus it can be difficult to distinguish whether effects are associated with O_3 or with seasonal or weather variables in statistical analyses.

Section 7.1.3.4 of the CD discusses statistical modeling approaches that have been used to adjust for time-varying factors, highlighting a series of analyses that were done in a Health Effects Institute-funded reanalysis of numerous time-series studies. While the focus of these reanalyses was on associations with PM, a number of investigators also examined the sensitivity of O_3 coefficients to the extent of adjustment for temporal trends and weather factors. In addition, several recent studies, including U.S. multi-city studies (Bell et al., 2005; Huang et al., 2005; Schwartz et al., 2005) and a meta-analysis study (Ito et al., 2005), evaluated the effect of model specification on O_3-mortality associations. As discussed in the CD (section 7.6.3.1), these studies generally report that associations reported with O_3 are not substantially changed with alternative modeling strategies for adjusting for temporal trends and meteorologic effects. However, significant confounding can occur when strong seasonal cycles are present, suggesting that season-specific results are more generally robust than year-round results in such cases. The CD concludes that "seasonal dependence of O_3-mortality effects complicates interpretation of O_3 risk estimates calculated from year-round data without adequate adjustment of temporal trends" (CD, p. 7-99), and that more work is needed in this area to reduce the uncertainty involved in the epidemiologic interpretation of O_3 effect estimates (CD, p. 7-141).

A number of epidemiological studies have conducted season-specific analyses, as discussed in section 7.6.3.2 of the CD. As observed above in section 3.3, such studies have generally reported stronger and more precise effect estimates for O_3 associations in the warm season than in analyses conducted in the cool seasons or over the full year. For assessing relationships between O_3 and health outcomes, the CD highlights several reasons to focus on warm season analyses: (1) the seasonal nature of O_3 concentrations; (2) the relationship between O_3 formation and temperature; (3) correlations between other pollutants, particularly fine particles, and O_3 variations across seasons in some areas; and (4) factors affecting exposure to ambient O_3, such as air conditioning use, varies seasonally in most areas of the U.S.. We have therefore focused on epidemiological findings from warm season analyses, where available, for qualitative assessments and for the quantitative risk assessment discussed in Chapter 5.

3.4.3 Consistency

Consistency refers to the persistent finding of an association between exposure and outcome in multiple studies of adequate power in different persons, places, circumstances and times (CDC, 2004). In considering results from multicity studies and single-city studies in different areas, the CD observes general consistency in effects of short-term O_3 exposure on mortality, respiratory hospitalization and other respiratory health outcomes (CD, p. 8-41). The variations in effects that are observed may be attributable to differences in relative personal exposure to O_3, as well as varying concentrations and composition of copollutants present in different regions. Thus, the CD concludes that "consideration of consistency or heterogeneity of effects is appropriately understood as an evaluation of the similarity or general concordance of results, rather than an expectation of finding quantitative results with a very narrow range" (CD, p.8-41).

3.4.4 Lag Structure in Short-term Exposure Studies

In the short-term exposure epidemiological studies, many investigators have tested associations for a range of lag periods between the health outcome and O_3 concentration (see CD, sections 7.1.3.3). The CD observes that the selection of an appropriate lag period can depend on the health outcome under study. For example, if cough is resulting from the irritant action of O_3, that would be expected to occur with a short lag time; however, exacerbation of asthma through an inflammatory response might occur up to several days after initial exposure (CD, p. 7-12). For both mortality and respiratory hospital admissions, the CD reports that most significant associations between O_3 and mortality were observed with O_3 measured on the same day or a 1-day lag period in studies using individual lag periods (CD, p. 7-14). In U.S. multi-city studies, larger effect estimate sizes were reported for the O_3-mortality relationship with the distributed lag structure (CD, p. 7-88). Field studies of lung function or respiratory symptoms reported associations with O_3 across a range of lag periods from exposure on the same day to exposures averaged over several days (CD, sections 7.2.3 and 7.2.4). Cardiovascular effects appeared to be associated with O_3 at shorter lag periods; cardiovascular health outcomes such as changes in cardiac autonomic control were associated with O_3 measured on the same day (CD, section 7.2.7.1). In addition, Peters et al. (2001) reported a positive but not statistically significant association between myocardial infarction onset and O_3 with very short lag times of 1- to 4 hr (CD, p. 7-64).

In focusing on an effect estimate reported for any individual lag period, the CD observes that it is important to consider the pattern of results across the series of lag periods. If there is an apparent pattern of results across the different lags, then selecting the single-day lag with the largest effect from a series of positive associations is likely to underestimate the overall effect size, since single-day lag effect estimates do not fully capture the risk that may be distributed over adjacent or other days (CD, p. 7-13). However, if the reported effect estimates vary substantially across lag periods, any result for a single day may well be biased (CD, p. 7-14). If the effect of O_3 on health outcomes persists over several days, distributed lag model results can provide more accurate effect estimates for quantitative assessment than an effect estimate for a single lag period (CD, p. 7-12). Conversely, if the underlying O_3-health relationship is truly an acute effect, then a distributed lag model would likely result in a reduced effect estimate size that may underestimate the effect (CD, p. 7-12).

On this basis, the CD focuses on effect estimates from models using 0- or 1-day lag periods, with some consideration of multi-day lag effects (CD, p. 7-14). For quantitative assessments, we conclude that it is appropriate to use results from lag period analyses consistent with those reported in the CD, focusing on single day lag periods of 0-1 days for associations with mortality or respiratory hospitalization, depending on availability of results (CD, p. 7-14). When available, distributed lag model results also have been used in the quantitative risk assessment. However, for those few studies that show inconsistent patterns, the use of single-day lag results is not appropriate for inclusion in the quantitative assessment.

3.4.5 Concentration-Response Relationships and Potential Thresholds

It has been recognized that it is reasonable to expect that there likely are biological thresholds for different health effects in individuals or groups of individuals with similar innate characteristics and health status. For O_3 exposure, individual thresholds would presumably vary substantially from person to person due to individual differences in genetic susceptibility, pre-existing disease conditions and possibly individual risk factors such as diet or exercise levels (and could even vary from one time to another for a given person). Thus, it would be difficult to detect a distinct threshold at the population level, below which no individual would experience a given effect, especially if some members of a population are unusually sensitive even down to very low concentrations (U.S. EPA, 2004, p. 9-43, 9-44).

Some studies have tested associations between O_3 and health outcomes after removal of days with higher O_3 levels from the data set; such analyses do not necessarily indicate the presence or absence of a threshold, but provide some information on whether the relationship is found using only lower-concentration data. For example, using data from 95 U.S. cities, Bell et al. (2004) found that the effect estimate for an association between short-term O_3 exposure and mortality was little changed when days exceeding 60 ppb (24-hr average) were excluded in the analysis (CD, p. 8-43). Using data from 8 U.S. cities, Mortimer and colleagues (2002) also reported that associations between O_3 and both lung function and respiratory symptoms remained statistically significant and of the same or greater magnitude in effect size when concentrations greater than 80 ppb (8-hr avg) were excluded (CD, p. 7-46). Several single-city studies are also summarized in section 7.6.5 of the CD that report similar findings of associations that remain or are increased in magnitude and statistical significance when data at the upper end of the concentration range are removed.

Other time-series epidemiological studies have used statistical modeling approaches to evaluate whether thresholds exist in associations between short-term O_3 exposure and mortality. As discussed in section 7.6.5 of the CD, one European multi-city study included evaluation of the shape of the concentration-response curve, and observed no deviation from a linear function across the range of O_3 measurements from the study (Gryparis et al., 2004; CD p. 7-154). Several single-city studies also observed a monotonic increase in associations between O_3 and morbidity that suggest that no population threshold exists (CD, p. 7-159).

On the other hand, a study in Korea used several different modeling approaches and reported that a threshold model provided the best fit for the data. The results suggested a potential threshold level of about 45 ppb (1-hr maximum concentration; < 35 ppb, 8-hr avg) for an association between mortality and short-term O_3 exposure during the summer months (Kim et al., 2004; CD, p. 8-43). The authors reported larger effect estimates for the association for data above the potential threshold level, suggesting that an O_3-mortality association might be underestimated in the non-threshold model. A threshold analysis recently reported by Bell et al. (2006) for 98 U.S. communities, including the same 95 communities in Bell et al. (2004), indicated that if a population threshold existed for mortality, it would likely fall below a 24-h average O_3 concentration of 15 ppb (< 25 ppb, 8-hr avg). In addition, Burnett and colleagues (1997) plotted the relationships between air pollutant concentrations and both respiratory and cardiovascular hospitalization, and it appears in these results that the associations with O_3 are found in the concentration range above about 30 ppb (1-hr maximum; < 25 ppb, 8-hr avg).

Vedal and colleagues (2003) reported a significant association between O_3 and mortality in British Columbia where O_3 concentrations were quite low (mean concentration of 27.3 ppb). The authors did not specifically test for threshold levels, but the fact that the association was found in an area with such low O_3 concentrations suggests that any potential threshold level would be quite low in this data set.

In summary, the CD finds that, taken together, the available evidence from toxicological, clinical and epidemiological studies suggests that no clear conclusion can now be reached with regard to possible threshold levels for O_3-related effects (CD, p. 8-44). Further, recognizing that limitations in epidemiological studies make discerning thresholds in populations difficult, the evidence suggests that if a population threshold level does exist, it is likely near the lower limit of ambient O_3 concentrations in the U.S. (CD, p. 8-44). We recognize, however, the possibility that thresholds for individuals may exist in reported associations at fairly low levels within the range of air quality observed in the studies but not be detectable as population thresholds in epidemiological analyses. Based on the CD's conclusions, we judge that there is insufficient evidence to support use of potential threshold levels in quantitative risk assessments and that it is appropriate to estimate risks within the range of air quality concentrations down to estimated policy-relevant background level.

3.4.7 Health Effects of Pollutant Mixtures Containing O_3

The potential for O_3-related enhancements of PM formation, particle uptake, and exacerbation of PM-induced cardiovascular effects underscores the importance of considering contributions of O_3 interactions with other often co-occurring air pollutants to health effects due to O_3-containing pollutant mixes. Chapters 4, 5, and 6 of the CD provide a discussion of experimental studies that evaluate interactions of O_3 with other co-occurring pollutants. Some examples of important pollutant mixture effects noted there are highlighted below.

In Chapter 4, the CD noted some important interactive effects of coexposures to O_3, and NO_2 and SO_2, two other common gaseous copollutants found in ambient air mixes. A study by Rigas et al. (1997) showed that continuous exposure of healthy human adults to SO_2 or to NO_2 increased inhaled bolus O_3 absorption, while continuous exposure to O_3 alone decreased bolus absorption of O_3. This suggests enhancement of O_3 uptake by NO_2 or SO_2 coexposure in ambient air mixes. Another study by Jenkins et al. (1999) showed that asthmatics exhibited enhanced airway responsiveness to house dust mite following exposures to O_3, NO_2, and the combination of the two gases (CD, Chapter 6). Spirometric responses, however, were impaired only by O_3 and O_3+NO_2 at higher concentrations. On the other hand, animal toxicology studies (CD, Chapter 5) that evaluated exposures to O_3 in mixture with NO_2, formaldehyde, and PM demonstrated additive, synergistic or antagonistic effects, depending on the exposure regimen and the specific health endpoints evaluated.

Several studies have demonstrated the enhancement by O_3 exposure of various respiratory responses of sensitive individuals to allergens. For example, Peden et al. (1995) showed O_3-induced increased response to nasal allergen challenge among allergic asthmatic subjects, and Michelson et al. (1999) showed promotion by 0.4 ppm O_3 exposure of inflammatory cell influx in response to nasal allergen challenge in asymptomatic dust-mite sensitive asthmatics. In addition, Jörres et al. (1996) demonstrated enhancement by 0.25 ppm O_3 exposure of airway responsiveness in mildly allergic asthmatics that was increased in response to an individual's historical allergen (grass and birch pollen, house dust mite, animal dander). These results were further extended by Holz et al. (2002) who showed that repeated daily exposure to 0.125 ppm O_3 for 4 days exacerbated lung function decrements (e.g., decreased FEV_1) in response to bronchial allergen challenges among subjects with preexisting allergic airway disease, with or without asthma (see Chapter 6 of the CD). This suggests that O_3 exposure can place allergic people who do not have asthma, as well as people who do have asthma, at increased risk for allergic respiratory effects. Consistent with and supporting the above findings are animal toxicology studies reviewed in detail by Harkema and Wagner (2005), which indicate that (a) O_3-induced epithelial and inflammatory responses in laboratory rodents are markedly enhanced by coexposure to inhaled biogenic substances (e.g., bacterial endotoxin or ovalbumin, an experimental aeroallergen) and (b) adverse airway effects of biogenic substances can be exacerbated by coexposure to O_3.

Also of much note is a newly emerging literature which indicates that O_3 can modify the biological potency of certain types of ambient PM, as shown by experimental tests. For example, as described in the CD, Section 5.4.2, the reaction of diesel PM with 0.1 ppm O_3 for 48 hr increased the potency (compared to non-exposed or air-exposed diesel PM) to induce neutrophil inflex, total protein, and LDH in lung lavage fluid in response to intratracheal PM instillation in rats (Madden et al., 2000). However, the potency of carbon black particles was not enhanced by exposure to O_3, suggesting that O_3 reaction with organic components of the diesel PM were responsible for the observed increased diesel PM effects.

Potential interaction of O_3 with fine PM in aged rats was examined by Kleinman et al. (2000). In this study the effects of fine PM containing two common toxic constituents, ammonium bisulfate (ABS, 0.3 µm 70 µg/m^3) and elemental carbon (C, 0.3 µm 50 µg/m^3) and a mixture (ABS + C) with 0.2 ppm O_3 was evaluated on aged rat lung structure and macrophage function. Exposures of O_3, elemental carbon or ABS alone did not cause significant lung injury, lung tissue collagen content or respiratory burst activity. On the other hand, mixtures (ABS + C + O_3) caused significant lung injury as assessed by increased cell proliferation response in lung epithelial and interstitial cells, loss of lung tissue collagen and increase in respiratory burst and phagocytic activity.

