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Provisional Assessment of Recent Studies on Health and Ecological Effects of Ozone Exposure

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1. INTRODUCTION

In March 2008, EPA announced its final rule on the national ambient air quality standards (NAAQS) for ozone (O_3)(73 FR 16436). The scientific basis for this O_3 NAAQS was the 2006 Air Quality Criteria for Ozone and Related Photochemical Oxidants, hereafter 2006 O_3 AQCD (U.S. EPA, 2006). The 2006 O_3 AQCD included a rigorous and thorough review of the pertinent literature accepted for publication through December 2004. A limited number of papers accepted for publication in 2005 and 2006 were also included in the 2006 O_3 AQCD. These papers were identified by EPA staff, by public comments, or by the Clean Air Scientific Advisory Committee (CASAC) as adding significantly to the existing body of data on critically important topics. Typically, these studies examined effects at lower O_3 levels than previously reported or discussed epidemiologic methodological issues.

The EPA has provisionally assessed the recent literature related to health and ecological effects of O_3 to identify pertinent new studies that were not included in the 2006 O_3 AQCD. This effort should not be considered a complete literature review. This provisional assessment has been through an internal EPA peer review process; however, it has not been subjected to review by the CASAC or open to the public comment process, as was done in the development of the 2006 O_3 AQCD. The intent of this provisional assessment is to determine if studies published since the 2006 O_3 AQCD materially change the conclusions of that document. Overall, EPA's provisional assessment of recent studies, as discussed below, concludes that, taken in context, the new information and findings do not materially change any of the broad scientific conclusions regarding the health and ecological effects of ozone exposure made in the 2006 O_3 AQCD. This new evidence strengthens conclusions in the 2006 O_3 AQCD related to the potential for health effects at exposure concentrations of less than 80 ppb. The following sections highlight findings of recent studies from four scientific disciplines that are the major focus of this provisional assessment: (1) controlled human exposure studies, (2) epidemiology, (3) toxicology, and (4) ecology.

2. CONTROLLED HUMAN EXPOSURE STUDIES

In this provisional assessment, EPA has generally limited its consideration to those studies conducted at or below 80 ppb O_3; unlike studies included in the 2006 O_3 AQCD, these studies have not been subjected to rigorous review and as such this review is not intended to supplement the 2006 document.

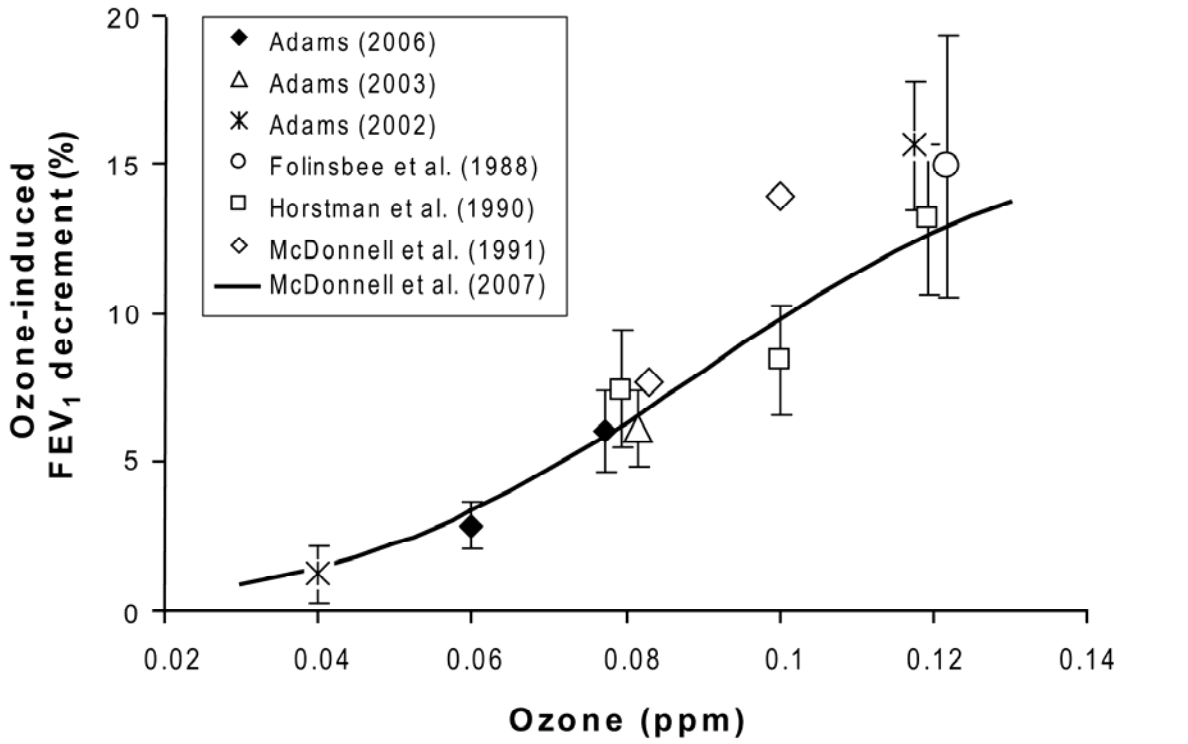
Numerous controlled human exposure studies, reviewed in the 2006 O_3 AQCD, showed that young healthy nonsmoking adults exposed to ≥ 80 ppb O_3 developed transient, reversible decrements in lung function; increased respiratory symptoms; increased nonspecific airway responsiveness; and inflammatory responses compared to filtered air as a control exposure. Two studies evaluated the effects of exposure to concentrations less than 80 ppb (i.e., 40 and 60 ppb) in healthy subjects exposed for 6.6 hours during quasi continuous exercise (Adams, 2002, 2006). Exposure to 40 ppb O_3 produced responses similar to filtered air exposure (Adams, 2002, 2006). However, a statistically significant increase in respiratory symptoms was reported following 5.6 and 6.6 hours of exposure to 60 ppb. Although not found to be statistically significant by Adams (2006), the group mean forced expiratory volume in one second (FEV_1) response during exposure to 60 ppb diverged from responses for filtered-air after 5.6 h of exposure. Some individuals had FEV_1 decrements of >10% after 6.6 h of exposure to 60 ppb. Thus, at the time the 2006 O_3 AQCD was completed, there was limited evidence of decreased pulmonary function and increased respiratory symptoms occurring with O_3 exposure below 80 ppb. Three new studies provide evidence of effects occurring in healthy young adults at O_3 concentrations below 80 ppb: Brown et al. (2008); McDonnell et al. (2007); and Schelegle et al. (2009).

McDonnell et al. (2007) provided an empirical model for predicting average FEV_1 responses as a function of O_3 concentration, exposure time, minute ventilation, and age of the exposed individual. This model was based on response data of healthy, nonsmoking, white males (n=541) between the ages of 18-35 yr from 15 studies conducted at the U.S. EPA Human Studies Facility in Chapel Hill, North Carolina. The model predicts temporal dynamics of FEV_1 change in response to any set of O_3 exposure conditions that might reasonably be experienced in the ambient environment. McDonnell et al. (2009) tested the predictive ability of this model against independent data (i.e., data that were not used to fit the model) of Adams (2000, 2002, 2003, 2006a, 2006b), Hazucha et al. (1992), and Schelegle et al. (2009). The model generally captured the dynamics of FEV_1 responses within about a one percentage point of the experimental data. Consistent with Bennett et al. (2007), an increased body mass index (BMI) was found to be associated with enhanced FEV_1 responses by

McDonnell et al. (2009). The BMI effect is of the same order of magnitude but in the opposite direction of the age effect where by FEV_1 responses diminish with increasing age. Although the effects of age and BMI are relatively strong, these characteristics account for only a small amount of the observed variability in individual responses.

Brown et al. (2008) show that the magnitude of the FEV_1 responses observed at 40 and 60 ppb by Adams (2002, 2006) were consistent with a smooth dose-response curve for exposures between 40 and 120 ppb O_3 (Figure 2-1). All studies in Figure 2-1 used the same 6.6 h exposure protocol in which volunteers alternated between 50 min of exercise (VE≈ 20 L/min/m2 body surface area) and 10 min of rest with an additional 35 min of rest after the third hour. Note that the Adams (2002, 2003, 2006) data illustrated on Figure 2-1 were not used in fitting the model developed by McDonnell et al. (2007). In the reanalysis of the Adams (2006) data, Brown et al. (2008) also showed that exposure to 60 ppb O_3 causes a biologically small but highly statistically significant ($p < 0.002$) decrease in mean FEV_1 responses of young healthy adults.

Schelegle et al. (2009) conducted a controlled human exposure study investigating the effects of 6.6 hour exposures to O_3 at mean concentrations of 60, 70, 80, and 87 ppb on respiratory symptoms and pulmonary function in 31 young healthy adults. The mean percent change in FEV_1 (±standard error) at the end of each protocol were 0.80 ± 0.90%, -2.72 ± 1.48%, -5.34 ± 1.42%, -7.02 ± 1.60%, and -11.42 ± 2.20% for exposure to filtered air, 60, 70, 80, and 87 ppb O_3, respectively. Compared to filtered air, statistically significant decrements in FEV_1 and increases in total subjective symptoms scores ($p < 0.05$) were found following exposure to mean concentrations of 70, 80 and 87 ppb O_3. Although not statistically significant, the magnitude of the mean FEV_1 responses (3.5% corrected for filtered air) at 60 ppb was about the same as reported by Adams (2006). This further supports a smooth dose-response curve without evidence of a threshold for exposures between 40 and 120 ppb O_3. Schelegle et al. (2009) also considered intersubject variability in FEV_1 responses. Sixteen percent of individuals had > 10% FEV_1 decrements at 60 ppb and this fraction increased to 18, 29, and 42% at 70, 80, and 87 ppb, respectively. Combined with the data from Adams (2006), Schelegle et al. (2009) confirm notable interindividual variability for O_3 exposure concentrations below 80 ppm.