The majority of toxicological studies discussed in the CD evaluated effects of individual pollutants or simple mixtures of the constituents of urban smog mixtures, and these toxicology studies may not fully explain epidemiologic findings that have increasingly shown ambient O_3, other gaseous pollutants, and/or PM to be associated with various health effects at relatively low concentrations. In a recent report, Sexton et al. (2004) utilized “smog chambers”, i.e., environmental irradiation chambers to generate synthetic photochemical oxidants mixtures similar to urban smog, and studied the toxicity of such mixtures on the inflammatory response of A549 cells in an in vitro exposure system. In this preliminary study, the authors found the simulated urban photochemical oxidant mixture generated with the addition of O_3 to have enhanced toxicity (as assessed by the expression of IL-8 mRNA). Additional toxicology studies using similar realistic air pollution smog mixtures in the future may provide more relevant biological understanding for the potential interactions that occur in the ambient air among various pollutants.

All of the above types of interactive effects of O_3 with other co-occurring gaseous and nongaseous viable and nonviable PM components of ambient air mixes argue for not only being concerned about direct effects of O_3 acting alone, but also the need for viewing O_3 as a surrogate indicator for air pollution mixes which may enhance risk of adverse effects due to O_3 acting in combination with other pollutants. Viewed from this perspective, those epidemiologic findings of morbidity and mortality associations, with ambient O_3 concentrations extending to concentrations below 0.08 ppm, become more understandable and plausible.

3.5 BIOLOGICAL PLAUSIBILITY AND COHERENCE OF EVIDENCE

This section summarizes material contained in section 8.4.3 and section 8.6 of the CD, which integrates epidemiological studies with mechanistic information from controlled human exposure studies and animal toxicological studies to draw conclusions regarding the coherence of evidence and biological plausibility of O_3-related health effects. For its assessment, the CD's discussion draws from epidemiological evidence on a range of relevant health endpoints (from cardiopulmonary and physiological changes to morbidity and mortality) and assessment of available toxicological and biochemical evidence on potential plausible causal relationships for the observed epidemiological associations (CD, p. 8-45).

3.5.1 Animal-to-Human Extrapolation Issues

Table 3-1 (Table 8-1, CD, p. 8-29) summarizes physiological and biochemical observations which represent the knowledge base available from toxicological studies in humans and animals that support conclusions drawn about biological alterations that cause acute O_3-induced health effects. Table 3-1 was based upon experimental data (contained in CD Chapters 5 and 6, as well as the chapter annexes), which used environmentally relevant exposure regimens. Although most of the acute O_3-induced biological alterations are transient and attenuate over time, this does not mean that injury at the cellular and tissue level does not continue. Most inflammatory markers (e.g., PMN influx) attenuate after 5 days of exposure, but markers of cell damage (e.g., LDH enzyme activity) do not attenuate and continue to increase. Also, the time-line for resolution of many of the physiological and biological parameters presented in Figure 3-2 (Figure 8-3, CD, p. 8-30) differ for healthy human subjects and those with underlying cardiopulmonary diseases. The CD further notes that alterations in acute O_3-

induced cellular and molecular changes observed in human airway epithelium evolve over time, as depicted in Figure 3-3 (Figure 8-4, CD, p. 8-31), and that the knowledge of this profile is important in assessing biological plausibility to integrate across evidence of various health endpoints.

The similarities in physiological, biochemical and pathological processes between humans and many animal species are due to the high level of genome sequence homology that exists across species (CD, p. 8-28). It is this homology that supports the use of knowledge gained on initiation, progression, and treatment regimes for disease processes across species, especially on the acute O_3-induced effects in the respiratory tracts of humans and various animal species, as depicted in CD Table 3-1 and Figures 3-2 and 3-3. The similarities observed in human and rat respiratory system effects (e.g., in spirometry, ventilatory response, host defense), attenuation, and at higher levels of cellular organization (e.g., neutrophilic inflammation, macrophage phagocytosis processes) lend support to animal-to-human extrapolation. This is particularly important in collecting information that would not be possible to gather in human exposure or epidemiological studies but may corroborate data from both types of studies.

Quantitative extrapolation requires a combination of dosimetry, end point homology, and species sensitivity. Although uncertainties continue to exist, animal-to-human extrapolation can be done for a number of health endpoints with sufficient accuracy to be useful in evaluating the potential for human health effects. For example, the amount of protein in lavage fluid shows a striking relationship when interspecies dosimetric adjustments are applied to the individual species and exposure studies. One study (Hatch et al., 1994) of inflammatory markers suggests that a 2 ppm O_3 exposure in sedentary rats approximates a 0.4 ppm exposure in exercising humans (i.e., if one considers the dosimetry, the sensitivities of rats and humans are consistent). This supports the use of some animal data collected at higher O_3 exposures to help understand molecular changes in acutely exposed humans (CD, 8-31). Also of importance are the chronic exposure studies (12 to 24 months) reporting lesions in animals caused by long-term O_3 exposures that may analogously occur in humans with long-term (months, years) exposure to relatively high levels of O_3. However, specific exposure patterns of O_3 concentrations that could produce comparable alterations in human lungs remain to be substantiated (CD, p. 8-32).

Table 3-1. Acute O_3-induced Physiological and Biochemical Changes in Human and Animals

Physiological/Biochemical Alterations	Human Exposure Studies [1,2]	Animal Toxicology Studies [3,4]
Pulmonary Function:	↓ FEV_1 ↑ Frequency of breathing (rapid, shallow) ↓ FVC (cough, breathing discomfort, throat irritation, wheezing) Mild bronchoconstriction	↑ Frequency of breathing (rapid, shallow) ↓ FVC
Airway Responsiveness:	↑ (neuronal involvement) Change in lung resistance	↑ (vagal mediation) Change in lung resistance
Inflammation:	Yes ↑ inflammatory mediators	Yes ↑ inflammatory mediators
Reactive Oxygen Species:	↑	↑
Host Defense:	↑ particle clearance ↑ permeability ↓ AM phagocytosis	↑ particle clearance ↑ permeability ↓ clearance of bacteria ↑ severity of infection ↑ mortality & morbidity
Lung Injury: Morphology:	Yes	Yes
Susceptibility:	Age, Interindividual variability Disease status Polymorphism in certain genes being recognized	Species-specific differences Genetic basis for susceptibility indicated
Cardiovascular Changes:	Impairment in arterial O_2 transfer Ventilation-perfusion mismatch (suggesting potential arterial vasoconstriction) ↑ rate pressure product[5] ↑ myocardial work[5]	Heart rate ↓ core body temperature ↑ atrial natriuretic factor Role for platelet activity factor (PAF) indicated Increased pulmonary vascular resistance

[1] Controlled chamber exposure studies in human volunteers were carried out for a duration of 1 to 6.6 h with O_3 concentration in the range of 0.08-0.40 ppm with intermittent exercise.
[2] Data on some of the biochemical parameters were obtained from in vitro studies using cells recovered from BALF.
[3] Responses were observed in animal toxicology studies with exposure for a duration of 2 to 72 h with O_3 concentration in the range of 0.1 to 2.0 ppm.
[4] Various species (mice, rat, guinea pigs and rabbit) and strains.
[5] In hypertensive subjects.

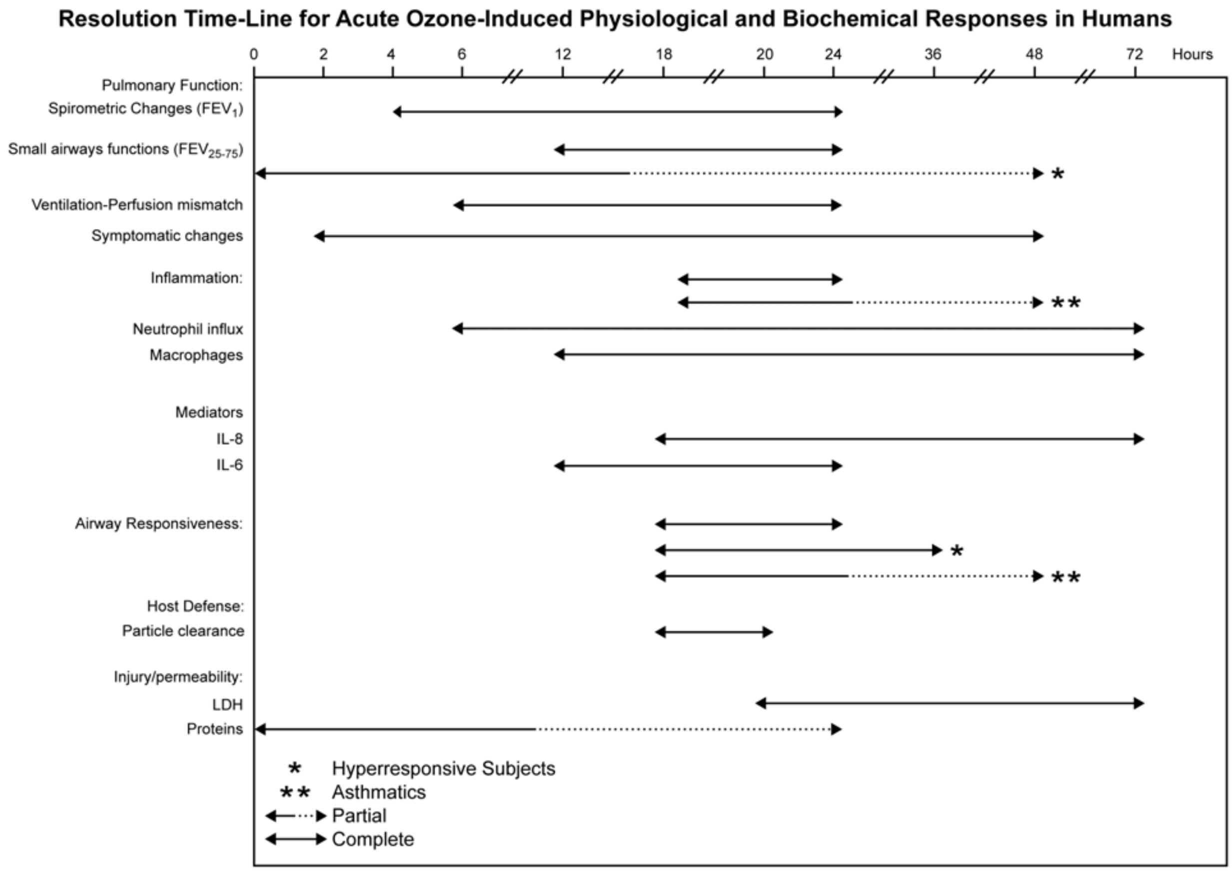


Figure 3-2. Resolution time-line for the respiratory, physiological, and biochemical parameters are derived from studies reported in the CD, Chapter 6 and Chapter 6 Annex.

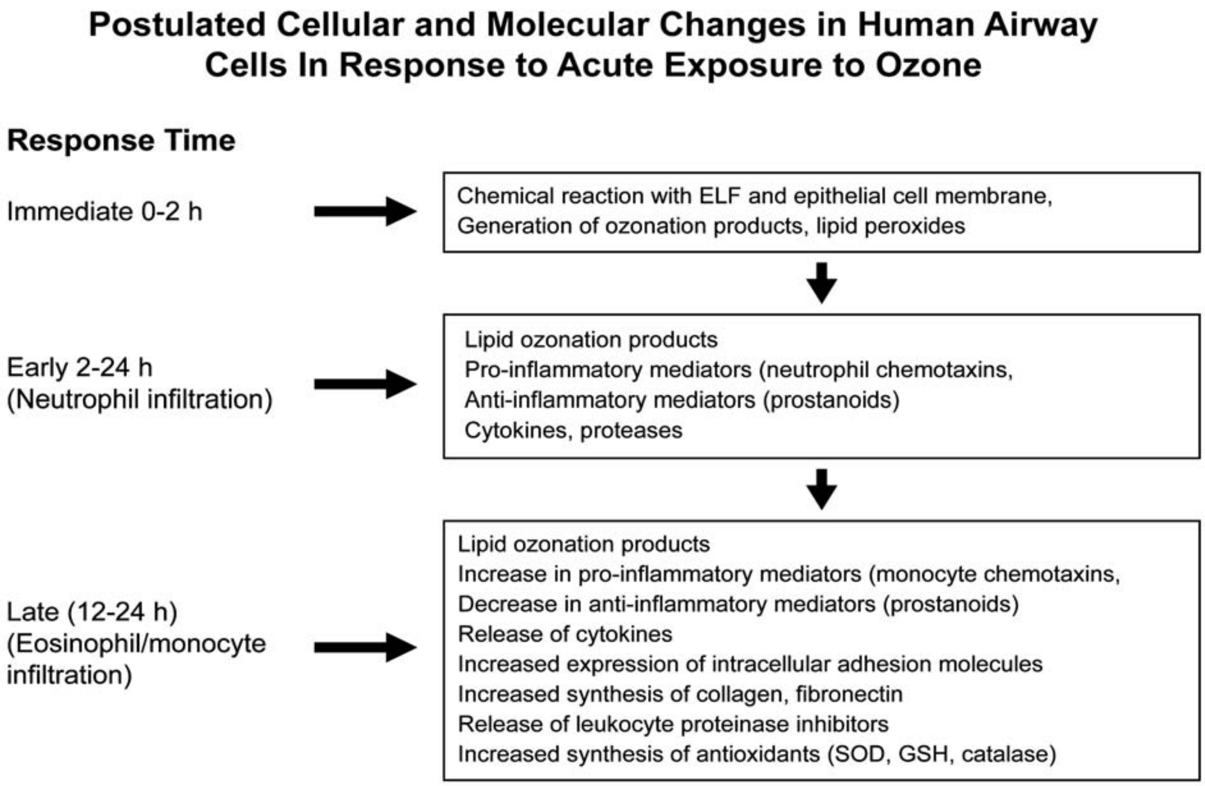


Figure 3-3. Acute (1-8 h) O_3 exposure-induced cellular and molecular changes and timelines for their resolution depicted here are derived from the data reported in Leikauf et al. (1995) and Mudway and Kelly (2000)3-4.Acute (1-8 h) O_3 exposure-induced cellular and molecular changes and timelines for their resolution depicted here are derived from the data reported in Leikauf et al. (1995) and Mudway and Kelly (2000).