Source: Brown et al. (2008)

Figure 2-1. Cross-study comparison of mean O_3-induced FEV_1 decrements following 6.6 h of constant, square-wave exposure to varied O_3 concentrations. The McDonnell et al. (2007) curve illustrates the predicted FEV_1 decrement at 6.6 h as a function of O_3 concentration for a 23-yr old (the average age of subjects that participated in the illustrated studies). Error bars (where available) are the standard error of responses. The data at 0.08 and 0.12 ppm have been offset for illustrative purposes.

3. EPIDEMIOLOGIC STUDIES

EPA has screened and surveyed the recent epidemiologic literature and identified a number of recent studies on the health effects associated with O_3 exposure. This process has identified slightly over 100 epidemiologic studies that encompass the majority of health outcomes addressed in the 2006 O_3 AQCD. The following sections summarize the results of EPA's provisional assessment of these epidemiologic studies for a range of health outcomes; the overall conclusions from the 2006 O_3 AQCD are presented at the beginning of each section.

3.1. Human Health Effects Associated with Short-Term Ozone Exposure

3.1.1.Mortality

The analysis of several large multicity studies, single-city studies, and additional meta-analyses of these studies in the 2006 O_3 AQCD found a "positive association between increasing ambient O_3 concentrations and excess risk for non-accidental and cardiopulmonary-related daily mortality" (U.S. EPA, 2006). The 2006 O_3 AQCD, therefore, concluded that the literature is "highly suggestive that O_3 directly or indirectly contributes to non-accidental and cardiopulmonary-related mortality," but the underlying mechanisms by which such effects occur are not entirely clear (U.S. EPA, 2006). An independent review of that literature by the National Research Council (NRC) also concluded, "short-term exposure to ambient ozone is likely to contribute to premature deaths" (NRC, 2008).

This provisional assessment identified a number of recent short-term O_3 exposure mortality studies. Overall the studies are consistent with the conclusions of the 2006 O_3 AQCD, supporting an association between O_3 and mortality (Bell et al., 2008; Burnett et al., 2004; Franklin et al., 2008; Knowlton et al., 2004; Kolb et al., 2007; Ren et al., 2008a, 2008b; Zanobetti and Schwartz, 2008a, 2008b). Some studies did not find a statistically significant association but showed elevated risk estimates (Dominici et al., 2005; Goldberg et al., 2006).

All studies that examined the association by season reported the association between O_3 exposure and mortality is strongest in the summer (Dominici et al., 2005; Franklin et al., 2008; Kolb et al., 2007; Zanobetti and Schwartz, 2008a, 2008b) but was null in the winter months (Kolb et al., 2008; Zanobetti and Schwartz, 2008b). A study of 48 cities in the U.S. found the effect of O_3 on all-

cause mortality increased in the early spring and summer and decreased to no association by September (Zanobetti and Schwartz, 2008b).

Additionally, some studies went further than examining simply the overall association between short-term exposure to O_3 and mortality. These studies are summarized below:

- Bell et al. (2008) utilized data from the National Morbidity, Mortality, and Air Pollution Study (NMMAPS), which included 98 urban communities from around the U.S. and found the association between O_3 (mean concentration: 26.8 ppb) and mortality was greater among areas of high unemployment, higher proportion of African-American residents, higher public transportation use, and a lower prevalence of central air conditioning.

- Dominici et al. (2005) also used NMMAPS data to examine the association between O_3 exposure (no concentration given) and mortality and observed a non-statistically significant positive association with lag of 0 days. The association became more pronounced when using only data from summer seasons.

- Although most of the point estimates were elevated, in their study population of individuals 65 yr and older who lived and died in Montreal, Goldberg et al. (2006) found no association between O_3 exposure (mean daily O_3 concentration: 15ppb) and mortality except among those who died during the warm season and were diagnosed with diabetes before their death.

- Kolb et al. (2007) identified a positive association between O_3 (mean daily concentration: 15 ppb) and mortality during the warm season in Montreal among individuals at least 65 yr of age who had been previously diagnosed with congestive heart failure for at least 1 yr prior to death. This association was not observed during the cold season.

- In addition to observing a positive association between O_3 (mean 8-h concentration ranged by city from 15.1 to 62.8 ppb) and all-cause mortality during the summer months, Zanobetti and Schwartz (2008a) reported a positive association between O_3 and cardiovascular disease mortality, respiratory mortality, and stroke mortality in their study of 48 cities in the U.S.

- Franklin et al. (2008) reported an association between summertime O_3 levels (mean daily O_3 concentration ranged by community from 21.4 to 48.7 ppb) and non-accidental mortality. These authors found no confounding of the association when including $PM_{2.5}$

in a copollutant model but the association between O_3 and mortality decreased to null when sulfate was included in the model.

The remaining short-term exposure mortality studies analyzed the potential modification and confounding of the association between O_3 and mortality due to various weather variables, including temperature. In two separate studies, Ren et al. (2008a, 2008b) analyzed whether temperature modified the O_3-mortality effect and whether O_3 modified the temperature-mortality effect, respectively. Ren et al. (2008a) found in a study of 60 large eastern U.S. communities, temperature synergistically modifies the O_3-mortality effect, but the modification varies depending on the geographic location. Specifically, the association was modified by high temperatures in the northeastern U.S. but not in the Southeast. In contrast, Ren et al. (2008b) found in a study of 95 large U.S. communities, using the NMMAPS data, that O_3 modified the temperature effect on cardiovascular mortality across all regions of the U.S. Rainham et al. (2005) analyzed the overall effect of weather on the air pollution-mortality association in a study in Toronto, Canada, and did not find a systematic pattern of modification, but a modification effect seemed dependent on the type of synoptic climatology category[1] analyzed. An additional study examined potential confounding of the O_3-mortality relationship by PM using NMMAPS data. In Bell et al. (2007), confounding was investigated by analyzing the effect of PM on the association between short-term exposure to O_3 and mortality using data from 98 U.S. communities. By estimating the correlation between daily PM and O_3 concentrations, along with including PM as a covariate in various models, Bell et al. (2007) concluded that neither PM_{10} nor $PM_{2.5}$ is a likely confounder of the observed relationship between O_3 and mortality.

3.1.2. Respiratory Morbidity

Results from controlled human exposure studies and animal toxicological studies analyzed during the completion of the 2006 O_3 AQCD "provide clear evidence of causality for the associations observed between acute ($\leq$ 24 h) O_3 exposure and relatively small, but statistically significant declines in lung function observed in numerous recent epidemiologic studies. Declines in lung function were particularly noted in children, asthmatics, and adults who work or exercise outdoors" (U.S. EPA, 2006).

Since the 2006 O_3 AQCD, many studies have been published examining the association between short-term exposure to O_3 (i.e., over a period of a few days) and respiratory morbidity. These studies have examined multiple respiratory outcomes, including lung function, airway inflammation, and asthma. Overall, the findings reported in the new studies of respiratory morbidity

[1] Synoptic categories, which are also referred to as air mass categories were derived through a complex statistical approach that classifies various meteorological components (i.e., temperature, dew point, components of wind, cloud cover, and sea level pressure) into six categories.

are consistent with those in the 2006 O_3 AQCD conclusions, particularly the numerous new studies of hospital admissions and emergency department visits.

3.1.2.1. Respiratory Hospital Admissions and Emergency Department Visits

The 2006 O_3 AQCD reported that numerous population time-series studies have "observed that ambient O_3 concentrations are positively and robustly associated with respiratory-related hospitalization and asthma emergency department (ED) visits during the warm season. These observations are strongly supported by the human clinical, animal toxicological, and epidemiologic evidence for lung function decrements, increased respiratory symptoms, airway inflammation, and airway hyperreactivity. Taken together, the overall evidence supports a causal relationship between acute ambient O_3 exposures and increased respiratory morbidity resulting in increased ED visits and hospitalizations during the warm season" (U.S. EPA, 2006).

This provisional assessment identified numerous studies that focus on respiratory hospitalization and ED visits conducted in the U.S. (Babin et al., 2007; Ito et al., 2007; Letz et al., 2005; Lin et al., 2008; Magas et al., 2007; Medina-Ramón et al., 2006; Moore et al., 2008; Tolbert et al., 2007) and Canada (Cakmak et al., 2006a; Fung et al., 2006; Lin et al., 2005; Szyskowicz et al., 2008; Villeneuve et al., 2007; Yang et al., 2005). Results from recent studies on hospitalization admissions and ED visits for all respiratory diseases and asthma individually, along with results of similar studies from the 2006 O_3 ACQD are included in Figure 3-1. A limited number of studies are not illustrated where authors did not provide quantitative results that allowed for presentation in a manner consistent with those studies in Figure 3-1. This figure does not include hospital admissions or ED visits exclusively for chronic obstructive pulmonary disease (COPD) or respiratory infections. Overall, the results of the recent studies are consistent with the 2006 O_3 AQCD in reporting associations during the warm season, but not during cool seasons or in all-year analyses.

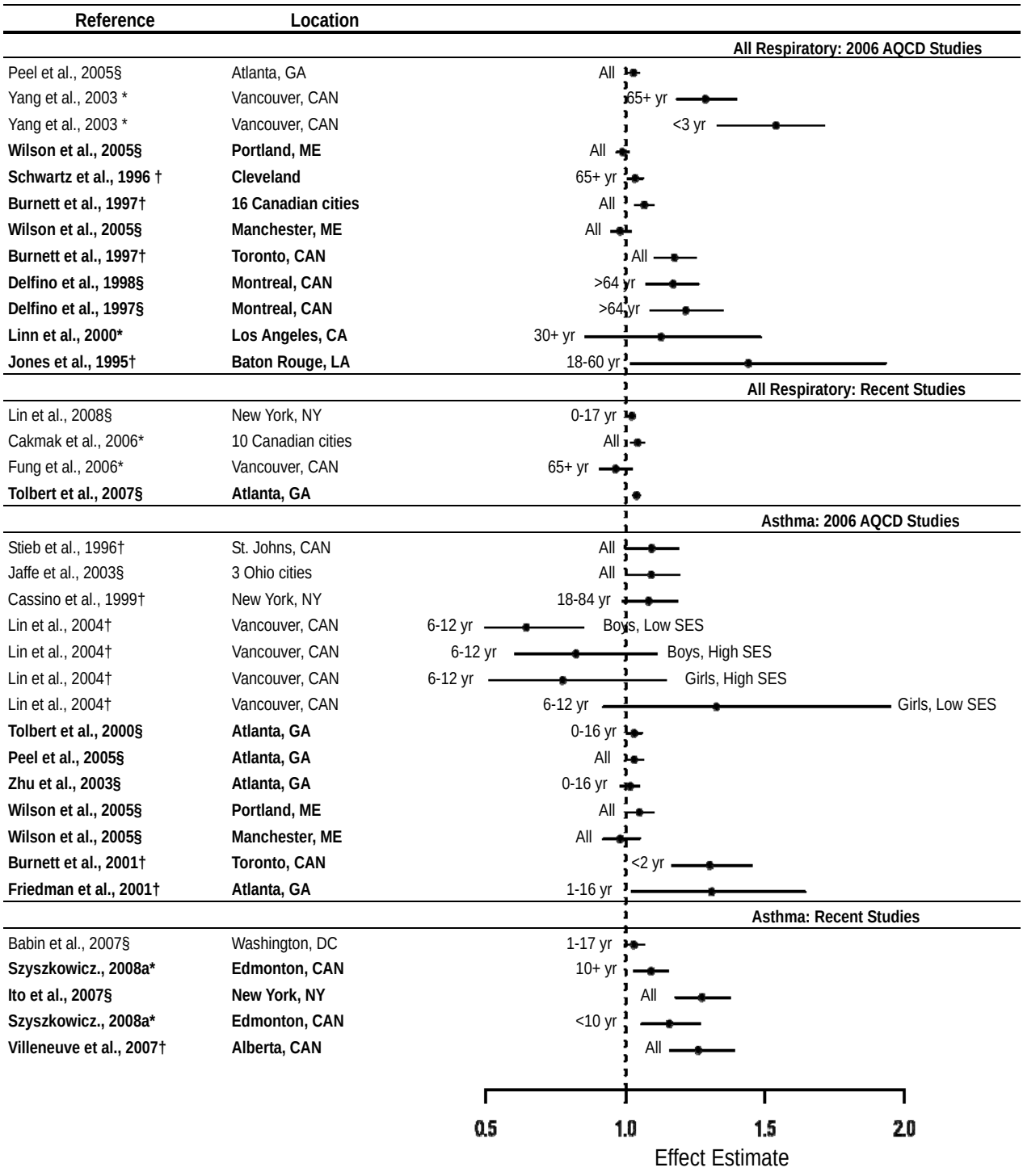


Figure 3-1. Association between short-term O_3 exposure and hospital admissions and ED visits for all respiratory diseases and asthma individually from recent studies and the 2006 AQCD. Bolded studies considered warm season only. Entries arranged by period evaluated (all year then warm season) and then by effect estimate precision. Effect estimates standardized depending on the averaging time in study: 20 ppb for 24-h avg (*); 30 ppb for 8-h max (§); 40 ppb for 1-h max (†).

Two multicity studies reported associations between O_3 and respiratory admissions:

- Medina-Ramón et al. (2006) evaluated the effect of ambient O_3 (mean concentration ranged by city from 15.0 to 63.0 ppb for the 35 cities with information during the warm season and 19.3 to 34.5 ppb for the 16 cities with information on the cold season) on respiratory hospital admissions among individuals 65 yr of age and older in 36 U.S. cities. The authors found an association between O_3 exposure and COPD and pneumonia hospital admissions during the warm season.

- Cakmak et al. (2006a) examined whether community income and education modified the effect of gaseous pollutants, including O_3, on respiratory hospitalizations in 10 large Canadian cities. Although the analysis focused on income and education variables, the study did find an association between O_3 exposure (mean daily O_3 concentration ranged by city from 17.0 to 23.7 ppb) and respiratory hospital admissions in both single and multipollutant models, which excluded variables for income and education. The association persisted within all categories for neighborhood-level income, but among neighborhood-level education categories, the association was only observed in the lowest education group.

Several single-city studies have also been conducted:

- A study of hospital admissions due to respiratory disease among children aged 0-17 yr performed in New York City found a positive association with ambient O_3 concentration in five of the eleven regions included in the study (mean 8h maximum O_3 concentration 44.1 ppb) (Lin et al., 2008a).

- Fung et al. (2006) performed an analysis of respiratory illness-related hospital admissions in Vancouver, Canada among individuals 65 yr of age and older and found no association with ambient levels of O_3 (mean daily concentration 14.3 ppb).

- A study performed in the U.S. by Tolbert et al. (2007) found a positive association between short-term O_3 exposure (mean 8-h O_3 concentration 53.0 ppb) and respiratory disease-related ED visits during non-winter months. This association remained robust in multipollutant models.

In addition, a number of single-city studies have reported generally positive associations with hospitalization for asthma, but provide little new evidence for associations with COPD or respiratory infection admissions.

- Babin et al. (2007) examined the association between O_3 exposure (no concentration given) and asthma-related pediatric ED visits among children age 1-17 yr. They observed a positive association of same-day O_3 exposure and ED visits. They also found a positive association between same-day exposure and subsequent hospital admission. These associations were strongest among children aged 5-12 yr. The authors found a positive association between O_3 exposure lagged for up to 4 days and ED visits for the 5-12-yr group.

- Moore et al. (2008) performed a study in California and reported that O_3 (mean daily maximum O_3 concentration Apr-Sep of 87.8 ppb) had a positive association with hospital discharge rates for asthma among children aged 0-19 yr. This study was not included in Figure 3-1 because results were not provided in a form that could be utilized in a manner consistent with other studies.

- Ito et al. (2007) examined the association between O_3 and asthma-related ED visits using 3 different models in order to analyze different methods to account for temporality and multicollinearity among pollutants and weather variables. The authors report a positive association during the warm months (mean 8-h maximum O_3 concentration 42.7 ppb), but an inverse association between O_3 concentrations and asthma-related ED visits during the cold months (mean 8-h maximum O_3 concentration 18.0 ppb). The positive association observed in the warm season remained in multipollutant models; robust results were observed for all 3 models.

- Villeneuve et al. (2007) reported an association between O_3 exposure and ED visits for asthma to be positive during the period of April-September (mean daily maximum O_3 concentration 38.0 ppb); however, the association did not persist during the winter months (October-March; mean daily maximum O_3 concentration 24.3 ppb). Overall, the association for the full year was positive, but when broken down into age groups, there was no association for individuals under the age of 5 or over the age of 65 yr.

- Another study of asthma-related ED visits conducted in Edmonton, Canada (Szyskowicz, 2008) found a positive association with same-day and one day lag in O_3 concentrations (mean daily O_3 concentration 18.6 ppb) among both individuals less than and older than 10 yr of age. The authors found an association persisted using a 2-day lag for those under 10 yr old; no difference in the association was observed for warm or cold months.

- A study among children in Oklahoma City, OK detected no association between short-term exposure to O_3 and pediatric hospital admissions for asthma. The authors state that

this is likely due to low levels of O_3 in that area (mean 1-h O_3 concentration 48.2 ppb) (Magas et al., 2007). This study was not included in Figure 3-1 because results were not provided in a form that could be utilized in a manner consistent with other studies.

- Yang et al. (2005) detected no association between short-term exposure to O_3 (mean daily concentration 14.1 ppb) and emergency or urgent hospitalizations for COPD among individuals 65 yr of age and older. The authors attempted to look at multiple periods of acute exposure by varying the lag days from 1-7 but there were no associations present with any lag period.

- Lin et al. (2005) conducted a study in Toronto, Canada and found no association for either boys or girls under the age of 15 yr for O_3 exposure (mean daily O_3 concentration 38.1 ppb) and hospital admissions for respiratory infections.

3.1.2.2. Lung Function

- In an observational study of healthy hikers, Girardot et al. (2006) found no association between exposure to ambient O_3 concentrations (mean of hikers' time weighted average O_3 concentration: 48.1 ppbv) and a decrease in lung function (i.e., FEV_1 or FVC).

- Another study (Thaller et al., 2008) conducted of individuals spending a large amount of time outdoors (i.e., lifeguards) in Texas demonstrated an inverse relationship between O_3 (median daily maximum concentration 35 ppb) and FEV_1/FVC ratio. However, the authors observed no change in FEV_1 or FVC alone in response to O_3 levels. No measures of exertion were included in this analysis; however, a separate analysis did show slight changes in lung function after 1 hr of exercise.

- A study by Alexeeff et al. (2007) reported an overall association between O_3 (mean 48-h concentration 24.4 ppb) and FEV_1 and FVC. For FVC, the association was stronger among those with airway hyperresponsiveness and among obese individuals.

- Lagorio et al. (2006) performed a panel study of individuals with co-morbid conditions (COPD, asthma, or ischemic heart disease), and found no association between exposure to ambient O_3 concentrations and a decrease in lung function (i.e., FEV_1 or FVC).