3.5.2 Coherence and Plausibility of Short-term Effects on the Respiratory System

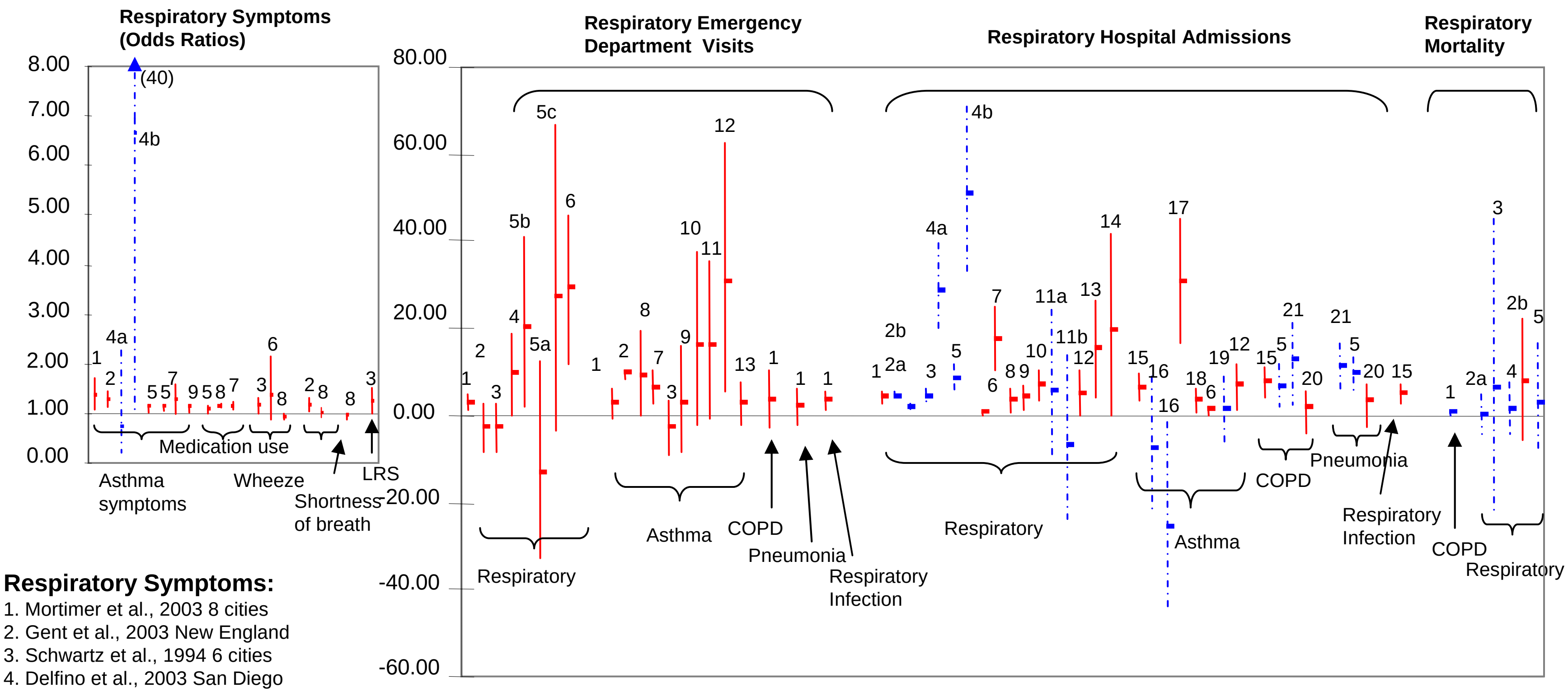
Acute respiratory morbidity effects that have been associated with short-term exposure to O_3 include such health endpoints as decrements in lung function, increased airway responsiveness, airway inflammation, epithelial injury, immune system effects, ED visits for respiratory diseases, and hospitalization due to respiratory illness

Recent epidemiological studies have supported evidence available in the previous O_3 NAAQS review on associations between ambient O_3 exposure and decline in lung function for children. Earlier observations that children and asthmatic individuals are particularly susceptible to ambient O_3 are supported by a meta-analysis (Kinney et al., 1996) of summer camp studies. The CD (p. 8-34) concludes that exposure to ambient O_3 has a significant effect on lung function, is associated with increased respiratory symptoms and medication use, particularly in asthmatics.

Short-term exposure to O_3 has also been associated with more severe morbidity endpoints, such as ED visits and hospital admissions for respiratory cases, including specific respiratory illness (e.g., asthma) (CD, sections 7.3.2 and 7.3.3). In addition, a few epidemiological studies have reported positive associations between short-term O_3 exposure and respiratory mortality, though the associations are not generally statistically significant, possibly due to a lack of statistical power for this mortality subcategory (CD, p. 7-108).

Considering the evidence from epidemiological studies, the results described above provide evidence for coherence in O_3-related effects on the respiratory system. Effect estimates from U.S. and Canadian studies are shown in Figure 3-4, where it can be seen that mostly positive associations have been reported with respiratory effects ranging from respiratory symptoms, such as cough or wheeze, to hospitalization for various respiratory diseases, and there is suggestive evidence for associations with respiratory mortality. Many of the reported associations are statistically significant.

Considering also evidence from toxicological, chamber, and field studies, the CD (section 8.6) discusses biological plausibility and coherence of evidence for acute O_3-induced respiratory health effects. Inhalation of O_3 for several hours while subjects are physically active can elicit both acute adverse pathophysiological changes and subjective respiratory tract symptoms (CD, section 8.4.2). Acute pulmonary responses observed in healthy humans exposed to O_3 at ambient concentrations include: decreased inspiratory capacity; mild bronchoconstriction; rapid, shallow breathing during exercise; subjective symptoms of tracheobronchial airway irritation, including cough and pain on deep inspiration; decreases in measures of lung function (e.g., FVC and FEV_1); and increased airway resistance (SR_{aw}). The severity of symptoms and magnitude of response depends on inhaled dose, individual O_3 sensitivity, and the degree of attenuation or



Respiratory Symptoms:
1. Mortimer et al., 2003 8 cities
2. Gent et al., 2003 New England
3. Schwartz et al., 1994 6 cities
4. Delfino et al., 2003 San Diego
(a=score>1; b=score>2)
5. Ross et al., 2002 East Moline
6. Neas et al., 1995 Uniontown
7. Delfino et al., 1998 San Diego
8. Ostro et al., 2001 S. California
9. Thurston et al., 1997 Connecticut

Emergency Department Visits:
1. Peel et al., 2005 Atlanta
2. Wilson et al., 2005 Portland NH
3. Wilson et al., 2005 Manchester NH
4. Stieb et al., 1996 St. John Canada
5. Jones et al., 1995 Baton Rouge
(a=0-17 yo; b=18-60 yo; c=>60 yo)
6. Delfino et al., 1997 Montreal
7. Tolbert et al., 2000 Atlanta
8. Jaffe et al., 2003 3 Ohio cities
9. Jaffe et al., 2003 Cleveland
10. Jaffe et al., 2003 Columbus
11. Jaffe et al., 2003 Cincinnati
12. Friedman et al., 2001 Atlanta
13. Zhu et al., 2003 Atlanta

Hospital Admissions:
1. Burnett et al., 1994 Toronto
2. Gwynn et al., 2001 New York City
(a=nonwhite; b=white)
3. Gwynn et al., 2000 Buffalo
4. Yang et al., 2003 Vancouver
(a=<3 yo; b=65+ yo)
5. Moolgavkar et al., Minneapolis/St. Paul
6. Thurston et al., 1992 New York City
7. Burnett et al., 1997 Toronto
8. Schwartz et al., 1996 Cleveland
9. Delfino et al., 1994 Montreal
10. Burnett et al., 1997 16 Canadian cities
11. Luginaah et al., 2003 Windsor
(a=males; b=females)
12. Thurston et al., 1992 Buffalo
13. Thurston et al., 1994 Toronto
14. Schwartz et al., 1996 Spokane
15. Burnett et al., 1999 Toronto
16. Lin et al., 2003 Windsor
17. Burnett et al., 2001Toronto
18. Sheppard et al., 2003 Seattle
19. Nauenberg and Basu, 1999 Los Angeles
20. Ito, 2003 Detroit
21. Schwartz et al., 1994 Detroit

Respiratory Mortality:
1. Moolgavkar, 2003 Cook County
2. Ito, 2003 Detroit
(a=1986-1990; b=1992-1994)
3. Vedal et al., 2003 Vancouver
4. Villeneuve et al., 2003 Vancouver
5. Ostro et al., 2003, Coachella Valley

Figure 3-4. Effect estimates (with 95% confidence intervals) for associations between short-term ozone exposure and respiratory health outcomes.

Effect estimates expressed as odds ratios for associations with respiratory symptoms and % increase for other outcomes, per standardized increments: 20 ppb for 24-hr O_3, 30 ppb for 8-hr O_3, and 40 ppb for 1-hr O_3, presented in order of decreasing statistical power from left to right in each category. Dotted line (blue) indicates all year analyses; solid line (red) indicates warm season results. LRS=lower respiratory symptoms; COPD=chronic obstructive pulmonary disease

enhancement of response resulting from previous O_3 exposures. Lung function studies of several animal species acutely exposed to relatively low O_3 levels (0.25 to 0.4 ppm) show responses similar to those observed in humans, including increased breathing frequency, decreased tidal volume, increased resistance, and decreased FVC. Alterations in breathing pattern return to normal within hours of exposure, and attenuation in functional responses following repeated O_3 exposures is similar to those observed in humans.

Physiological and biochemical alterations investigated in controlled human exposure and animal toxicology studies tend to support certain hypotheses of underlying pathological mechanisms which lead to the development of respiratory-related effects reported in epidemiology studies (e.g., increased hospitalization and medication use). Some of these are: (a) decrements in lung function, (b) bronchoconstriction, (c) increased airway responsiveness, (d) airway inflammation, (e) epithelial injury, (f) immune system activation, (g) host defense impairment, and sensitivity of individuals, such as age, genetic susceptibility, and the degree of attenuation present due to prior exposures. The time sequence, magnitude, and overlap of these complex events, both in terms of development and recovery (as depicted in Figures 3-2 and 3-3), illustrate the inherent difficulty of interpreting the biological plausibility of O_3-induced cardiopulmonary health effects (CD, p. 8-48).

The interaction of O_3 with airway epithelial cell membranes and epithelial lining fluid (ELF) to form lipid ozonation products and ROS is supported by numerous human, animal and in vitro studies. Ozonation products and ROS initiate a cascade of events that lead to oxidative stress, injury, inflammation, airway epithelial damage and increased epithelial damage and increased alveolar permeability to vascular fluids. Repeated respiratory inflammation can lead to a chronic inflammatory state with altered lung structure and lung function and may lead to chronic respiratory diseases such as fibrosis and emphysema (CD, section 8.6.2). Continued respiratory inflammation also can alter the ability to respond to infectious agents, allergens and toxins. Acute inflammatory responses to O_3 are well documented, and lung injury can become apparent within 3 hr after exposure in humans. Ozone-induced lung injury and subsequent disruption of the airway epithelial barrier has been implicated in increased mucociliary clearance of particles in human subjects.

Taken together, the CD concludes that the evidence from experimental human and animal toxicology studies indicates that acute O_3 exposure is causally associated with respiratory system effects, including O_3-induced pulmonary function decrements, respiratory symptoms, lung inflammation, and increased lung permeability, airway hyperresponsiveness, increased uptake of nonviable and viable particles, and consequent increased susceptibility to PM-related toxic effects and respiratory infections (CD, p. 8-48).

3.5.3 Coherence and Plausibility of Effects on the Cardiovascular System

Only a few experimental studies of animals and humans have evaluated possible mechanisms or physiological pathways by which acute O_3 exposures may induce cardiovascular system effects. Ozone induces lung injury, inflammation, and impaired mucociliary clearance, with a host of associated biochemical changes all leading to increased lung epithelial permeability. As discussed in section 3.2.1.3, the generation of lipid ozonation products and reactive oxygen species in lung tissues can influence pulmonary hemodynamics, and ultimately the cardiovascular system.

Other potential mechanisms by which O_3 exposure may be associated with cardiovascular disease outcomes have been described. Laboratory animals exposed to relatively high O_3 concentrations (≥ 0.5 ppm) demonstrate tissue edema in the heart and lungs. Ozone-induced changes in heart rate, edema of heart tissue, and increased tissue and serum levels of ANF found with 8-h 0.5 ppm O_3 exposure in animal toxicology studies (Vesely et al., 1994a,b,c) also raise the possibility of potential cardiovascular effects of acute ambient O_3 exposures

Animal toxicology studies have found both transient and persistent ventilatory responses with and without progressive decrease in heart rate (Arito et al., 1997). Observations of O_3-induced vasoconstriction in a controlled human exposure study by Brook et al. (2002) suggests another possible mechanism for O_3-related exacerbations of preexisting cardiovascular disease. One controlled human study (Gong et al., 1998) evaluated potential cardiovascular health effects of O_3 exposure. The overall results did not indicate acute cardiovascular effects of O_3 in either the hypertensive or control subjects. The authors observed an increase in rate-pressure product and heart rate, a decrement for FEV_1, and a >10 mm Hg increase in the alveolar/arterial pressure difference for O_2 following O_3 exposure. The mechanism for the decrease in arterial oxygen (O_2) tension study could be due to an O_3-induced ventilation-perfusion mismatch. Foster et al. (1993) demonstrated that even in relatively young healthy adults, O_3 exposure can cause ventilation to shift away from the well-perfused basal lung. This effect of O_3 on ventilation distribution may persist beyond 24-hr post-exposure (Foster et al., 1997). These findings suggest that O_3 may exert cardiovascular effects indirectly by impairing alveolar-arterial O_2 transfer and potentially reducing O_2 supply to the myocardium. Ozone exposure may increase myocardial work and impair pulmonary gas exchange to a degree that could perhaps be clinically important in persons with significant preexisting cardiovascular impairment.

As noted in section 3.3.1.3, a limited number of new epidemiological studies have reported associations between short-term O_3 exposure and effects on the cardiovascular system. Among these studies, three were population-based and involved relatively large cohorts. Two studies, the ARIC (Liao at al, 2004) and the NAS (Parks et al., 2005) evaluated associations between O_3 and HRV. The other study, MONICA (Ruidavets et al., 2005) evaluated the association between O_3 levels and the relative risk of MI. Such studies may offer more informative results based on their large subject-pool and design. Results from these three studies were suggestive of an association between O_3 exposure and the cardiovascular endpoints studies. In other recent studies on incidence of myocardial infarction and some more subtle cardiovascular health endpoints, such as changes in heart rate variability or cardiac arrhythmia, some but not all studies reported associations with short-term exposure to O_3 (CD, section 7.2.7.1). From these studies, the CD concludes that the "current evidence is rather limited but suggestive of a potential effect on HRV, ventricular arrhythmias, and MI incidence" (CD, p. 7-65).