Lung function has been assessed among elderly and young populations. A study of elderly individuals from the Normative Aging Study determined O_3 exposure was associated with a decrease in FEV_1 and FVC, which was strongest when examining the 2-day average of O_3 concentration

(mean O_3 concentration 24.4 ppb) (Alexeeff et al., 2008). The authors also determined that some antioxidant genes polymorphisms may modify the effect of O_3 exposure on lung function. In a study of 86 school age children in Detroit, MI, Lewis et al. (2005), found an association between increasing ambient O_3 concentrations (mean daily O_3 concentration 27 ppb) and reduced lung function (FEV_1), but greater than 75% of the children included in the study were classified as having persistent asthma. Also, in a study of high school athletes, no association was observed between post-exercise lung function and ambient O_3 (mean 1-h maximum O_3 concentration 71 ppb) (Ferdinands et al., 2008). In addition, Liu et al. (2009) examined O_3 exposure (median 2-day average concentration 14.1 ppb) and FEV_1 and forced expiratory flow $(FEF)_{25-75}$% among asthmatic children aged 9-14 yr, living in nonsmoking households and found no association.

3.1.2.3. Airway Inflammation

Three studies measuring the association between short-term exposure to O_3 and airway inflammation have been performed recently:

- Adamkiewicz et al. (2004) conducted a study in a group of elderly individuals from Ohio and found no association between O_3 (mean daily concentration 15.3 ppb) and the fraction of exhaled nitric oxide (FENO), a marker for airway inflammation.

- Ferdinands et al. (2008) observed no association between O_3 (mean 1-h maximum concentration 71 ppb) and breath pH, another marker of airway inflammation, among a group of nonsmoking high school athletes after they completed their exercise.

- Liu et al. (2009) observed an inverse association between the average 2-day O_3 concentration (median 2-day average concentration 14.1 ppb) and FENO. The association was robust in the multipollutant analysis. The authors called the association "counterintuitive" and were not able to identify a reason for this inverse association. An oxidative stress marker, thiobarbituric acid reactive substances (TBARS), was positively associated with O_3 in the multipollutant model, although the results were not statistically significant.

3.1.2.4. Asthma Exacerbation

Respiratory morbidity studies analyzed in the 2006 O_3 AQCD found "significant associations between acute exposure to ambient O_3 and increases in a wide variety of respiratory symptoms … in asthmatic children." Epidemiologic studies also indicate that acute O_3 exposure is likely associated with increased asthma medication use in asthmatic children" (U.S. EPA, 2006). The present evaluation identified three studies that analyzed the effect of ambient O_3 concentrations on asthma

symptoms (Babin et al., 2008; Rabinovitch et al., 2004; Schildcrout et al., 2006) and one study on physician visits (Burra et al., 2009). Although a few studies did not find an association between O_3 concentrations and asthma exacerbation, this does not imply the results are inconsistent with those previously found. A thorough evaluation of study populations, uncertainty in parameter estimates, precise scientific questions, season in which the study was performed, and additional comparisons between studies that examined the effect of O_3 exposure on asthma exacerbations has not been conducted and is necessary to interpret and compare the studies.

The following observations were made from the studies of children:

- Schildcrout et al. (2006) investigated the relation between ambient criteria pollutant concentrations and asthma exacerbations (defined as having any asthma episode ranging from a mild episode for less than 2 h to an episode greater than 2 h that resulted in the shortening of normal activity and/or hospitalization/doctor visits) in a cohort of children in 8 U.S. cities (median 1h maximum O_3 concentration ranged by city from 43.0 to 65.8 ppb). The authors included a population of children in which the severity of their asthma was not clearly identified. However, the overall study included 990 children with, on average, 12 children being examined every day. The O_3 analysis included the months May through September, which resulted in the study population being less than the 990 children observed during the course of the full study. As a result, the total number of children observed is not comparable to other large multicity studies that examined the effect of O_3 concentrations on asthma exacerbation. In this study, Schildcrout et al. (2006) reported no association between O_3 concentrations and asthma exacerbation.

- Rabinovitch et al. (2004), in a study that examined the association between asthma symptoms and O_3 during the winter months (mean daily 1-h maximum O_3 concentration 28.2 ppb), reported no association between O_3 levels and FEV_1 or bronchodilator use among children. However, a positive association was observed between daily O_3 concentration and current day symptoms.

- Burra et al. (2009) conducted a study of children and adults in Toronto, Canada. Slightly inverse associations were found between short-term O_3 exposure (mean daily 1-h maximum O_3 concentration 33.3 ppb) and asthma-related physician visits for both children (1-17 yr old) and adults (18-64 yr old). Babin et al. (2008) examined asthma exacerbations among a Medicaid population (0-65+ yr old) in the Washington, D.C. area. Overall, no association was observed between short-term exposure to O_3 (concentration not provided) and asthma exacerbations, but when restricting the analysis to include only

the spring and summer months, the authors found a positive association between O_3 and general acute care for asthma exacerbations.

3.1.2.5. Other Respiratory Symptoms

Finally, a study was conducted examining building related symptoms (heath symptoms present when an individual is in a building but are absent or decreased when the individual is not in the building) and found outdoor levels of O_3 (during the regular workday, the late workday, and the 24-h mean) were associated with reports of upper respiratory (nose/sinus congestion, sore throat, sneeze) and lower respiratory (wheeze, shortness of breath, chest tightness) building-related symptoms (Apte et al., 2008).

3.1.3. Cardiovascular Morbidity

The 2006 O_3 AQCD concluded that the "generally limited body of evidence is highly suggestive that O_3 directly and/or indirectly contributes to cardiovascular-related morbidity," including physiologic effects (i.e., release of platelet activating factor [PAF]), heart rate variability (HRV), arrhythmias, and myocardial infarctions (U.S. EPA, 2006). However, the available body of evidence reviewed during the 2006 O_3 AQCD does not "fully substantiate links between ambient O_3 exposure and adverse cardiovascular outcomes" (U.S. EPA, 2006). The results of the more recent studies presented here are consistent with those of the 2006 O_3 AQCD.

Four studies were identified (Metzger et al., 2007; Rich et al., 2006a; Rich et al., 2006b; Sarnat et al., 2006) that investigated the effect of O_3 on arrhythmias. Each study used different cardiac episodes to identify an arrhythmia event: Sarnat et al. (2006) (mean daily O_3 concentration 22 ppb) used supraventricular and ventricular ectopy; Rich et al. (2006a) (mean daily O_3 concentration 22.6 ppb) used paroxysmal atrial fibrillation episodes; Rich et al. (2006b) (mean daily O_3 concentration 27.5 ppb) used ventricular arrhythmias; and Metzger et al. (2007) (mean 8-h O_3 concentration 53.9 ppb) used tachyarrhythmic events. Of these studies, Sarnat et al. (2006) and Rich et al. (2006a) found an association between O_3 concentrations and the onset of arrhythmias in a study of non-smoking older adults, and in a study of patients with implantable cardiac devices (ICDs) in Boston, MA, respectively. The Sarnat et al. (2006) study was performed from June to December. The study by Rich et al. (2006a) was conducted throughout the year but when the researchers compared the results for warm versus cold seasons, they observed them to be similar. Rich et al. (2006b) in a study of 56 patients with ICD in St. Louis, MO observed a weak association between O_3 concentrations and arrhythmias although the researchers did not assess seasonal variation. Metzger et al. (2007) did not find any association for the warm season in a study of 518 patients with tachyarrhythmia that had ICDs in Atlanta, GA.

In addition, numerous studies were identified that examined physiologic effects in response to O_3 exposure (Goldberg et al., 2008; Liao et al., 2005; Lisabeth et al., 2008; Park et al., 2007; Wellenius et al., 2007; Wheeler et al., 2006; Zanobetti et al., 2004). None of these studies assessed seasonal effects. These studies include:

- A study of 50-85 yr olds with limited physical function and ejection fraction no greater than 35% (lower ejection fraction indicates poor efficiency of the heart; ejection fraction of a normal heart is about 55%) were examined at a McGill University Heart Failure and Transplant Center to determine the effect of O_3 on oxygen saturation and pulse rate (Goldberg et al., 2008). There was a moderate, positive association between O_3 exposure (concentration not provided) and oxygen saturation. No association was present between O_3 exposure and pulse rate.

- The Atherosclerosis Risk in Communities (ARIC) cohort found O_3 exposure (mean daily 8-h O_3 concentration 0.04 ppm) was associated with some but not all markers of hemostasis and inflammation. Instead of a strictly concentration-dependent association, the association between O_3 exposure and the markers was relatively small or absent at low levels of O_3 exposure but much greater at higher levels (approximately 70 ppb and higher). Fibrinogen was associated only among those with a history of cardiovascular disease (Liao et al., 2005).

- Wellenius et al. (2007) did not observe any fluctuations in B-type natriuretic peptide (BNP), a marker of congestive heart failure severity, with O_3 exposure (mean daily O_3 concentration 25.1 ppb).

- A study by Park et al. (2007) assessed the effect of O_3 concentrations (mean daily O_3 concentration ranged by location from 17 to 29 ppb) and the origin of the ambient air on HRV in a cohort of men in Boston, MA. An association was detected but only when the air originated from the west.

- Wheeler et al. (2006) conducted a study on individuals living in Atlanta, GA who either had a myocardial infarction 3-12 mo before the start of the study or who had self-reported a physician's diagnosis of moderate to severe COPD. In this study O_3 exposure (mean 4-h O_3 concentration ranged by community from 8.0 to 33.8 ppb) was not associated with the standard deviation of normal R-R intervals (a marker of HRV).

- A study of outpatients with cardiac disease conducted in Boston, MA reported an association between short-term exposure to O_3 (mean 120-h concentration 24 ppb) and

higher resting diastolic blood pressure in a single-pollutant model. However, in a multipollutant model no association with O_3 was observed (Zanobetti et al., 2004).

- Lisabeth et al. (2008) performed a study in Texas to assess the association between exposure to O_3 (median 24-h concentration 25.6 ppb) and stroke/transient ischemic attacks, and found a positive but not statistically significant association.

3.1.3.1. Hospital Admissions and Emergency Department Visits

Highly suggestive evidence for O_3-induced cardiovascular effects [has been] provided by a few population studies of cardiovascular hospital admissions, which reported positive O_3 associations during the warm season between ambient O_3 concentrations and cardiovascular hospitalizations [and ED visits]" (U.S. EPA, 2006). The O_3 AQCD, therefore, concluded, that the "generally limited body of evidence is highly suggestive that O_3 directly and/or indirectly contributes to cardiovascular morbidity, but more research is needed to further substantiate the links between ambient O_3 exposure and adverse cardiovascular outcomes" (U.S. EPA, 2006).

Six recent cardiovascular hospital admission and ED visit studies were identified from the U.S. and Canada (Cakmak et al., 2006b; Peel et al., 2007; Symons et al., 2006; Szyszkowicz, 2008b; Villeneuve et al., 2006; Wellenius et al., 2005), four of which found no association between ambient O_3 concentrations and either hospital admissions or ED visits, one which found a positive association among younger men, and one which overall found a positive association but found no association for some cities. Comparison between recent studies and those in the 2006 O_3 AQCD is difficult because the majority of recent studies included all seasons unlike previous studies that concentrated on the warm season when levels of O_3 are greater and the likelihood of exposure is increased. Individual observations for these studies are presented below:

- Peel et al. (2007) examined the effect of ambient O_3 concentrations (mean 8-h O_3 concentration 55.6 ppb) on cardiovascular ED visits in 31 Atlanta, GA hospitals for individuals inflicted with chronic conditions (e.g., hypertension, diabetes, COPD). The authors observed no overall association between O_3 and cardiovascular disease ED visits. ED visits for peripheral and cerebrovascular disease increased with ambient O_3 levels among individuals who had COPD. These results add to the evidence that individuals having various co-morbid conditions, including COPD, have an increased susceptibility to ambient O_3 air pollution. Seasonal variation in the association was not assessed.

- Cakmak et al. (2006b) examined the relationship between O_3 exposure and hospital admissions for cardiac disease in 10 large Canadian cities (mean O_3 concentration ranged by city from 13.5 to 23.7 ppb). Overall the authors found a positive association,

although the association varied between cities, with some cities showing no association. In addition, they reported the association between O_3 and hospital admissions was not modified by sex, neighborhood-level income, or neighborhood-level education. Seasonal variation in the association was not assessed.

- A study of five hospitals in Edmonton, Canada found a positive association between ED visits for acute ischemic stroke and one day lagged O_3 concentration (mean daily concentration 18.6 ppb) among men aged 20-64 yr during the warm season (Szyszkowicz 2008b). A similar association was not seen for men 65-100 yr of age or for women. Also, no association was seen with same-day O_3 levels.

- A study performed from April to December of 2002 reported no association between O_3 (mean 8-h concentration 31 ppb) and hospital admissions for symptom exacerbation among individuals already diagnosed with congestive heart failure (Symons et al., 2006).

- Villeneuve et al. (2006) did not detect an association between O_3 levels and ED visits for hemorrhagic and acute ischemic strokes during either the summer (mean daily O_3 concentration 21.8 ppb) or winter (mean daily O_3 concentration 12.2 ppb) months.

- Wellenius et al. (2005) reported no association between O_3 (mean daily concentration 24.3 ppb) and rate of hospital admissions for congestive heart failure among Medicare recipients performed a study in the Pittsburgh, PA area. Seasonal variation in the association was not assessed.

In addition to the respiratory and cardiovascular specific hospital admission and ED visit studies already presented, two U.S. studies examined the effect of ambient O_3 concentrations on both respiratory and cardiovascular hospital admissions and ED visits (Tolbert et al., 2007; Zanobetti and Schwartz 2006). Zanobetti and Schwartz (2006) found that O_3 concentration (median O_3 concentration 22.4 ppb) was not associated with an increase in myocardial infarction and pneumonia hospital admissions. Similarly, Tolbert et al. (2007) found no association (mean 8-h O_3 concentration 53.0 ppb) with ED visits for cardiovascular disease during non-winter months.

3.2. Health Effects Associated with Long-Term Ozone Exposures

3.2.1.Mortality

Few epidemiologic studies have assessed the relationship between long-term exposure to O_3 and mortality. As a result, the 2006 O_3 AQCD concluded that an insufficient amount of evidence exists "to suggest a causal relationship between chronic O_3 exposure and increased risk for mortality in humans" (U.S. EPA, 2006).

This provisional assessment identified a few studies that examined the association between long-term exposure to O_3 and mortality. Two of these studies focused specifically on traffic density (Lipfert et al., 2006a, 2006b), and therefore, were not addressed in this analysis.

Chen et al. (2005) utilized data from the AHSMOG study and reported no significant associations between long-term O_3 exposure (mean O_3 concentration 26.2 ppb) and fatal coronary heart disease. However, in 2-pollutant models, O_3 strengthened the association between PM and death from coronary heart disease.

One recent study that examined long-term exposure to O_3 did report a positive association between ambient O_3 concentration and respiratory causes of death (Jerrett et al., 2009). Jerrett et al. (2009) utilized the ACS cohort with data from 1977 through 2000 (mean O_3 concentration ranged from 33.3 to 104.0 ppb during this time period). The average O_3 concentrations were determined from April through September, which the authors state is because "O_3 concentrations tend to be elevated during the warmer seasons and because fewer data were available for the cooler seasons." Exposure to O_3 was positively associated with risk of death from respiratory causes, and this association remained after controlling for $PM_{2.5}$ using copollutant models. Further examination of the association between O_3 exposure and respiratory-related mortality revealed the association was modified by temperature, with the association being present at higher temperatures. There was also geographic variation in the association. Jerrett et al. (2009) observed an association between long-term O_3 exposure and cardiopulmonary, cardiovascular, and ischemic heart disease mortality in single pollutant models as well, but the associations were not present when $PM_{2.5}$ was included in the model.

Another recent study also utilized data from the ACS cohort (Krewski et al., 2009) and observed a positive association between O_3 exposure between April through September 1980 and all-cause and cardiopulmonary disease mortality. This association was robust to control for ecologic variables. No association was observed between summer O_3 exposure (mean individual O_3 concentration 30.2 ppb) and deaths related to ischemic heart disease or lung cancer. In addition,

Krewski et al. (2009) found no association with mortality when examining year-round O_3 exposure (mean individual O_3 concentration 22.9 ppb).

3.2.2.Lung Function and Respiratory Symptoms

The 2006 O_3 AQCD concluded that, "the epidemiologic data, collectively, indicates that the current evidence is suggestive, but inconclusive for respiratory health effects from long-term O_3 exposure" (U.S. EPA, 2006). This provisional review identified multiple studies that assessed the effect of long-term exposure to O_3 on lung function and its development (Gauderman et al., 2007; Islam et al., 2007; Karr et al., 2007; Li et al., 2006; Lin, 2008b; Meng et al., 2007; Millstein et al., 2004; Mortimer et al., 2008; Parker et al., 2009; Qian et al., 2005; Tager et al., 2005; Wilhelm et al., 2008). The results of recent studies are generally mixed. A description of each of the aforementioned studies and their findings are presented below:

- A study of infants aged 3 wk to 1 yr of age found no association between either chronic or subchronic O_3 exposure (both chronic and subchronic: mean 8-h maximum O_3 concentration 23 ppb) and hospital admissions for acute bronchiolitis when controlling for $PM_{2.5}$ exposure (Karr et al., 2007). In single pollutant models, O_3 had a slightly negative association with hospital admissions.

- A study of asthmatic children 6-11 yr of age conducted in Fresno, CA examined if prenatal exposure to high ambient O_3 concentrations was predictive of current lung function (Mortimer et al., 2008). Prenatal exposure was evaluated for each trimester and the entire pregnancy. The authors found no association between O_3 exposure (median 8-h O_3 concentration almost 50 ppb) and lung function among asthmatic children. There was also no association with exposure during 0-3 yr of life (median 8-h O_3 concentration 50 ppb).

- Islam et al. (2007) investigated the relationship between air pollution, lung function, and the subsequent development of asthma in a cohort of 9-10 yr old children without asthma or wheeze from the Children's Health Study. The authors found long-term O_3 exposure (concentration not provided) did not have any observable effect on FEF, and, therefore, was not associated with lung damage or asthma development.

- Asthmatic children from the Children's Health Study in California were assessed and no association was found between O_3 and asthma or wheezing outcomes (Li et al., 2006). However, a protective effect from a certain genotype (TNF-308GG genotype) was observed for wheezing outcomes but only in communities with low-O_3 levels (mean

annual O_3 concentration 37.5 ppb). In addition, the TNF-308GG genotype was less protective in high O_3 areas (mean annual O_3 concentration 57.8 ppb) among individuals with the GSTM1 null or GSTP1 105 Val alleles.

- Gauderman et al. (2007) utilized the Children's Health Study to examine lung function growth among adolescents during an 8-yr study period. They found no association between O_3 exposure (concentration not provided) and lung function development.