An increasing number of studies have evaluated the association between O_3 exposure and cardiovascular hospital admissions. As shown in Figure 7-13 and discussed in section 7.3.4 of the CD, many reported negative or inconsistent associations, whereas other studies, especially those that examined the relationship when O_3 exposures were higher, have found positive and robust associations between O_3 and cardiovascular hospital admissions. The CD finds that the overall evidence from these studies remains inconclusive regarding the effect of O_3 on cardiovascular hospitalizations (CD, p. 7-83).

The CD notes that the suggestive positive epidemiologic findings of O_3 exposure on cardiac autonomic control, including effects on HRV, ventricular arrhythmias and MI, and reported associations between O_3 exposure and cardiovascular hospitalizations in the warm season gain credibility and scientific support from the results of experimental animal toxicology and human clinical studies, which are indicative of plausible pathways by which O_3 may exert cardiovascular effects (CD, Section 8.6.1).

3.5.4 Coherence and Plausibility of Effects Related to Long-Term O_3 Exposure

As discussed in section 8.6.2 of the CD, previous epidemiological studies have provided only inconclusive evidence for either mortality or morbidity effects of long-term O_3 exposure. The CD observes that the inconsistency in findings may be due to a lack of precise exposure information, the possibility of selection bias, and the difficulty of controlling for confounders (CD, p. 8-50). Several new longitudinal epidemiology studies have evaluated associations between long-term O_3 exposures and morbidity and mortality and suggest that these long-term exposures may be related to changes in lung function in children; however, little evidence is available to support a relationship between chronic O_3 exposure and mortality or lung cancer incidence (CD, p. 8-50).

Although human chamber studies have not evaluated effects with long-term exposures to O_3, there is some evidence available from toxicological studies. While early animal toxicology studies of long-term O_3 exposures were conducted using continuous exposures, more recent studies have focused on exposures which mimic diurnal and seasonal patterns and more realistic O_3 exposure levels (CD, p. 8-50). Studies of monkeys that compared these two exposure scenarios found increased airway pathology only with the latter design. Persistent and irreversible effects reported in chronic animal toxicology studies suggest that additional complementary human data are needed from epidemiologic studies (CD, p. 8-50).

A long-term study of infant rhesus monkeys exposed to simulated seasonal O_3 (0.5 ppm , 8 hr/day for 5 days every 14 days for 11 episodes) reported remodeling of the distal airways, abnormalities in tracheal basement membrane, accumulation of eosinophils in conducting airways, and decrements in airway innervation. Another long-term exposure study of monkeys exposed to 0.61 ppm O_3 for a year and studies of rats exposed for 20 months (0.5-1.0 ppm O_3 for 6 hr/day) reported increased deposition of collagen and thickening of the CAR, suggestive of irreversible long-term O_3 impacts on the lungs. Although some earlier seasonal exposure studies of rats reported small, but significant, decrements in lung function consistent with focal fibrogenesis in the proximal alveolar region, other chronic exposure studies with exposures of 0.5 to 1.0 ppm O_3 report epithelial hyperplasia that disappears in a few days. At this time, however, there is little evidence from human studies for long-term O_3–induced effects on lung function .

The CD (p. 8-51) concludes that evidence from animal toxicology studies strongly suggests that chronic O_3 exposure is capable of damaging the distal airways and proximal alveoli, resulting in lung tissue remodeling leading to apparent irreversible changes. Such structural changes and compromised pulmonary function caused by persistent inflammation may exacerbate the progression and development of chronic lung disease. Together with the limited evidence available from epidemiological studies, these findings offer some insight into potential biological mechanisms for suggested associations between long-term or seasonal exposures to O_3 and reduced lung function development in children which have been observed in epidemiologic studies (CD, p. 8-51).

3.5.5 Coherence and Plausibility of Mortality-Related Health Endpoints

An extensive epidemiological literature on air pollution related mortality risk estimates from the U.S., Canada, and Europe is discussed in the CD (sections 7.4 and 8.6.3). These single- and multi-city mortality studies coupled with meta-analyses generally indicate associations between acute O_3 exposure and elevated risk for all-cause mortality, even after adjustment for the influence of season and PM. Several single-city studies that specifically evaluated the relationship between O_3 exposure and cardiopulmonary mortality also reported results suggestive of a positive association (CD, p. 8-51). These mortality studies suggest a pattern of effects for causality that have biologically plausible explanations, but our knowledge regarding potential underlying mechanisms is very limited at this time and requires further research. Most of the physiological and biochemical parameters investigated in human and animal studies suggest that O_3-induced biochemical effects are relatively transient and attenuate over time. The CD (p. 8-52) hypothesizes a generic pathway of O_3-induced lung damage, potentially involving oxidative lung damage with subsequent inflammation and/or decline in lung function leading to respiratory distress in some sensitive population groups (e.g., asthmatics), or other plausible pathways noted below that may lead to O_3-related contributions to cardiovascular effects that ultimately increase risk of mortality.

The third National Health and Nutrition Examination Follow-up data analysis indicates that about 20% of the adult population has reduced FEV_1 values, suggesting impaired lung function. Most of these individuals have COPD, asthma or fibrotic lung disease (Manino et al., 2003), which are associated with persistent low-grade inflammation. Furthermore, patients with COPD are at increased risk for cardiovascular disease, and lung disease with underlying inflammation may be linked to low-grade systemic inflammation associated with atherosclerosis, independent of cigarette smoking (CD, p. 8-52). Lung function decrements in persons with cardiopulmonary disease have been associated with inflammatory markers, such as C-reactive protein (CRP) in the blood. At a population level it has been found that individuals with the lowest FEV_1 values have the highest levels of CRP, and those with the highest FEV_1 values have the lowest CRP levels (Manino et al., 2003; Sin and Man, 2003). This complex series of physiological and biochemical reactions following O_3 exposure may tilt the biological homeostasis mechanisms which could lead to adverse health effects in people with compromised cardiopulmonary systems.

Of much interest are several other types of newly available data that support reasonable hypotheses that may help to explain the findings of O_3-related increases in cardiovascular mortality observed in some epidemiological studies. These include the direct effect of O_3 on increasing PAF in lung tissue that can then enter the general circulation and possibly contribute to increased risk of blood clot formation and the consequent increased risk of MI, cerebrovascular events (stroke), or associated cardiovascular-related mortality. Ozone reactions with cholesterol in lung surfactant to form epoxides and oxysterols that are cytotoxic to lung and heart muscles and that contribute to atherosclerotic plaque formation in arterial walls represent another potential pathway. Stimulation of airway irritant receptors may lead to increases in tissue and serum levels of ANF, changes in heart rate, and edema of heart tissue. A few new field and panel studies of human adults have reported associations between ambient O_3 concentrations and changes in cardiac autonomic control (e.g., HRV, ventricular arrhythmias, and MI). These represent plausible pathways that may lead to O_3-related contributions to cardiovascular effects that ultimately increase the risk of mortality.

In addition, O_3-induced increases in lung permeability allow more ready entry for inhaled PM into the blood stream, and O_3 exposure would increase the risk of PM-related cardiovascular effects. Furthermore, increased ambient O_3 levels contribute to ultrafine PM formation in the ambient air and indoor environments. Thus, the contributions of elevated ambient O_3 concentrations to ultrafine PM formation and human exposure, along with the enhanced uptake of inhaled fine particles, consequently contribute to exacerbation of PM-induced cardiovascular effects in addition to those more directly induced by O_3 (CD, p. 8-53).

3.6 OZONE-RELATED IMPACTS ON PUBLIC HEALTH

The following discussion draws from section 8.7 of the CD to characterize factors which modify responsiveness to O_3, subpopulations potentially at risk for O_3-related health effects, and potential public health impacts associated with exposure to ambient O_3. Providing appropriate protection of public health requires that a distinction be made between those effects that are considered adverse health effects and those that are not adverse. What constitutes an adverse health effect depends not only on the type and magnitude of effect but also on the population group being affected. While some changes in healthy individuals would not be considered adverse, similar changes in susceptible individuals would be seen as adverse. In order to estimate the potential public health impact, it is important to consider both the susceptible subpopulations for O_3 exposure and the definition of adversity for O_3 health effects.

3.6.1 Factors which Modify Responsiveness to Ozone

There are numerous factors which can modify individual responsiveness to O_3. These include: influence of physical activity; age; gender and hormonal influences; racial, ethnic and socioeconomic status (SES) factors; environmental factors; and oxidant-antioxidant balance. These factors are discussed in more detail in section 6.5 of the CD.

It is well established that physical activity increases an individual's minute ventilation and will thus increase the dose of O_3 inhaled (CD, section 6.5.4). Increased physical activity results in deeper penetration of O_3 into more peripheral regions of the lungs, which are more sensitive to acute O_3 response and injury. This will result in greater lung function decrements for acute exposures of individuals during increased physical activity. Research has shown that respiratory effects are observed at lower O_3 concentrations if the level of exertion is increased and/or duration of exposure and exertion are extended. Predicted O_3-induced decrements in lung function have been shown to be a function of exposure duration and exercise level for healthy, young adults (McDonnell et al., 1997)

Most of the studies investigating the influence of age have used lung function decrements and symptoms as measures of response. For healthy adults, lung function and symptom responses to O_3 decline as age increases. The rate of decline in O_3 responsiveness appears greater in those 18 to 35 years old compared to those 35 to 55 years old, while there is very little change after age 55. In one study (Seal et al., 1996) analyzing a large data set, a 5.4% decrement in FEV_1 was estimated for 20 year old individuals exposed to 0.12 ppm O_3, whereas similar exposure of 35 year old individuals were estimated to have a 2.6% decrement. While healthy children tend not to report respiratory symptoms when exposed to low levels of O_3, for subjects 18 to 36 years old symptom responses induced by O_3 tend to decrease with increasing age (McDonnell et al., 1999).

Limited evidence of gender differences in response to O_3 exposure has suggested that females may be predisposed to a greater susceptibility to O_3. Lower plasma and NL fluid levels of the most prevalent antioxidant, uric acid, in females relative to males may be a contributing factor (Housley et al., 1996). Consequently, reduced removal of O_3 in the upper airways may promote deeper penetration. However, most of the evidence on gender differences appears to be equivocal, with one study (Hazucha et al., 2003) suggesting that physiological responses of young healthy males and females may be comparable (CD, section 6.5.2).

A few studies have suggested that ethnic minorities might be more responsive to O_3 than Caucasian population groups (CD, section 6.5.3). This may be more the result of a lack of adequate health care and socioeconomic status than any differences in sensitivity to O_3. The limited data available, which have investigated the influence of race, ethnic or other related factors on responsiveness to O_3, prevent drawing any clear conclusions at this time.

Few human studies have examined the potential influence of environmental factors such as the sensitivity of individuals who voluntarily smoke tobacco (i.e., smokers) and the effect of high temperatures. New controlled human exposure studies have confirmed that smokers are less responsive to O_3 than nonsmokers; however, time course of development and recovery of these effects, as well as reproducibility, was not different from nonsmokers (CD, section 6.5.5). Influence of ambient temperature on pulmonary effects induced by O_3 has been studied very little, but additive effects of heat and O_3 exposure have been reported.

Antioxidants, which scavenge free radicals and limit lipid peroxidation in the ELF, are the first line of defense against oxidative stress. Ozone exposure leads to absorption of O_3 in the ELF with subsequent depletion of ELF antioxidant level in the nasal ELF, but concentration and antioxidant enzyme activity in ELF or plasma don't appear related to O_3 responsiveness (CD, section 6.5.6). Controlled studies of the protective effects of dietary antioxidant supplements have shown some protective effects of lung function but not of subjective symptoms or inflammatory response. Dietary antioxidant supplements have provided some protection to asthmatics by attenuating post-exposure airway hyperresponsiveness. Animal studies have also supported the protective effects of ELF antioxidants.

3.6.2 Susceptible Population Groups

Several characteristics that may increase the extent to which a population group shows sensitivity to O_3 have been discussed in the CD, in the sections on clinical studies in Chapter 6, epidemiological studies in Chapter 7, and in the integrated assessment in Chapter 8; this section will draw on all of these. The characteristics that likely increase susceptibility to O_3 are based on: (1) activity patterns; (2) lung disease; (3) age; and (4) biological responsiveness to O_3. Other groups that might have enhanced sensitivity to O_3, but for which there is currently very little evidence, include: people with heart disease; groups based on race, gender and socioeconomic status; and those with nutritional deficiencies.

3.6.2.1 Active People

A large group of individuals at risk from O_3 exposure consists of outdoor workers and children, adolescents, and adults who engage in outdoor activities involving exertion or exercise during summer daylight hours when ambient O_3 concentrations tend to be higher. This conclusion is based on a large number of controlled-exposure human studies which have been conducted with healthy children and adults and those with preexisting respiratory diseases (CD, sections 6.2 and 6.3). These studies show a clear O_3 exposure-response relationship with increasing spirometric and symptomatic response as exercise level increases. Furthermore, O_3-induced response increases as time of exposure increases. Studies of outdoor workers and others who participate in outdoor activities indicate that extended exposures to O_3 at elevated exertion levels can produce marked effects on lung function.

The effects of O_3 on the respiratory health of outdoor workers and others who participate in outdoor activities have been investigated in several recent epidemiologic studies. These individuals may experience increased vulnerability for O_3 health effects, because they are typically exposed to high doses of O_3 as they spend long hours outdoors often at elevated exertion levels. In a group of berry pickers in Fraser Valley, Canada, large decrements in lung function (~5% decrease in FEV_1 per 40 ppb increase in 1-hr max O_3) were associated with acute exposure to O_3 (Brauer et al., 1996). The mean ambient 1-hr max O_3 was 40.3 ppb (SD 15.2) over the study period of June to August 1993. The berry pickers worked outdoors for an average of 11 hr at elevated heart rates (on average, 36% higher than resting levels). These results indicate that extended exposures to O_3 at elevated exertion levels can produce marked effects on lung function among outdoor workers.