- Other researchers (Millstein et al., 2004) using the Children's Health Study reported an association between monthly average O_3 concentrations (mean monthly O_3 concentration ranged by communities from 15 to 40 ppb for winter months and 30 to 105 ppb for summer months) and use of asthma medication among asthmatic children approximately 9 yr of age. The association was stronger among children who spent more time outdoors. Overall, no association was observed between O_3 and the presence of wheeze; however the association was positive among children who spent the most time outdoors. O_3 exposure appeared to have a protective effect for wheeze during the fall and winter months. The authors report that this may be due to "…an artifact created by correlated exposures, meteorology, or behavioral responses to meteorological conditions."

- Tager et al. (2005) examined the effect of O_3 exposure (mean 8-h "time outdoors" monthly O_3 concentration 36 ppb for men and 33 ppb for women) on individuals who had grown-up in either the Los Angeles or San Francisco, CA area. Tager et al. (2005) estimated lifetime exposure to O_3 and found it to be associated with decreased lung function among college freshman.

- Parker et al. (2009) conducted a study examining summer exposure to O_3 (median concentration 31.5 ppb) and report of respiratory allergy/hay fever among children aged 3-17 yr old. The authors observed a positive association in both single and multipollutant models. This association was robust to adjustment for demographic and geographic variables. In addition, the authors observed a positive association for annual O_3 exposure and respiratory allergy/hay fever among children.

- A study of asthmatic children (age 0-17 yr old) living in California was conducted to examine the association between annual-average O_3 concentrations (mean hourly O_3 concentration 21 ppb) and asthma exacerbations/hospital admissions (Wilhelm et al., 2008). Wilhelm et al. (2008) found a positive association between annual-average O_3 concentrations and both daily/weekly asthma symptoms and ED visits/hospital

admissions. The association persisted after inclusion of PM, race/ethnicity, and poverty-level as covariates.

- Lin et al. (2008b) followed children (1-6 yr) born in New York until their first asthma hospitalization (those without a hospitalization reported were followed until the end of the study). The authors observed a positive dose-response association between O_3 exposure (mean 8-h concentration 41.1 ppb) and asthma hospitalizations. The association was strongest in New York City (compared to other regions of New York state) and among children 1-2 yr of age (compared to those older than 2 yr).

- Meng et al. (2007) reported that among their study population (those ever diagnosed by a physician as having asthma) continuous O_3 (concentration not provided) was positively associated with poorly controlled asthma among men but no association was present for women. Poorly controlled asthma was defined as having daily or weekly asthma symptoms or having at least one hospital or ED visit due to asthma during the previous year. In addition, O_3 exposure above the 90 percentile (based on the distribution of exposure among the study population) was associated with poorly controlled asthma among individuals 65 yr of age and older. This study did not examine categories of older men versus younger men to determine if one of these groups was driving the association.

- A study conducted in three communities across the U.S. detected an association between lung function and O_3 (mean concentration ranged by community from 29.6 to 49.5 ppb) (Qian et al., 2005). The association remained among groups of individuals, such as those with current respiratory symptoms and those with chronic lung diseases. The authors concluded, "…Our results suggest negative effects of long-term exposure to …O_3 on pulmonary function, even at levels below current national standards."

In addition, one study examined the association between O_3 exposure and oxidative stress. Among individuals living in California, a positive association was observed between 2-wk, 1-mo, and lifetime O_3 exposure (mean monthly O_3 concentration 30.5 ppb) and 8-isoprostane (8-iso-PGF), a measure of lipid peroxidation (Chen et al., 2007a). However, no association was found between O_3 and a biomarker for ferric reducing ability of plasma (FRAP), a biomarker for antioxidant capacity.

3.2.3.Lung Cancer

The 2006 O_3 AQCD concluded that, "the weight of evidence from recent animal toxicological studies and a very limited number of epidemiologic studies do not support ambient O_3 as a pulmonary carcinogen" (U.S. EPA, 2006). This provisional assessment identifies two studies (Chen

et al., 2006; Huen et al., 2006), which both observed cytogenic damage (i.e., micronuclei formation and degenerated cells) in response to an increase in O_3 exposure (Huen et al: mean 8-h monthly O_3 concentrations ranged from about 0.03 ppm in April to 0.014 ppm in November; Chen et al: concentrations not provided). These studies included children, college students, and adult women. Although cytogenic damage could potentially lead to cancer development, neither study concluded that O_3 is a pulmonary carcinogen. No studies were identified that directly examined the association between exposure to O_3 and lung cancer incidence. One study, discussed in the section reviewing long-term exposure to ozone and mortality (Section 3.2.1), observed no association between O_3 exposure and lung cancer mortality.

3.2.4.Reproductive and Developmental Outcomes

A limited number of studies have examined the relationship between O_3 exposure and birth-related outcomes, including mortality, premature births, low birth weight (LBW), and birth defects. The 2006 O_3 AQCD concluded that "O_3 [is] not an important predictor of several birth-related outcomes including intrauterine and infant mortality, premature births, and low birth weight" (U.S. EPA, 2006).

This provisional assessment identifies recent studies that analyzed the effect of O_3 exposure on various birth outcomes, including preterm birth (Currie et al., 2008; Wilhelm et al., 2005); fetal growth (Brauer et al., 2008; Dugandzic et al., 2006; Liu et al., 2007; Salam et al., 2005; Wilhelm et al., 2005); respiratory effects/hospitalizations (Dales et al., 2006; Triche et al., 2006); mortality (Dales et al., 2004; Ritz et al., 2006; Woodruff et al., 2008) and birth defects (Gilboa et al., 2005; Strickland et al., 2009). Although some of these studies show a positive association, overall, the results are inconsistent. Future studies examining the relationship between O_3 and reproductive and developmental outcomes will be important in understanding more about these associations. A synopsis of the findings for each birth outcome given in recent studies is presented below:

- **Preterm Birth**: Wilhelm et al. (2005) analyzed the association between O_3 exposure during varying periods of pregnancy (mean O_3 concentration of about 21-22 ppb for all periods) and preterm birth in California from 1994-2000. The authors found a positive association between O_3 levels in both the first trimester of pregnancy and the first month of pregnancy and preterm birth. No association was observed between O_3 in the 6 weeks before birth and preterm delivery. Currie et al (2008) performed a study in New Jersey and observed a negative association between O_3 (mean 8-h concentration 36.0 ppb) in the second trimester and the number of weeks of gestation. When CO was included in the models, this association was no longer present although there was an association between O_3 during the third trimester and gestational period in this multipollutant model.

- **Fetal Growth**: Salam et al. (2005) assessed the effect of increasing O_3 concentrations on LBW in a population of infants born in California from 1975-1987. The authors reported that a positive association exists between an increase in O_3 concentrations and LBW over the entire pregnancy (mean 8-h O_3 concentration 50.6 ppb) with the association being the strongest in the 2nd and 3rd trimesters. Two studies performed in Canada (Dugandzic et al., 2006; Liu et al., 2007) and one study performed in California (Wilhelm et al., 2005) also analyzed the effect of O_3 on LBW/intrauterine growth restriction and did not detect an association between O_3 and LBW. The mean concentrations reported in these studies were 21 ppb daily (Dugandzic et al., 2006), 16.5 ppb daily (Liu et al., 2007), and 2.2 ppb (Wilhelm et al., 2005). One study performed in Vancouver, Canada reported an inverse association between O_3 and small-for-gestational age infants; however, the authors state that this was likely due to the high negative correlation between traffic-related air pollutants and O_3 (mean concentration 14 ppb) (Brauer et al., 2008).

- **Respiratory**: Triche et al. (2006) examined respiratory effects of O_3 in infants of asthmatic mothers. The authors found for every interquartile range (IQR) increase in 24-h average O_3 (mean concentration 35.2 ppb), infants of asthmatic mothers had a greater likelihood of wheeze and difficulty breathing compared to infants whose mother did not have asthma. An association was not observed for wheeze for an IQR increase in 8-h maximum or 1-h maximum O_3 concentrations (mean O_3 concentration 54.5 and 60.8 ppb, respectively). In addition, Dales et al. (2006) tested the association between daily neonatal respiratory hospitalizations and ambient O_3 concentrations in 11 large Canadian cities (mean daily concentration ranged by city from 16.4 to 23.1 ppb). The authors concluded current O_3 levels are responsible for a significant proportion of respiratory hospitalizations in neonates.

- **Mortality**: Two studies have reported no association between ambient levels of O_3 (Ritz et al.: mean O_3 concentration 22 ppb; Dales et al.: mean daily O_3 concentration ranged by city from 27.0 to 36.9 ppb) and sudden infant death syndrome (SIDS) (Dales et al., 2004; Ritz et al., 2006) or between O_3 and respiratory causes of postnatal death (Ritz et al., 2006). Another study found no association between O_3 exposure and deaths from respiratory causes; however, the researchers did detect a positive association between O_3 exposure (median O_3 concentration approximately 27 ppb) and deaths from SIDS (Woodruff et al., 2008).

- **Birth Defects**: Two studies have been conducted examining the relationship between O_3 exposure during pregnancy and birth defects. A recent study conducted in Atlanta, GA examined O_3 exposure during the third through seventh week of pregnancy and reported no association with risk of cardiovascular malformations (mean 8-h O_3 concentration excluding November through February ranged by 5-yr groups from 39.8 to 43.3 ppb) (Strickland et al., 2009). A study conducted in Texas (Gilboa et al., 2005) looked at a similar period of exposure but reported no association with most of the birth defects studied (O_3 concentration was studied using quartiles with the lowest representing <18 ppb and the highest representing ≥ 31 ppb). The authors found slightly elevated odds ratios for pulmonary artery and valve defects but the results were not statistically significant. Gilboa et al. (2005) also detected an inverse association between O_3 exposure and isolated ventricular septal defects.