Höppe et al. (1995) examined forestry workers for O_3-related changes in pulmonary function in Munich, Germany. Ventilation rates, estimated from their average activity levels, were elevated. When comparisons were made between high O_3 days (mean ½-hr max O_3 of 64 ppb) and low O_3 days (mean ½-hr max O_3 of 32 ppb), 59% of the forestry workers experienced a notable decrement in lung function (i.e., at least a 20% increase in specific airway resistance or at least a 10% decrease in FEV_1, FVC, or PEF) on high O_3 days. None experienced improved lung function. This study also examined athletes following a 2-hr outdoor training period in the afternoon yielding a ventilation rate double the estimate for the forestry workers. Though a significant association between ambient O_3 levels and decrements in FEV_1 was observed overall, a smaller percentage of the athletes (14%) experienced a notable decrement in lung function on high O_3 days compared to the forestry workers; and 19% of the athletes actually showed an improvement.

A large field study by Korrick et al. (1998) examined the effects of multi-hour O_3 exposures (on average, 8 hr) on adults hiking outdoors on Mount Washington, in NH. The mean of the hourly O_3 concentrations during the hike was 40 ppb (range 21-74). After the hike, all subjects combined experienced a relatively small mean decline in FEV_1 (1.5% decrease per 30 ppb increase in mean hourly O_3 concentrations) during the hike. Ozone-related changes in lung function parameters were estimated. Stratifying the data by hiking duration indicated that individuals who hiked 8 to 12 hr experienced a >2-fold decline in FEV_1 versus those only hiking 2 to 8 hr.

Results from the above field studies are consistent with those from earlier summer camp studies (Avol et al., 1990; Higgins et al., 1990; Raizenne et al., 1987, 1989; Spektor et al., 1988, 1991), which also observed strong associations between acute O_3 exposure and decrements in lung function among children who spent long hours outdoors. In a recent analysis by the Southern California Children's Health Study, a total of 3,535 initially nonasthmatic children (ages 9 to 16 years at enrollment) were followed for up to 5 years to identify new-onset asthma cases associated with higher long-term ambient O_3 concentrations (McConnell et al., 2002). Communities were stratified by pollution levels, with six high-O O_3 communities (mean 1-hr max O_3 of 75.4 ppb [SD 6.8] over four years) and six low-O_3 communities (mean 50.1 ppb [SD 11.0]). In the combined analysis using all children, asthma risk was not found to be higher for residents of the six high-O_3 communities versus those from the six low-O_3 communities. However, within the high-O_3 communities, asthma risk was more than 3 times greater for children who played three or more sports versus those who played no sports, an association not observed in the low-O_3 communities. Therefore, among children repeatedly exposed to higher O_3 levels, increased exertion outdoors (and resulting increased O_3 dose) was associated with excess asthma risk.

These field studies with subjects at elevated exertion levels support the extensive evidence derived from controlled human exposure studies. The majority of human chamber studies have examined the effects of O_3 exposure in subjects performing continuous or intermittent exercise for variable periods of time. Significant O_3-induced respiratory responses have been observed in clinical studies of exercising individuals. The epidemiologic studies discussed above also indicate that prolonged exposure periods, combined with elevated levels of exertion or exercise, may magnify O_3 effects on lung function. Thus, outdoor workers and others who participate in higher exertion activities outdoors during the time of day when high peak O_3 concentrations occur appear to be particularly vulnerable to O_3 effects on respiratory health. Although these studies show a wide variability of response and sensitivity among subjects and the factors contributing to this variability continue to be incompletely understood, the effect of increased exertion is consistent.

3.6.2.2 People with Lung Disease

People with preexisting pulmonary disease are likely to be among those at increased risk from O_3 exposure. Altered physiological, morphological and biochemical states typical of respiratory diseases like asthma, COPD and chronic bronchitis may render people sensitive to additional oxidative burden induced by O_3 exposure. The new results from controlled exposure and epidemiologic studies continue to indicate that asthmatics are a sensitive subpopulation for O_3 health effects.

A number of epidemiological studies have been conducted using asthmatic study populations. The majority of epidemiological panel studies that evaluated respiratory symptoms and medication use related to O_3 exposures focused on children. These studies suggest that O_3 exposure may be associated with increased respiratory symptoms and medication use in children with asthma. Other reported effects include respiratory symptoms, lung function decrements, and ED visits, as discussed in the CD (section 7.6.7.1). Strong evidence from a large multi-city study (Mortimer et al., 2002), along with support from several single-city studies suggest that O_3 exposure may be associated with increased respiratory symptoms and medication use in children with asthma. With regard to ambient O_3 levels and increased hospital admissions and ED visits for asthma and other respiratory causes, strong and consistent evidence establishes a correlation between O_3 exposure and increased exacerbations of preexisting respiratory disease for 1-hr maximum O_3 concentrations <0.12 ppm. Several hospital admission and ED visit studies in the U.S. (Peel et al., 2005), Canada (Burnett et al., 1997a; Anderson et al., 1997), and Europe (Anderson et al., 1997) have reported positive associations between increase in O_3 and increased risk of ED visits and hospital admissions, especially during the warm season.

Several clinical studies reviewed in the 1996 CD on atopic and asthmatic subjects had suggested but not clearly demonstrated enhanced responsiveness to acute O_3 exposure compared to healthy subjects. The majority of the newer studies reviewed in Chapter 6 of the CD indicate that asthmatics are as sensitive as, if not more sensitive than, normal subjects in manifesting induced pulmonary function decrements.

Ozone-induced increases in neutrophils, protein, and IL-8 were found to be significantly higher in the BAL fluid from asthmatics compared to healthy subjects, suggesting mechanisms for the increased sensitivity of asthmatics. Similarly, subjects with allergic asthma exhibited increased airway responsiveness to inhaled allergens upon acute O_3 exposure. Asthmatics present a differential response profile for cellular, molecular, and biochemical parameters (CD, Figure 8-1) that are altered in response to acute O_3 exposure. Increases in O_3-induced nonspecific airway responsiveness incidence and duration could have important clinical implications for asthmatics.

Bronchial constriction following provocation with allergens presents a two-phase response. The early response is mediated by release of histamine and leukotrienes that leads to contraction of smooth muscle cells in the bronchi, narrowing the lumen and decreasing the airflow. In asthmatics, these mediators also cause accumulation of eosinophils, followed by production of mucus and a late-phase bronchial constriction and reduced airflow. Holz et al. (2002) reported an early phase response in subjects with rhinitis after a consecutive 4-day exposure to 0.125 ppm O_3 that resulted in a clinically relevant (>20%) decrease in FEV_1. Allergen challenge in mild asthmatics 24 hr postexposure to 0.27 ppm O_3 for 2 hr resulted in significantly increased eosinophil counts in BALF compared to healthy subjects (Vagaggini et al., 2002). Epithelial cells from mucosal biopsies of allergic asthmatics indicated significant increases in the expression of IL-5, IL-8 and GM-CSF, suggesting increased neutrophilic inflammation compared to healthy subjects (Bosson et al., 2003).

Several human exposure studies have shown differences between asthmatics and healthy human subjects with regard to PMN influx in BAL fluid. In vitro studies (Schierhorn et al., 1999) of nasal mucosal biopsies from atopic and nonatopic subjects exposed to 0.1 ppm O_3 found significant differences in release of IL-4, IL-6, IL-8, and *TNF*-α. Another study by Schierhorn et al. (2002) found significant differences in the O_3-induced release of the neuropeptides neurokinin A and substance P for allergic patients in comparison to nonallergic controls, suggesting increased activation of sensory nerves by O_3 in the allergic tissues. Another study by Bayram et al. (2002) using in vitro culture of bronchial epithelial cells recovered from atopic and nonatopic asthmatics also found significant increases in epithelial permeability in response to O_3 exposure. In addition, some controlled human O_3 exposure studies in asthmatics (Hiltermann et al., 1999; Scannell et al., 1996) reported increased secretion of IL-8, suggesting increased neutrophilic inflammation. Two studies (Jörres et al., 1996; Holz et al., 2002) observed increased airway responsiveness to repeated daily O_3 exposure to bronchial allergen challenge in subjects with preexisting allergic airway disease.

Newly available reports from controlled human exposure studies (see Chapter 6 in the CD) utilized subjects with preexisting cardiopulmonary diseases such as COPD, asthma, allergic rhinitis, and hypertension. The data generated from these studies that evaluated pulmonary function changes in spirometry did not find clear differences between filtered air and O_3 exposure in COPD and asthmatic subjects. However, the new data on airway responsiveness, inflammation, and various molecular markers of inflammation and bronchoconstriction indicate that people with atopic asthma and allergic rhinitis comprise susceptible groups for O_3-induced adverse health effects.

Although controlled human exposure studies have not found evidence of larger spirometric changes in people with COPD relative to healthy subjects, this may be due to the fact that most people with COPD are older adults who would not be expected to have such changes based on their age. However, in Section 8.7.1, the CD notes that new epidemiological evidence indicates that people with COPD may be more likely to experience other effects, including emergency room visits, hospital admissions, or premature mortality. For example, results from an analysis of five European cities indicated strong and consistent O_3 effects on unscheduled respiratory hospital admissions, including COPD (Anderson et al., 1997). Also, an analysis of a 9-year data set for the whole population of the Netherlands provided risk estimates for more specific causes of mortality, including COPD (Hoek et al., 2000, 2001; reanalysis Hoek, 2003); a positive, but nonsignificant, excess risk of COPD-related mortality was found to be associated with short-term O_3 concentrations. Moreover, as indicated by Gong et al. (1998), the effects of O_3 exposure on alveolar-arterial oxygen gradients may be more pronounced in patients with preexisting obstructive lung diseases. Relative to healthy elderly subjects, COPD patients have reduced gas exchange and low SaO_2. Any inflammatory or edematous responses due to O_3 delivered to the well-ventilated regions of the COPD lung could further inhibit gas exchange and reduce oxygen saturation. In addition, O_3-induced vasoconstriction could also acutely induce pulmonary hypertension. Inducing pulmonary vasoconstriction and hypertension in these patients would perhaps worsen their condition, especially if their right ventricular function was already compromised (CD, Section 6.10).

3.6.2.3 Children and Older Adults

Supporting evidence exists for heterogeneity in the effects of O_3 by age. As discussed in section 6.5.1 of the CD, children, adolescents, and young adults (<18 yrs of age) appear, on average, to have nearly equivalent spirometric responses to O_3, but have greater responses than middle-aged and older adults when exposed to comparable O_3 doses. Symptomatic responses to O_3 exposure, however, do not appear to occur in healthy children, but are observed in asthmatic children, particularly those who use maintenance medications. For adults (>17 yrs of age) symptoms gradually decrease with increasing age. In contrast to young adults, the diminished symptomatic responses in children and symptomatic and spirometric responses in the elderly may put them at an increased risk for continued exposure.

As described in the section 7.6.7.2 of the CD, many epidemiological field studies focused on the effect of O_3 on the respiratory health of school children. In general, children experienced decrements in pulmonary function parameters, including PEF, FEV_1, and FVC. Increases in respiratory symptoms and asthma medication use were also observed in asthmatic children. In one German study, children with and without asthma were found to be particularly susceptible to O_3 effects on lung function. Approximately 20% of the children, both with and without asthma, experienced a greater than 10% change in FEV_1, compared to only 5% of the elderly population and athletes (Höppe et al., 2003).

The American Academy of Pediatrics (2004) notes that children and infants are among the population groups most susceptible to many air pollutants, including O_3. This is in part because their lungs are still developing. For example, eighty percent of alveoli are formed after birth, and changes in lung development continue through adolescence (Dietert et al., 2000). Children are also likely to spend more time outdoors than adults do, which results in increased exposure to air pollutants (Wiley et al., 1991a,b). Moreover, children have high minute ventilation rates and high levels of physical activity which also increases their dose (Plunkett et al., 1992).

Several mortality studies have investigated age-related differences in O_3 effects. Among the studies that observed positive associations between O_3 and mortality, a comparison of all age or younger age ($\leq$65 years of age) O_3-mortality effect estimates to that of the elderly population (>65 years) indicates that, in general, the elderly population is more susceptible to O_3 effects (Borja-Aburto et al. 1997; Bremner et al., 1999; Gouveia and Fletcher 2000; O'Neill et al., 2004; Simpson et al., 1997; Sartor et al., 1995; Sunyer et al., 2002). For example, a study by Gouveia and Fletcher (2000) examined the O_3-mortality effect by age in São Paulo, Brazil. Among all ages, O_3 was associated with a 0.6% excess risk in all cause mortality per 40 ppb increase in 1-hr max O_3. In comparison, in the elderly population, the O_3-mortality risk estimate was nearly threefold greater, at 1.7%. Similarly, a Mexico City study found that O_3-mortality effect estimates were 1.3% and 2.8% per 20 ppb increase in 24-hr average O_3 concentration in all ages and the elderly, respectively (O'Neill et al., 2004).

The meta-analysis by Bell et al. (2005) found a larger effect estimate for the elderly (2.92% per 20 ppb increase in 24-hr average O_3) than for all ages (1.75%). In the large U.S. 95 communities study (Bell et al., 2004), effect estimates were slightly higher for those aged 65 to 74 years, 1.40% excess risk per 20 ppb increase in 24-hr average O_3, compared to individuals less than 65 years and 75 years or greater, 1.00% and 1.04%, respectively, using a constrained distributed 7-day lag model. Bell et al. (2004) note that despite similar effects estimates, the absolute effect of O_3 is substantially greater in the elderly population due to the higher underlying mortality rates, which lead to a larger number of extra deaths for the elderly compared to the general population. The CD concludes that the elderly population (>65 years of age) appear to be at greater risk of O_3-related mortality and hospitalizations compared to all ages or younger populations (CD, p. 7-177).

The CD notes that, collectively, there is supporting evidence of age-related differences in susceptibility to O_3 health effects. The elderly population (>65 years of age) appear to be at increased risk of O_3-related mortality and hospitalizations, and children (<18 years of age) experience other potentially adverse respiratory health outcomes with increased O_3 exposure (CD, section 7.6.7.2).

3.6.2.4 People with Increased Responsiveness to Ozone

Biochemical and molecular parameters extensively evaluated in animal toxicology and controlled human exposure experiments were used to identify specific loci on the chromosomes and, in some cases, to relate the differential expression of specific genes to biochemical and physiological differences observed among these species. Utilizing O_3-sensitive and O_3-resistant species, it has been possible to identify the involvement of AHR and inflammation processes in O_3 susceptibility. However, most of these studies were carried out using relatively high doses of O_3, making the relevance of these studies questionable in human health effects assessment. The molecular parameters identified in these studies may serve as useful biomarkers with the availability of suitable technologies and, ultimately, can likely be integrated with epidemiological studies. Interindividual differences in O_3 responsiveness have been observed across a spectrum of symptoms and lung function responses but do not yet allow identification of important underlying factors, except a significant role for age.

3.6.2.5 Other Population Groups

There is limited, new evidence supporting associations between short-term O_3 exposures and a range of effects on the cardiovascular system. Some but not all, epidemiological studies have reported associations between short-term O_3 exposures and the incidence of myocardial infarction and more subtle cardiovascular health endpoints, such as changes in heart rate variability and cardiac arrhythmia. Others have reported associations with hospitalization or ED visits for cardiovascular diseases, although the results across the studies are not consistent. Studies also report associations between short-term O_3 exposure and mortality from cardiovascular or cardiopulmonary causes. The CD concludes that current cardiac physiologic effects evidence from some field studies is rather limited but supportive of a potential effect of short-term O_3 exposure and HRV, cardiac arrhythmia, and MI incidence (CD, p. 7-65). In the CD's evaluation of studies of hospital admissions for cardiovascular disease (CD, section 7.3.4), it is concluded that evidence from this growing group of studies is generally inconclusive regarding an association with O_3 in studies conducted during the warm season (CD, p. 7-83). This body of evidence suggests that people with heart disease may be at increased risk from short-term exposures to $O_{3;}$ however, more evidence is needed to conclude that people with heart disease are a susceptible population.

Other groups that might have enhanced sensitivity to O_3, but for which there is currently very little evidence, include groups based on race, gender and socioeconomic status, and those with nutritional deficiencies, as discussed above in section 3.6.1 about factors which modify responsiveness to O_3, above.

3.6.3 What Constitutes an Adverse Health Impact from Ozone Exposure?

In making judgments as to when various O_3-related effects become regarded as adverse to the health of individuals, in previous NAAQS reviews staff has relied upon the guidelines published by the American Thoracic Society (ATS) and the advice of CASAC. While recognizing that perceptions of "medical significance" and "normal activity" may differ among physicians, lung physiologists and experimental subjects, the ATS (1985) defined adverse respiratory health effects as "medically significant physiologic changes generally evidenced by one or more of the following: (1) interference with the normal activity of the affected person or persons, (2) episodic respiratory illness, (3) incapacitating illness, (4) permanent respiratory injury, and/or (5) progressive respiratory dysfunction."

During the 1997 review, it was concluded that there was evidence of causal associations from controlled human exposure studies for effects in the first of these five ATS-defined categories, evidence of statistically significant associations from epidemiological studies for effects in the second and third categories, and evidence from animal toxicology studies, which could be extrapolated to humans only with a significant degree of uncertainty, for the last two categories. For the current review, the evidence of O_3-related effects is stronger across all the categories. For ethical reasons, clear causal evidence from controlled human exposure studies still covers only effects in the first category. However, for this review there are results from epidemiological studies, upon which to base judgments about adversity, for effects in all of the categories. Statistically significant and robust associations have been reported in epidemiology studies falling into the second and third categories. These more serious effects include respiratory illness that may require medication (e.g., asthma), but not necessarily hospitalization, as well as respiratory hospital admissions. Less conclusive, but still positive associations have been reported for school absences, ED visits for respiratory causes, and cardiovascular hospital admissions. Human health effects for which associations have been suggested through evidence from epidemiological and animal toxicology studies, but have not been conclusively demonstrated still fall primarily into the last two categories. In the last review of the O_3 standard, evidence for these more serious effects came from studies of effects in laboratory animals, and could be extrapolated to humans only with a significant degree of uncertainty. Evidence from animal studies evaluated in this CD strongly suggests that O_3 is capable of damaging the distal airways and proximal alveoli, resulting in lung tissue remodeling leading to apparently irreversible changes. Recent advancements of dosimetry modeling also provide a better basis for extrapolation from animals to humans. Information from epidemiological studies provides supporting, but limited evidence of irreversible respiratory effects in humans (as described in section 6.3.3.2 below). Moreover, the CD concludes that the findings from single-city and multi-city time-series epidemiology studies and meta-analyses of these epidemiology studies support a likely causal association between short-term O_3 exposure and mortality particularly in the warm season.

While O_3 has been associated with effects that are clearly adverse, application of these guidelines, in particular to the least serious category of effects related to ambient O_3 exposures, involves judgments about which medical experts on the CASAC panel and public commenters have in the past expressed diverse views. To help frame such judgments, we have defined gradations of individual functional responses (e.g., decrements in FEV_1 and airway responsiveness) and symptomatic responses (e.g., cough, chest pain, wheeze), together with judgments as to the potential impact on individuals experiencing varying degrees of severity of these responses, that have been used in previous NAAQS reviews. These gradations and impacts are summarized in Tables 3-2 and 3-3.

For active healthy people, moderate levels of functional responses (e.g., FEV_1 decrements of $\geq$10% but < 20%, lasting up to 24 hrs) and/or moderate symptomatic responses (e.g., frequent spontaneous cough, marked discomfort on exercise or deep breath, lasting up to 24 hrs) would likely interfere with normal activity for relatively few sensitive individuals; whereas large functional responses (e.g., FEV_1 decrements $\geq$ 20%, lasting longer than 24 hrs) and/or severe symptomatic responses (e.g., persistent uncontrollable cough, severe discomfort on exercise or deep breath, lasting longer than 24 hrs) would likely interfere with normal activities for many sensitive individuals and therefore would be considered adverse under ATS guidelines. However, for people with lung disease, even moderate functional (e.g., FEV_1 decrements $\geq$ 10% but < 20%, lasting up to 24 hrs) or symptomatic responses (e.g., frequent spontaneous cough, marked discomfort on exercise or with deep breath, wheeze accompanied by shortness of breath, lasting up to 24 hrs) would likely interfere with normal activity for many individuals, and would likely result in additional and more frequent use of medication. For people with lung disease, large functional responses (e.g., FEV_1 decrements $\geq$ 20%, lasting longer than 24 hrs) and/or severe symptomatic responses (e.g., persistent uncontrollable cough, severe discomfort on exercise or deep breath, persistent wheeze accompanied by shortness of breath, lasting longer than 24 hrs) would likely interfere with normal activity for most individuals and would increase the likelihood that these individuals would seek medical treatment or go to an ED for relief.

In judging the extent to which these impacts represent effects that should be regarded as adverse to the health status of individuals, an additional factor that has been considered in previous NAAQS reviews is whether such effects are experienced repeatedly during the course of a year or only on a single occasion. While some experts would judge single occurrences of

Table 3-2. Gradation of Individual Responses to Short-Term Ozone Exposure in Healthy Persons[1]

Functional Response	**None**	**Small**	**Moderate**	**Large**
FEV_1	Within normal range (±3%)	Decrements of 3 to ≤10%	Decrements of >10 but <20%	Decrements of ≥20%
Nonspecific bronchial responsiveness[2]	Within normal range	Increases of <100%	Increases of ≤300%	Increases of >300%
Duration of response	None	<4 hrs	>4 hrs but ≤24 hrs	>24 hrs
Symptom Response	**Normal**	**Mild**	**Moderate**	**Severe**
Cough	Infrequent cough	Cough with deep breath	Frequent spontaneous cough	Persistent uncontrollable cough
Chest pain	None	Discomfort just noticeable on exercise or deep breath	Marked discomfort on exercise or deep breath	Severe discomfort on exercise or deep breath
Duration of response	None	<4 hrs	>4 hrs but ≤24 hrs	>24 hrs
Impact of Responses	**Normal**	**Normal**	**Mild**	**Moderate**
Interference with normal activity	None	None	A few sensitive individuals choose to limit activity	Many sensitive individuals choose to limit activity

[1] This table is reproduced from the 1996 O_3 AQCD (Table 9-1, page 9-24) (U.S. Environmental Protection Agency, 1996).
[2] An increase in nonspecific bronchial responsiveness of 100% is equivalent to a 50% decrease in PD_{20} or PD_{100}.

Table 3-3. Gradation of Individual Responses to Short-Term Ozone Exposure in Persons with Impaired Respiratory Systems

Functional Response	**None**	**Small**	**Moderate**	**Large**
FEV_1 change	Decrements of <3%	Decrements of 3 to ≤10%	Decrements of >10 but <20%	Decrements of ≥20%
Nonspecific bronchial responsiveness [3]	Within normal range	Increases of <100%	Increases of ≤300%	Increases of >300%
Airway resistance (SRaw)	Within normal range (±20%)	SRaw increased <100%	SRaw increased up to 200% or up to 15 cm H2O/s	SRaw increased >200% or more than 15 cm H2O/s
Duration of response	None	<4 hr	>4 hr but ≤24 hr	>24 hr
Symptom Response	**Normal**	**Mild**	**Moderate**	**Severe**
Wheeze	None	With otherwise normal breathing	With shortness of breath	Persistent with shortness of breath
Cough	Infrequent cough	Cough with deep breath	Frequent spontaneous cough	Persistent uncontrollable cough
Chest pain	None	Discomfort just noticeable on exercise or deep breath	Marked discomfort on exercise or deep breath	Severe discomfort on exercise or deep breath
Duration of response	None	< 4 hr	>4 hr but ≤24 hr	>24 hr
Impact of Responses	**Normal**	**Mild**	**Moderate**	**Severe**
Interference with normal activity	None	Few individuals choose to limit activity	Many individuals choose to limit activity	Most individuals choose to limit activity
Medical treatment	No change	Normal medication as needed	Increased frequency of medication use or additional medication	Physician or emergency room visit

[3] An increase in nonspecific bronchial responsiveness of 100% is equivalent to a 50% decrease in PD_{20} or PD_{100}.

moderate responses to be a "nuisance," especially for healthy individuals, a more general consensus view of the adversity of such moderate responses emerges as the frequency of occurrence increases. Thus it has been judged that repeated occurrences of moderate responses, even in otherwise healthy individuals, may be considered to be adverse since they could well set the stage for more serious illness (61 FR 65723). The CASAC panel in the last review expressed a consensus view that these "criteria for the determination of an adverse physiological response was reasonable" (Wolff, 1995).

In 2000, the American Thoracic Society (ATS) published an official statement on "What Constitutes an Adverse Health Effect of Air Pollution?" (ATS, 2000), which updated its earlier guidance (ATS, 1985). The revised guidance was intended to address new investigative approaches used to identify the effects of air pollution, and to reflect the concern for the impacts of air pollution on specific groups that had been expressed through the environmental justice movement.

The new guidance builds upon and expands the 1985 definition of adversity in several ways. There is an increased focus on quality of life measures as indicators of adversity. There is also a more specific consideration of population risk. Exposure to air pollution that increases the risk of an adverse effect to the entire population is adverse, even though it may not increase the risk of any individual to an unacceptable level. For example, a population of asthmatics could have a distribution of lung function such that no individual has a level associated with significant impairment. Exposure to air pollution could shift the distribution to lower levels that still do not bring any individual to a level that is associated with clinically relevant effects. However, this would be considered to be adverse because individuals within the population would have diminished reserve function, and therefore would be at increased risk if affected by another agent.

Of the various effects of O_3 exposure that have been studied, many would meet the ATS definition of adversity. Such effects include, for example, any detectible level of permanent lung function loss attributable to air pollution, including both reductions in lung growth or acceleration of the age-related decline of lung function; exacerbations of disease in individuals with chronic cardiopulmonary diseases; reversible loss of lung function in combination with the presence of symptoms; as well as more serious effects such as those requiring medical care including hospitalization and, obviously, mortality.

As discussed above, relatively small, reversible declines in lung function parameters may be of questionable significance in healthy people. However, a 5 to 15 % change in FEV_1 is considered to have clinical importance to asthma morbidity (ATS 1991; Lebowitz et al. 1987; Lippmann, 1988). The National Institutes of Health (1997) has stated that a PEF below 80% of a person's personal best indicates a need for continued medication use in asthmatics. In Mortimer et al. (2002), O_3 was associated with increased incidence of $\geq$ 10% declines in morning PEF as well as morning symptoms, suggesting that O_3 exposure may have clinically significant effects on asthmatic children.

Reflecting new investigative approaches, the ATS statement describes the potential usefulness of research into the genetic basis for disease, including responses to environmental agents that will provide insights into the mechanistic basis for susceptibility, and provide markers of risk status. Likewise biomarkers, that are indicators of exposure, effect or susceptibility, may someday be useful in defining the point at which a response should be equated with an adverse effect. Based on concern for segments of the population that may be disproportionately exposed to environmental contaminants, or have other factors that may increase susceptibility (e.g., genetic or nutritional factors), there was a call for increased research in these areas.

Overall, the new guidance does not fundamentally change the approach previously taken to define adversity, nor does it suggest a need at this time to change the structure or content of the tables describing gradation of severity and adversity of effects in Tables 3-2 or 3-3 above.

3.6.4 Estimation of Potential Numbers of People in At-Risk Susceptible Population Groups in the United States

Although O_3-related health risk estimates may appear to be numerically small, their significance from an overall public health perspective is affected by the large numbers of individuals in potential risk groups. Several subpopulations may be identified as having increased susceptibility or vulnerability to adverse health effects from O_3, including: older adults, children, individuals with preexisting pulmonary disease, and those with higher exposure levels, such as outdoor workers.

One consideration in the assessment of potential public health impacts is the size of various population groups that may be at increased risk for health effects associated with O_3-related air pollution exposure. Table 8-4 in the CD summarizes information on the prevalence of chronic respiratory conditions in the U.S. population in 2002 and 2003 (Dey and Bloom, 2005; Lethbridge-Çejku et al., 2004). Individuals with preexisting cardiopulmonary disease constitute a fairly large proportion of the population, with tens of millions of people included in each disease category. Of most concern here are those individuals with preexisting respiratory conditions, with approximately 11% of U.S. adults and 13% of children having been diagnosed with asthma and 6% of adults having COPD (chronic bronchitis and/or emphysema). Table 8-5 in the CD provides further information on the number of various specific respiratory conditions per 100 persons by age among the U.S. population during the mid-1990s. Asthma prevalence tends to be higher in children than adults.

In addition, subpopulations based on age group also comprise substantial segments of the population that may be potentially at risk for O_3-related health impacts. Based on U.S. census data from 2003, about 26% of the U.S. population are under 18 years of age and 12% are 65 years of age or older. Hence, large proportions of the U.S. population are included in age groups that are considered likely to have increased susceptibility and vulnerability for health effects from ambient O_3 exposure.