In addition to prenatal and neonatal outcomes, Sokol et al. (2006) conducted a study in Los Angeles, CA to examine the association between air pollution and sperm quality and sperm count. The authors found increased levels of O_3 (mean daily concentration 21.7 ppb) were associated with a decrease in sperm quality. No association was detected between O_3 and sperm count.

3.2.5.Neurobehavioral Effects

The epidemiology section of the 2006 O_3 AQCD did not include a summary statement on the effect of O_3 on neurobehavioral effects because, although multiple toxicological studies have been performed examining the association between O_3 exposure (mean O_3 concentration 26.5 ppb) and neurobehavioral effects, there were no epidemiologic studies published at the time. Only one epidemiologic study has been conducted since then. Chen et al. (2009) utilized data from the NHANES III cohort to study the relationship between O_3 and neurobehavioral effects. The authors observed an association between annual exposure to O_3 and tests measuring coding ability and attention/short-term memory. There was no association between O_3 exposure and reaction time tests. The authors conclude that overall, there is a positive association between annual O_3 exposure and reduced performance on neurobehavioral tests.

3.3. Vulnerability or Susceptibility

Epidemiologic studies reviewed in the 2006 O_3 AQCD suggest that "exercising (moderate to high physical exertion) children and adolescents appear to demonstrate increased responsiveness to ambient concentrations of O_3 and may be more likely to experience O_3-induced health effects" (U.S. EPA, 2006). Since the 2006 O_3 AQCD, only one study in the U.S. or Canada has been identified that

examined the role of exercising and responsiveness to O_3. As previously discussed in the Short-term Respiratory Morbidity section (Section 3.1.2), high school athletes were examined before and after exercise but no association was found between O_3 levels (mean 1-h maximum O_3 concentration 71 ppb) and breath pH, an airway inflammation marker (Ferdinands et al., 2008). However, the study had a small sample size of only 16 participants.

Human clinical and epidemiologic studies analyzed in the 2006 O_3 AQCD demonstrated that "genetic polymorphisms for antioxidant enzymes and inflammatory genes (GSTM1, NQO1, and *Tnf-α*) may modulate the effect of O_3 exposure on pulmonary function and airway inflammation" (U.S. EPA, 2006). This provisional assessment identified three studies (Alexeeff et al., 2008; Chen et al., 2007b; Islam et al., 2009) along with two review papers (London 2007; McCunney 2005), which found that genetic polymorphisms in antioxidant genes can lead to a decrease in lung function upon exposure to O_3. (Islam et al.: mean 8-h O_3 concentration varied by community from 46.5 to 64.9 ppb; Chen et al.: mean 8-h O_3 concentration 37 ppb for males and 33 ppb for females; Alexeeff et al.: mean O_3 concentration 24.4 ppb).

4. TOXICOLOGICAL STUDIES

A survey of the peer-reviewed literature published since the 2006 O_3 AQCD has identified a number of recent toxicological studies of health effects related to O_3 exposure conducted at or below 1 ppm. Overall, the nearly 70 animal studies and 18 in vitro studies support and extend the findings of the most recent assessment. EPA's provisional assessment of these studies is summarized in the following sections for individual health outcomes in the context of the conclusions made in the 2006 O_3 AQCD.

4.1. Respiratory Tract Effects of Ozone

Based on the cumulative evidence from the animal and human studies, the 2006 O_3 AQCD concluded that acute O_3 exposure is causally associated with respiratory effects, including O_3-induced pulmonary function decrements, respiratory symptoms, lung inflammation, increased lung permeability, decreased host defenses against infectious lung disease, and airway hyperresponsiveness. More recent evidence in these areas is presented under the headings outlined in the 2006 document.

4.1.1.Biochemical Effects

Ozone has the potential to interact with a wide range of different cellular components, and the resulting reaction products may act downstream to mediate toxicity. A number of new studies examine the ability of O_3 to exert oxidative stress and modify biological molecules (or other pollutants as discussed in Section 4.3 below) (Doyle et al., 2007; Foucaud et al., 2006; Franze et al., 2005; Janic et al., 2005; Kafoury and Kelley, 2005; Stagos et al., 2007; Valavanidis et al., 2009). One of the major postulated molecular mechanisms of action of O_3 is peroxidation of fatty acids and lipids in the lung. The generation of oxidized lipids or lipoproteins is implicated in the pathogenesis of atherosclerosis and neurodegenerative diseases. Stewart et al. (2005) have shown O_3 treatment of low-density lipoproteins induces amyloid-like structures that are recognized by macrophages. Macrophages or similar cells containing these structures are a feature of both atherosclerotic and neurodegenerative plaques.

4.1.2.Effects on Immune Function

4.1.2.1. Lung Host Defenses

As described in the 2006 AQCD, O_3 causes complex changes in the immune system, skewing immune responses toward allergy while inhibiting responses required for defense against bacterial and viral infection. Cumulative findings from previous assessments of O_3 in models of infectious lung disease included increased mortality and morbidity, decreased pathogen clearance, increased bacterial growth, and increased severity of infection at exposure levels of 0.1-1 ppm. A few recent studies further illustrate impaired innate and acquired immune function after O_3 exposure in vitro and in vivo. In mice, O_3 exposure impaired natural killer cell activity, which is an innate defense against viral infection and tumors. Antigen-specific reactivity also decreased, indicating a weakening of the acquired immunity for subsequent memory responses (Feng et al., 2006). In vitro exposure to 0.03 ppm O_3 for five minutes significantly decreased macrophage-like cell mobility in response to pathogen-related chemotactic stimulation (Klestadt et al., 2005). O_3 mediated oxidation of surfactant proteins reduced their ability to enhance phagocytosis of both gram-positive and gram-negative bacteria by macrophages (Mikerov et al., 2008). In addition, reduced phagocytic capacity was observed in pulmonary macrophages recovered from O_3 exposed marine toads (Dohm et al., 2005).

4.1.2.2. Allergic Responses

Effects resulting from combined exposures to O_3 and allergens continue to be studied in a variety of animal species, generally as models of experimental asthma. When combined with NO_2, O_3 has been shown to enhance nitration of common protein allergens, which may increase their allergenicity (Franze et al., 2005). Five weeks of continuous exposure to 0.4 ppm O_3 (but not at 0.1 or 0.2 ppm O_3) augmented sneezing and nasal secretions in a guinea pig model of nasal allergy. Nasal eosinophils and allergic antibody levels in serum were also elevated by exposure to concentrations as low as 0.2 ppm (Iijima and Kobayashi, 2004). O_3 exposure enhanced eosinophil accumulation, along with IL-5 and IL-13, in allergic rats (Wagner et al., 2007). Long-term studies in infant monkeys demonstrated reduced airway eosinophils with allergen and O_3 compared to allergen alone, although hyperresponsiveness after the combined exposure was still evident (Joad et al., 2006). O_3 alone or combined with allergen increased lymphocyte frequency in peripheral blood and pulmonary lavage fluid. Exposure to O_3 and allergen altered the distribution of lymphocytes in the airways, but the implications of these results are not clear in the absence of further analysis of the lymphocyte population (Miller et al., 2009).

4.1.3.Inflammation and Lung Permeability Changes

The 2006 O_3 AQCD states that the extensive human clinical and animal toxicological evidence, together with the limited epidemiologic evidence available, suggests a causal role for O_3 in inflammatory responses in the airways. Numerous recent in vitro and in vivo studies add to these observations of O_3-induced inflammation and injury, and provide new information regarding the underlying mechanisms (Carey et al., 2007; Castagna et al., 2009; Cho et al., 2007; Dahl et al., 2007; Damera et al., 2009; Fakhrzadeh et al., 2008; Han et al., 2008; Huffman et al., 2006; Inoue et al., 2008; Jang et al., 2005; Janic et al., 2005; Johnston et al., 2005a, 2005b, 2006, 2007; Kenyon et al., 2006; Kooter et al., 2007; Manzer et al., 2006; Oslund et al., 2008; Oyarzun et al., 2005; Plopper et al., 2006; Servais et al., 2005; Vancza et al., 2009; Voynow et al., 2008; Wagner et al., 2007; Wang et al., 2007; Yoon et al., 2007). Protective roles have been identified for nitric oxide synthase (Kenyon et al., 2006), metallothionein (Inoue et al., 2008), matrix metalloproteinases (Yoon et al., 2007), Clara cell secretory protein (Plopper et al., 2006), and the recognition of oxidized lipids by alveolar macrophages (Dahl et al., 2007). The molecular mechanisms of TNF receptor mediated lung injury induced by O_3 and associated signaling pathways have been examined (Cho et al., 2007; Fakhrzadeh et al., 2008), along with the changes in gene expression which characterize O_3 induced stress and inflammation (Wang et al., 2007). Other contributors to injury and inflammation include the IL-1 and neurokinin receptors (Johnston et al., 2007; Oslund et al., 2008), and NQO1 (Voynow et al., 2008), an enzyme involved in oxidative stress. Studies indicate a role for oxidative stress in mediating inflammation (Jang et al., 2005; Wagner et al., 2007).