The health statistics data illustrate what is known as the "pyramid" of effects. At the top of the pyramid, there are approximately 2.5 millions deaths from all causes per year in the U.S. population, with about 100,000 deaths from chronic lower respiratory diseases (Kochanek et al., 2004). For respiratory health diseases, there are nearly 4 million hospital discharges per year (DeFrances et al., 2005), 14 million ED visits (McCaig and Burt, 2005), 112 million ambulatory care visits (Woodwell and Cherry, 2004), and an estimated 700 million restricted activity days per year due to respiratory conditions (Adams et al., 1999). Combining small risk estimates with relatively large baseline levels of health outcomes can result in quite large public health impacts. Thus, even a small percentage reduction in O_3 health impacts on cardiopulmonary diseases would reflect a large number of avoided cases.

Another key input for public health impact assessment is the range of concentration response functions for various health outcomes. Epidemiologic studies have reported associations between short-term exposure to O_3 with mortality, hospitalizations for pulmonary diseases, ED visits for asthma, reduced lung function, and incidence of respiratory symptoms. Effect estimates for morbidity responses to short-term changes in O_3 tend to be larger and more variable in magnitude than those for mortality.

In addition to attribution of risks for various health outcomes related to O_3 and other copollutants, important considerations in assessing the impact of O_3 on public health include the size of population groups at risk, as well as the concentration-response relationship and potential identification of threshold levels. Taken together, based on the above information, it can be concluded that exposure to ambient O_3 likely has a significant impact on public health in the U.S.

3.7 SUMMARY AND CONCLUSIONS FOR OZONE HEALTH EFFECTS

Based on dosimetric, experimental, and epidemiological evidence assessed in the 1996 CD, a set of findings and conclusions were drawn regarding potential health effects of O_3 exposure as of 1996. These conclusions are integrated into the Summary and Conclusions for Ozone Health Effects in the 2006 CD (section 8.8). (The revised CD will be referred to as the "2006 CD" in this section to be more easily distinguished from the "1996 CD.") Section 8.8 of the 2006 CD also has summarized the main conclusions derived from the integrated analysis of animal toxicology (2006 CD, Chapter 5), human experimental (2006 CD, Chapter 6) and epidemiological (2006 CD, Chapter 7) studies that evaluated evidence of health effects associated with short-term, prolonged, and long-term exposures to O_3 alone or in combination with other pollutants commonly found in the ambient air. This section summarizes conclusions drawn from section 8.8 of the 2006 CD with respect to the health effects associated with exposure to O_3 that are most relevant to our assessment of the adequacy of the current primary O_3 standard and the identification of options to consider concerning potential alternative standards to protect public health with an adequate margin of safety.

3.7.1 Respiratory Morbidity Effects of Short-term Exposures to Ozone

In the 1996 CD, it was concluded from assessment of controlled human exposure studies that short-term O_3 exposures to O_3 concentrations of $\geq$ 0.08 ppm for 6.6 to 8 hr under moderate exertion and $\geq$ 0.12 ppm for 1 hr under heavy exertion cause decrements in lung function in children and increased lung function and respiratory symptoms in healthy adults and asthmatic individuals exposed (2006 CD, p. 8-73). Lung inflammatory responses have been observed in healthy human adults following 6.6 hr O_3 exposures as low as 0.08 ppm (2006 CD, p. 8-75). Changes in lung function, respiratory symptoms, and lung inflammatory responses occur as a function of exposure concentration, duration, and level of exertion. Such experimentally demonstrated effects were consistent with and helped support the plausibility of epidemiological findings assessed in the 1996 CD regarding daily hospital admissions and ED visits for respiratory causes.

The 1996 CD concluded that group mean data from numerous controlled human exposure and field studies of healthy subjects (18 to 45 years of age) exposed for 1 to 3 hr indicate that, in general, statistically significant pulmonary function decrements beyond the range of normal measurement variability (e.g., 3 to 5% for FEV_1) occur

- at >0.12 ppm O_3 with very heavy exercise (competitive running).
- at >0.18 ppm O_3 with heavy exercise (easy jogging),
- at >0.30 ppm O_3 with moderate exercise (brisk walking),
- at >0.37 ppm O_3 with light exercise (slow walking), and
- at >0.50 ppm O_3 when at rest.

Small group mean changes (e.g., <5%) in FEV_1 have been observed in healthy young adults at levels as low as 0.12 ppm O_3 for 1 to 3 hr exposure periods. Also, lung function decrements have been observed in children and adolescents at concentrations of 0.12 and 0.14 ppm O_3 with heavy exercise. Some individuals within a study may experience FEV_1 decrements in excess of 15% under these conditions, even when group mean decrements are less than 5%.

For exposures of healthy, young adult subjects performing moderate exercise during longer duration exposures (6 to 8 hr), 5% group mean decrements in FEV_1 were observed at

- 0.08 ppm after O_3 5.6 hr,
- 0.10 ppm after O_3 4.6 hr, and
- 0.12 ppm after O_3 3 hr.

For these same subjects, 10% group mean FEV_1 decrements were observed at 0.12 ppm O_3 after 5.6 and 6.6 hr. As in the shorter duration studies, some individuals experience changes larger than those represented by group mean changes.

The 2006 CD (section 8.8) concludes that newer meta-analyses confirmed interindividual differences in lung function decrements reported in the 1996 CD. Age-specific differences in lung function responses were also observed. Spirometric responses (due to decrements in lung function) in healthy adults exposed to near ambient O_3 levels typically resolve to near baseline within 4-6 hr. Meta-analyses of four controlled human exposure studies (two new and two assessed in the 1996 CD) reporting the effects of prolonged (6.6 hr) exposures to 0.08 ppm O_3 during moderate exertion on lung function in young healthy adults (M=90, F=30; mean age 23 years) indicate an absolute FEV_1 decrease of 6%, whereas FEV_1 increased by 1% following fresh air exposures. Newer studies from Adams (2002, 2006), as illustrated earlier in Figure 3-1B, demonstrate notable interindividual variability for O_3 exposure concentrations of 0.04, 0.06 and 0.08 ppm. In these studies, following a continuous exposure to 0.08 ppm O_3 during intermittent, moderate exertion, the group mean FEV_1 decrement was 5%, but 17 % of subjects had FEV_1decrements of 10% or more. Following exposure to 0.06 ppm O_3, the group mean FEV_1 decrement was less than 2%, but five subjects had greater than 5% FEV_1 decrements, with only one experiencing this magnitude of effect when exposed to filtered air (2006 CD, p. 8-18). A few controlled human exposure studies (Adams, 2003; 2006; Hazucha et al., 1992) investigated a triangular exposure pattern at O_3 concentrations that had 6.6 to 8-hr averages between 0.08 and 0.12 ppm in order to more closely mimic typical ambient O_3 exposure patterns. Greater overall FEV_1 decrements were observed with triangular exposures compared to the constant or square-wave exposures. Furthermore, peak FEV_1 decrements observed during triangular exposures were greater than those observed during square-wave patterns. At a lower average O_3 concentration of 0.06 ppm, no temporal (i.e., hour by hour responses) differences were observed in FEV_1 decrements between square-wave and triangular exposure patterns. Results of these studies suggest the potential for somewhat greater effects on lung function in ambient O_3 exposure scenarios that typically involve gradually increasing daily exposure up to a peak in the late afternoon and a subsequent gradual decline (2006 CD, p. 8-19). The quantitative risk assessment, discussed below in Chapter 5, provides estimates addressing what percentage of active school age children are estimated to experience FEV_1 decrements greater than or equal to 10, 15, and 20% after 8-hr exposures to O_3 while engaged in moderate exertion.

Decrements in lung function associated with ambient O_3 levels have also been found in children attending summer camps in southern Ontario, Canada, in the northeastern U.S., and in southern California (2006 CD, p. 8-74). Meta-analyses indicate that a 0.50-mL decrease in FEV_1 is associated with a 1 ppb increase in O_3 concentration. For preadolescent children exposed to 120 ppb (0.12 ppm) ambient O_3, this amounts to an average decrement of 2.4 to 3.0% in FEV_1. Similar responses are reported for exercising children and adolescents exposed to O_3 in ambient air or O_3 in purified air for 1-2 hours.

The 1996 CD concluded that an increase in the incidence of cough has been reported at O_3 concentrations as low as 0.12 ppm in healthy adults during 1 to 3 hr of exposure with very heavy exercise. Other respiratory symptoms, such as pain on deep inspiration, shortness of breath, and lower respiratory scores (i.e., a combination of several symptoms), have been observed at 0.16 ppm to 0.18 ppm O_3, 1-hr average, with heavy and very heavy exertion. Respiratory symptoms also have been observed following exposure to 0.08, 0.10 and 0.12 ppm O_3 for 6.6 hr with moderate exertion levels. Also, increases in nonspecific airway responsiveness in healthy adults at rest have been observed after 1 to 3 hr of exposures to 0.40 ppm but not to 0.20 ppm O_3; during very heavy exertion, these increases were observed at concentrations as low as 0.18 ppm but not at 0.12 ppm O_3. Increases in nonspecific airway responsiveness during the 6.6 hr exposures with moderate levels of exertion have been observed at 0.08, 0.10 and 0.12 ppm O_3.

The majority of asthma panel studies evaluated the associations of ambient O_3 with lung function and respiratory symptoms in asthmatic children. Results obtained from these studies show some inconsistencies, with some indicating significant positive associations and other smaller studies not finding such effects. Overall, however, the multicity study by Mortimer et al. (2002) and several credible single-city studies (e.g., Gent et al., 2003) indicate a fairly robust association between ambient O_3 concentrations and increased respiratory symptoms in moderate to severe asthmatic children (2006 CD, p. 8-35).

The 2006 CD (p. 8-75) concludes that lung inflammatory responses have been observed in healthy human adults following 6.6 hr O_3 exposures as low as 0.08 ppm. These responses have been found even in the absence of O_3-induced lung function decrements for some individuals. Attenuation of most inflammatory markers occurs with repeated exposures over several days, but none of the several markers of lung injury and permeability show attenuation, which is indicative of continued lung tissue damage during repeated exposure. Laboratory animal studies have reported that 1 to 3 hr O_3 exposures as low as 0.1 to 0.5 ppm can cause (1) lung inflammatory responses (e.g., increased ROS and inflammatory cytokines, influx of PMNs, and activation of AMs); (2) damage to epithelial airway tissues, (3) increases in permeability of both lung endothelium and epithelium, and (4) increases in susceptibility to infectious diseases due to modulation of lung host defenses. Consistent with the above results of human and animal experimental studies, there is limited epidemiologic evidence of an association between acute ambient O_3 exposure (1-hr max of about 0.1 ppm) and airway inflammation in children, all of which taken together is indicative of a causal role for O_3 in inflammatory responses in the airways (2006 CD, p. 8-76). See Table 3.4 for a summary of short-term health effects of O_3 based on clinical studies assessed in both the 1996 CD and 2006 CD.

The 1996 CD concluded that increased O_3 levels are associated with increased hospital admissions and ED visits for respiratory causes. Analyses from data in the northeastern U.S. suggested that O_3 air pollution is associated with a substantial portion of all summertime respiratory hospital visits and admissions. The 2006 CD concludes (CD, p. 8-36) that a large multi-city and several single-city studies have indicated a positive association between increased O_3 levels (especially during the warm season) and increased risk for hospital admissions.

Table 3-4. Summary of Ozone-Induced Respiratory Health Effects from Clinical Studies[2]

Health Effect	Exercise Level	Prolonged Exposure	Short-term Exposure	Lowest Ozone Effect Level
Pulmonary Function Decrements	Moderate	6.6 hr		0.08 ppm
	Moderate	4.6 hr		0.10 ppm
	Moderate	3.0 hr		0.12 ppm
	Competitive		1 hr	0.12-0.14 ppm
	Very Heavy		1-3 hr	0.16 ppm
	Heavy		1-3 hr	0.18 ppm
	Moderate		1-3 hr	0.30 ppm
	Light		1-3 hr	0.37 ppm
	At rest		1-3 hr	0.50 ppm
Increased Respiratory Symptoms	Moderate	6.6 hr		0.08 ppm
	Very Heavy		1-3 hr	0.12 ppm
Airway Responsiveness	Moderate	6.6 hr		0.08 ppm
	Very Heavy		1-3 hr	0.18 ppm
	At rest		1-3 hr	0.40 ppm
Respiratory Inflammation	Moderate	6.6 hr		0.08 ppm
	Very Heavy		1-3 hr	0.20 ppm
Changes in Host Defenses	Moderate	6.6 hr		0.08 ppm
Decreased Exercise Performance	Competitive		1 hr	0.18 ppm

[2] Information contained in this table is based on scientific data assessed in Chapters 6 and 8 of the 2006 CD.

3.7.2 Cardiovascular Morbidity Effects of Short-term Exposures to Ozone

One health endpoint that was unrecognized in the 1996 CD, but is addressed in the 2006 CD, is O_3-induced cardiovascular effects. Newly available evidence has emerged since 1996 which provides considerable plausibility for how O_3 could exert cardiovascular effects (2006 CD, p. 8-77). Examples of such O_3-induced cardiovascular effects include: (1) O_3-induced release from lung epithelial cells of PAF that may contribute to blood clot formation that would increase the risk of serious cardiovascular outcomes (e.g., heart attack, stroke, mortality); (2) interactions of O_3 with surfactant components in ELF of the lung resulting in production of oxysterols and ROS that may exhibit PAF-like activity contributing to clotting and/or exerting cytotoxic effects on lung and heart cells; (3) possible mechanisms that may involve O_3-induced secretions of vasoconstrictive substances and/or effects on neuronal reflexes that may result in increased arterial blood pressure and/or altered electrophysiologic of heart rate or rhythm; (4) associations between O_3 and various cardiac physiologic endpoints suggesting a potential relationship between O_3 exposure and altered HRV, ventricular arrhythmias, and incidence of MI; and (5) positive associations during the warm season only between ambient O_3 concentrations and cardiovascular hospitalizations. While the only controlled human exposure study that evaluated effects of O_3 exposure on the cardiovascular system found no O_3-induced differences in ECG, heart rate, or blood pressure in healthy or hypertensive subjects, the study did report an overall increase in myocardial work and impairment in pulmonary gas exchange.

Also, animal toxicological studies have reported O_3-induced decreases in heart rate, mean arterial pressure and core temperature. Overall, the 2006 CD (p. 8-77) concludes that this generally limited body of evidence is highly suggestive that O_3 directly and/or indirectly contributes to cardiovascular-related morbidity, but much remains to be done to more fully substantiate links between short-term ambient O_3 exposures and adverse cardiovascular effects.

3.7.3 Mortality-Related Effects of Short-term Exposures to Ozone

The 1996 CD concluded that an association between daily mortality and O_3 concentration for areas with high O_3 levels (e.g., Los Angeles) was suggested. However, due to a very limited number of studies available at that time, there was insufficient evidence to conclude that the observed association was likely causal. Since 1996, new data are available from large multicity studies conducted in the U.S. and several single-city studies conducted all over the world, as well as from several meta-analyses that have combined information from multiple studies. The majority of these studies suggest an elevated risk of total nonaccidental mortality associated with acute exposure to O_3, especially in the summer or warm season when O_3 levels are typically high, with somewhat larger effect estimate sizes for associations with cardiovascular mortality (2006 CD, p. 7-175). The 2006 CD finds that the results from U.S. multicity time-series studies provide the strongest evidence to-date for associations between short-term O_3 exposure and mortality. These studies, along with recent meta-analyses, showed consistent effect estimates that are unlikely to be confounded by PM, though the 2006 CD observes that future work is needed to better understand the influence of model specifications on the effect estimates (2006 CD, p. 7-175). For cardiovascular mortality, the 2006 CD reports that effect estimates are consistently positive, falling in the range of 1 to 8% increases per 40 ppb in 1-hr O_3 (2006 CD, p. 7-107). Overall, the 2006 CD concludes that the majority of these findings suggest an elevated risk of all-cause mortality associated with short-term O_3 exposure, especially in the summer or warm season when O_3 levels are typically high. Slightly greater effects were observed for cardiovascular mortality (2006 CD, p. 7-175).

3.7.4 Health Effects of Repeated Short-term Exposures to Ozone

The 1996 CD drew several conclusions regarding repeated short-term O_3 exposures (2006 CD, p. 8-15). Partial or complete attenuation is observed for some of the O_3-induced responses after more than 2 days of exposure. After 5 days of exposure, lung function changes return to control levels with the greatest changes usually occurring on the second day, but the attenuation was reversed after 7 to 10 days without O_3 exposure. Most inflammatory markers (e.g., PMN influx) attenuate after 5 days of exposure, but markers of cell damage (e.g., LDH enzyme activity) do not attenuate and continue to increase. Recovery of some inflammatory markers occurred a week to 10 days after exposure ceased, but some responses were not normal after 20 days. Animal studies suggest underlying cell damage continues throughout the attenuation process. Also, attenuation may alter normal distribution of O_3 within the lungs, allowing more O_3 to reach sensitive regions, possibly affecting lung defenses. Newer studies assessed in the 2006 CD (p. 8-74 and 8-75) supported all of these conclusions in addition to which it was concluded that repeated daily, multi-hour exposure to lower concentrations of O_3 (0.125 ppm for 4 days) causes an increased response to bronchial allergen challenge in subjects with preexisting allergic airway disease, with or without asthma. In these subjects, changes in airway responsiveness after O_3 exposure appear to be resolved more slowly than changes in FEV_1 or respiratory symptoms.

3.7.5 Confidence in Various Health Outcomes Associated with Short-term Exposures to Ozone

In characterizing the extent to which relationships between the various health outcomes discussed above and short-term exposures to ambient O_3 are likely causal, we note that several different factors have informed the judgments made in the CD and here. These factors include the nature of the evidence (i.e., controlled human exposure, epidemiological, and/or toxicological studies) and the weight of evidence, including such considerations as biological plausibility, coherence of evidence, strength of association, and consistency of evidence.

In assessing the health effects data base for O_3, it is clear that human studies provide the most directly applicable information because they are not limited by the uncertainties of dosimetry differences and species sensitivity differences, which would need to be addressed in extrapolating animal toxicology data to human health effects. Controlled human exposure studies provide data with the highest level of confidence since they provide human effects data under closely monitored conditions and can provide clear exposure-response relationships. Epidemiological data provide evidence of associations between ambient O_3 levels and more serious acute and chronic health effects (e.g., hospital admissions and mortality) that cannot be assessed in controlled human exposure studies. For these studies the degree of uncertainty regarding potential confounding variables (e.g., other pollutants, temperature) and other factors affects the level of confidence that the health effects being investigated are attributable to O_3 exposures, alone and in combination with other copollutants.

In using a weight of evidence approach to inform judgments about the degree of confidence that various health outcomes are likely caused by exposure to O_3, our increases as the number of studies and other factors, such as strength, consistency, and coherence of evidence, consistently reporting a particular health endpoint grows. For example, there is a very high level of confidence that O_3 induces lung function decrements in healthy adults and children due in part to the dozens of studies consistently showing that these effects were observed. As noted above, the 2006 CD (p. 8-74) states that studies provide clear evidence of causality for associations between short-term O_3 exposures and statistically significant declines in lung function in children, asthmatics and adults who exercise outdoors. An increase in respiratory symptoms (e.g., cough, shortness of breath) has been observed in controlled human exposure studies of short-term O_3 exposures, and significant associations between ambient O_3 exposures and a wide variety of symptoms have been reported in epidemiology studies (2006 CD, p. 8-75). Aggregate population time-series studies showing robust associations with respiratory hospital admissions and ED visits are strongly supported by human clinical, animal toxicologic, and epidemiologic evidence for lung function decrements, respiratory symptoms, airway inflammation, and airway hyperreactivity. Taken together, the 2006 CD (p. 8-77) concludes that the overall evidence supports the inference of a causal relationship between acute ambient O_3 exposures and increased respiratory morbidity outcomes resulting in increased ED visits and hospitalizations during the warm season. Recent epidemiologic evidence has been characterized in the CD (p. 8-78) as highly suggestive that O_3 directly or indirectly contributes to non-accidental and cardiopulmonary-related mortality.

As discussed above in section 3.5 and in section 8.6 of the 2006 CD, conclusions regarding biological plausibility, consistency, and coherence of evidence of O_3-related health effects are drawn from the integration of epidemiological studies with mechanistic information from controlled human exposure studies and animal toxicological studies. This type of mechanistic linkage has been firmly established for several respiratory endpoints (e.g., lung function decrements, lung inflammation) but remains far more equivocal for cardiovascular endpoints (e.g., cardiovascular-related hospital admissions). Finally, for epidemiological studies, strength of association refers to the magnitude of the association and its statistical strength, which includes assessment of both effects estimate size and precision (section 3.4.1). In general, when associations yield large relative risk estimates, it is less likely that the association could be completely accounted for by a potential confounder or some other bias. Consistency refers to the persistent finding of an association between exposure and outcome in multiple studies of adequate power in different persons, places, circumstances and times (section 3.4.3). For example, the magnitude of effect estimates is relatively consistent across recent studies showing association between short-term, but not long-term, O_3 exposure and mortality.

Figure 3-5 summarizes our judgments for the various health outcomes discussed above concerning the extent to which relationships between various health outcomes and ambient O_3 exposures are likely causal. These judgments are informed by the conclusions and discussion in the CD and in earlier sections of this chapter, reflecting the nature of the evidence and overall weight of the evidence, and are taken into consideration in our quantitative risk assessment, presented below in Chapter 5.

3.7.6 Health Effects of Long-term Exposures to Ozone

In the 1996 CD, available data, primarily from animal toxicology studies, indicated that exposure to O_3 for periods of months to years causes structural changes in several regions of the respiratory tract (2006 CD, p. 8-79). Effects may be of greatest importance in the CAR, where the alveoli and conducting airways meet. This region of the lungs is typically affected in most human airway diseases. However, data from epidemiological and clinical studies is lacking, and most information on chronic O_3 effects in the distal lungs continues to come from animal toxicology studies.

What had been previously been viewed as an apparent lack of reversibility of effects during clean air exposures has been investigated since 1996 with animal toxicology studies using exposure regimens simulating a seasonal exposure pattern. One long-term study exposed rhesus monkeys to a simulated seasonal O_3 pattern (0.5 ppm O_3 8hr/day for 5 days, every 14 days for 11 episodes) and reported: (1) remodeling in the distal airways; (2) abnormalities in tracheal basement membrane; (3) eosinophil accumulation in conducting

Figure 3-5. Qualitative Characterization of Ozone-Related Health Effect Outcomes

Characterization	Overall Confidence in Causal Relationship With Ambient Ozone
Causal	-Lung function decrements in healthy children -Lung function decrements in asthmatic children -Lung function decrements in healthy adults -Respiratory symptoms in asthmatic children -Respiratory symptoms in healthy adults -Increased lung inflammation -Aggravation of asthma (i.e., increased medication usage, increased asthma attacks)
↓	-Respiratory-related hospital admissions -Respiratory related emergency department visits -Respiratory-related doctors visits -Increased school absences -Respiratory-related mortality during the O_3 season
↓	-Cardiorespiratory-related mortality during the O_3 season -Total nonaccidental mortality during the O_3 season
Suggestive	-Cardiovascular-related hospital admissions

airways; and (4) decrements in airway innervation. These findings support and advance the earlier information suggestive of injury and repair processes which are caused by seasonal O_3 exposures (2006 CD, p.8-79). Although adverse physiological changes associated with long-term O_3 exposures reported in animal studies suggest similar changes in humans, interspecies differences in sensitivity to chronic effects of O_3 continue to be a limiting factor in extrapolation of effect responses in animals to levels at which these responses would be expected to occur in human health effects.

Epidemiological studies investigating chronic effects in humans following long-term exposures to O_3 previously provided only limited suggestive evidence. However, recent studies of lung function changes observed in children living in cities with high O_3 levels support the conclusion that long-term O_3 exposure may play a role in causing irreversible lung damage. Further investigation, however, is necessary before we are able to draw firmer conclusions about chronic health effects of O_3 in human populations.

3.7.7 Health Effects of Pollutant Mixtures Containing Ozone

In the 1996 CD, it was recognized that coexposure of humans and animals to O_3 and other pollutants, such as NO_2, SO_2, H_2SO_4, HNO_3, or CO, showed additive response for lung spirometry or respiratory symptoms (2006 CD, p. 8-82). Since 1996, most animal toxicology studies investigating O_3 in a mixture with NO_2 and H_2SO_4 have shown that effects can be additive, synergistic, or even antagonistic, depending on the exposure regimen and the endpoint studied. Ozone has served for a long time as a surrogate or indicator for the overall photochemical oxidant mix. It is well recognized that the observed effects may be due to components of that mix alone or in combination with O_3 and other gases and PM in the ambient air. Although the issue of exposure to copollutants was previously described as poorly understood, especially with regard to chronic effects, newer information from human and animal studies of binary mixtures containing O_3 suggest potential interactions depending on the exposure regimen and pollutant mix (CD, p. 8-82). Examples of this newer information include: (1) continuous exposure to SO_2 and NO_2 increased inhaled O_3 bolus absorption, while continuous exposure to O_3 decreased O_3 bolus absorption; (2) asthmatics exhibited enhanced airway reactivity to house dust mite allergen following exposures to O_3, NO_2 and the combination of the two gases; however, spirometric response was impaired only by O_3 and O_3+ NO_2 at higher concentrations; and (3) animal toxicology studies with O_3 in mixture with NO_2, formaldehyde, and PM demonstrated additive, synergistic, or antagonistic effects depending on the exposure regimen and the endpoints evaluated.

One controlled-exposure study of children, designed to approximate conditions of an epidemiological study by matching population and exposure atmosphere (0.1 ppm O_3, 0.1 ppm

SO_2, and 101 ug/m^2 H_2SO_4), failed to support the findings of the epidemiological study. This demonstrates the difficulty of trying to link outcomes of epidemiological studies and controlled-exposure studies with pollutant mixtures.

3.7.8 Populations at Risk/Susceptibility Factors Associated with Ozone Exposure

The 1996 CD (2006 CD, p. 8-80) identified several factors that may increase sensitivity to O_3 of population groups, including: (1) biological variation in responsiveness to O_3; (2) preexisting lung disease (e.g., asthma); (3) activity patterns (e.g., exertion levels); (4) personal exposure history (e.g., time spent indoors v. outdoors); and (5) personal factors (e.g., age, nutritional status, gender, smoking history, ethnicity). Based on the information assessed in the 1996 CD (2006 CD, p. 8-80), population groups that demonstrated increased responsiveness to ambient concentrations of O_3 consisted of exercising, healthy and asthmatic individuals, including children, adolescents, and adults. Since 1996, evidence from controlled-exposure human and animal studies, as well as from epidemiological studies, has provided further support for these and other susceptibility factors and populations at risk. For example, controlled-exposure human studies continue to show differential biological response to O_3 based on physical activity (exertion) and age. These studies demonstrate a large variation in sensitivity and responsiveness to O_3, although specific factors that contribute to this intersubject variability are yet to be identified. Associations of increased summertime hospital admissions for asthma and COPD with ambient O_3 levels suggest that individuals with these respiratory diseases are populations at risk to O_3 exposure effects. Also, based on O_3-induced differential response in lung inflammation and airway responsiveness, asthmatic adults and children appear to have potentially increased susceptibility to O_3. There is no evidence from controlled-exposure human studies which suggests that individuals with COPD are more sensitive to health effects of O_3.

There is some animal toxicology evidence which has demonstrated the importance of genetic background in O_3 susceptibility. Genetic and molecular characterization studies of experimental animals have identified genetic loci responsible for both sensitivity and resistance.

Taking all of this information into account, the CD (p. 8-80 to 8-81) concludes that all exercising (moderate to high physical exertion) healthy and asthmatic adults, adolescents, and children appear to exhibit increased responsiveness to ambient O_3 levels and continue to be considered at increased risk of O_3-induced health effects. Also, any individual with respiratory or cardiovascular disease or any healthy individual who is engaged in vigorous physical activity outdoors during periods when O_3 levels are high (e.g., active outdoor children) is potentially at increased risk to O_3-induced health effects. In addition, healthy individuals and those with cardiorespiratory impairment (e.g., those with COPD or cardiovascular disease) who are "hyperresponsive" to O_3 exposure (i.e., exhibit much higher than normal lung function decrements and/or respiratory symptoms) would be considered at greater risk to O_3 exposure. Finally, individuals who are more likely to be exposed to air pollution while engaged in physical activity (e.g., outdoor workers) and those with genetic polymorphisms for antioxidant enzymes and inflammatory genes may be at heightened risk of effects of O_3 (2006 CD, p. 8-81).

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