4.1.4.Morphological Effects

The 2006 O_3 AQCD reports the collective evidence from animal studies strongly suggests that chronic O_3 exposure causes damage leading to irreversible lung tissue remodeling. Compromised pulmonary function and structural changes due to persistent inflammation may exacerbate the progression and development of chronic lung disease, and may underlie the suggested association between seasonal O_3 exposure and reduced lung function development in children as observed in epidemiologic studies. Further evidence of these effects is provided by several new studies which expand on the findings of previously described studies in infant rhesus monkeys exposed episodically to 0.5 ppm O_3 alone or in combination with house dust mite antigen (HDMA) over 5 mo (Evans et al., 2004; Fanucchi et al., 2006; Kajekar et al., 2007). Two of these studies examined morphological changes after a 6 month recovery period. Kajekar et al. (2007) showed exposure to O_3 and/or HDMA resulted in hyperinnervation and abnormal nerve distribution in pulmonary airways consistent with that found in asthmatic lungs. O_3 exposure alone resulted in these effects, more so than HDMA alone but not to the same extent as O_3 and HDMA combined. Evans et al. (2004)

demonstrated thickening of the basement membrane zone these monkeys immediately following exposure to O_3 alone compared to filtered air. When O_3 was combined with HDMA, the basement membrane zone exhibited atypical development. After a recovery period with intermittent allergen challenge in the absence of O_3 this atypical appearance resolved, but thickening was significantly greater than that observed after filtered air exposure. In allergic rats, O_3 exposure resulted in thickening of the walls of the terminal bronchioles and proximal alveolar ducts (Wagner et al., 2007).

4.1.5.Effects on Pulmonary Function

Pulmonary function decrements occur in a number of species with acute exposures (≤ 1 week) ranging from 0.25 to 0.4 ppm O_3. Similar to humans, lung function responses in rodents become attenuated with repeated daily exposures. The 2006 O_3 AQCD did not specifically discuss pulmonary function effects from chronic O_3 exposure. The 1996 O_3 AQCD characterized these effects as difficult to summarize; ranging from none or minimal, to obstructive, or restrictive lung function abnormalities. In the few cases where recovery was evaluated, physiological alterations resolved over several months post O_3 exposure. Information published more recently adds to the evidence of ventilation defects induced by acute or subchronic exposure (Cremillieux et al., 2008), but only one study in mice chronically exposed to a high (1 ppm) level of O_3 was identified (Funabashi et al., 2004). In this study, O_3 alone had little effect on baseline pulmonary function parameters after 5 wk of exposure (6 h/day, 5 days/wk). However, significantly increased respiratory resistance and decreased dynamic compliance were observed during O_3 exposure in allergic mice, consistent with other studies indicating that preexisting allergic disease confers susceptibility.

The 2006 O_3 AQCD concluded that evidence from human clinical and animal toxicological studies clearly indicates that acute exposure to O_3 can induce airway hyperresponsiveness (AHR). A number of new studies build upon previous findings (Joad et al., 2006; Johnston et al., 2005a; Lotriet et al., 2007; Pichavant et al., 2008; Voynow et al., 2008), including a study by Jang et al. (2005) demonstrating significantly increased AHR in mice after a three hour exposure to 0.12 ppm O_3. This study is notable in that AHR is observed in a non-allergic animal model at a level considerably lower than previously reported. As in the 2006 O_3 AQCD, AHR with repeated or subchronic exposures is not as evident, especially at lower levels. In a recent study by Johnston et al. (2005b), 3 h but not 72 h of exposure to 0.3 ppm O_3 induced AHR in mice.

4.1.6.Genotoxicity Potential of Ozone

The 2006 O_3 AQCD concluded that the weight of evidence from the new experimental animal studies (using non-lifetime exposures) does not support ambient O_3 as being a pulmonary

carcinogen. One or two studies since then have observed O_3-induced DNA damage, but as an indicator of oxidative stress rather than carcinogenicity (Chuang et al., 2009; Servais et al., 2005).

4.2. Systemic Effects of Ozone Exposure

Ozone indirectly affects extrapulmonary sites through a number of proposed mechanisms, including subsequent reactions induced by soluble mediators (induced or produced by O_3) or cell trafficking. More recent evidence of systemic effects is presented under the individual headings outlined in the 2006 document.

4.2.1.Neurobehavioral Effects

The 2006 O_3 AQCD included evidence that acute exposures to O_3 are associated with alterations in neurotransmitters, motor activity, short and long term memory, and sleep patterns. Additionally, histological signs of neurodegeneration have been observed. Research in the area of O_3-induced neurotoxicity has notably increased over the past few years. A number of new studies demonstrate various perturbations in neurologic function or histology, including changes consistent with Parkinson's and Alzheimer's disease pathologies. Oxidative stress has been proposed as a major contributor to premature death of substantia nigra dopamine neurons in Parkinson's disease. Angoa-Pérez et al. (2006) have shown lipoperoxidation in the substantia nigra and a decrease in nigral dopamine neurons in rats exposed to 0.25 ppm, 4h/day, for 7, 15, 30, or 60 days. Estrogen attenuated O_3-induced oxidative stress and nigral neuronal death, consistent with the higher incidence of Parkinson's disease in men and the amelioration of Parkinsonian symptoms by estrogen therapy. Martínez-Canabal et al. (2008) showed exposure of rats to 0.25 ppm, 4h/day, for 7, 15, or 30 days increased lipoperoxides in the hippocampus, a region of the brain which is important for higher cognitive function including memory acquisition. This effect was observed at day 7 and continued to increase with time, indicating cumulative oxidative damage. The study also observed a loss of neurons and increased expression of COX-2, which has a role in neurodegenerative disease and is observed in the tissues of Alzheimer's patients. Consistent with Alzheimer's incidence in the elderly, the administration of growth hormone was protective.

Other neurobehavioral observations include disruption of the sleep-wake cycle (Alfaro-Rodriguez and Gonzalez-Pina, 2005), overexpression of injury repair factors in the brain (Araneda et al., 2008), altered cerebral reactivity to stress (Boussouar et al., 2009), inflammation and oxidative stress in brain tissues (Calderon-Garciduenas et al., 2007; Calderon Guzman et al., 2005; Calderon Guzman et al., 2006; Colin-Barenque et al., 2005; Escalante-Membrillo et al., 2005; Guevara-Guzman et al., 2009; Pereyra-Munoz et al., 2006), altered neurotransmitter levels (Gonzalez-Pina et al., 2008; Soulage et al., 2004), impaired olfactory perception and memory (Guevara-Guzman

et al., 2009), increased defensive/submissive behavior and reduced social investigation (Santucci et al., 2006), and altered vasoregulatory markers in the brain, indicating potential cerebrovascular effects (Thomson et al., 2007).

4.2.2.Neuroendocrine Effects

No recent studies have become available to add to the limited evidence regarding neuroendocrine effects presented in the 2006 assessment.

4.2.3.Cardiovascular Effects

It was concluded in the 2006 O_3 AQCD that the generally limited body of evidence was highly suggestive that O_3 directly and/or indirectly contributes to cardiovascular-related morbidity. Five new in vivo studies have been identified which show adverse cardiovascular effects of O_3, either alone or in combination with particles (Chuang et al., 2009; Hamade et al., 2008; Hamade and Tankersley, 2009; Thomson et al., 2005, 2006). A recent study by Chuang et al. (2009) demonstrated vascular mitochondrial damage in infant macaque monkeys after acute exposure to 0.5 ppm O_3 (8 h/day for 5 days) and general vascular dysfunction in mice exposed from 6-14 wk of age (0.5 ppm, 8 h/day, 5 days/wk). In apoE -/- mice, this cyclic intermittent exposure resulted in significantly increased atherogenesis.

4.2.4.Reproductive and Developmental Effects

Very few reproductive or developmental effects at low O_3 levels were evident at the time of the 2006 O_3 AQCD. Since then, a few additional studies of developmental outcomes have been identified, predominantly in the area of neurobehavioral development. Santucci et al. (2006) demonstrated behavioral alterations in male mice born to dams exposed continuously to 0.3 or 0.6 ppm O_3 from 30 days prior to breeding through gestational day (GD)17. Gestational rat lung development was altered by acute exposure to 1 ppm O_3 (Lopez et al. 2008). Gonzalez-Pina et al. (2008) showed disruptions in the cerebellar catecholamine system of male rats born to dams exposed to 1 ppm O_3 throughout pregnancy, and changes suggestive of disrupted neuronal plasticity were observed in rats exposed gestationally to 0.5 ppm O_3 from GD5-GD20 (Boussouar et al. 2009).

4.2.5.Effects on the Liver, Spleen, and Thymus

According to the 2006 O_3 AQCD, most effects on the liver (NO production, protein synthesis) and thymus (shrinkage, altered T cell mediated systemic immunity) occur only with high (1-2 ppm) O_3 exposures. Low levels (0.1 ppm) affect xenobiotic metabolism by the liver but this is species specific. Only one additional study, conducted at a high 1 ppm O_3 exposure, has been identified (Last

et al., 2005) in which alterations in gene expression underlying O_3-induced cachexia and downregulation of xenobiotic metabolism were examined.

4.2.6.Effects on Cutaneous and Ocular Tissues

The 2006 O_3 AQCD reported that although there is evidence of oxidative stress at near ambient O_3 levels, skin and eyes are only affected at high concentrations (greater than 1-5 ppm). A recent study demonstrated that 0.25 ppm O_3 differentially alters expression of metalloproteinases in the skin of young and aged mice, indicating age-related susceptibility to oxidative stress (Fortino et al., 2007).

4.3. Interactions of Ozone with Other Co-Occurring Pollutants

The importance of considering the contributions of O_3 interactions with other co-occurring air pollutants to health effects due to O_3 containing pollutant mixes was highlighted in the 2006 O_3 AQCD. The interaction of O_3 with PM has been an area of continued focus since the 2006 O_3 AQCD, which concluded that O_3 may enhance PM formation and particle uptake, modify the biological potency of certain types of ambient PM, and exacerbate PM-induced cardiovascular effects. Approximately ten additional studies have investigated O_3-PM interactions and combined exposure effects. An in vitro study by Valavanidis et al. (2009) demonstrated that O_3 substantially increases the reactive oxygen species generating capacity of various samples of traffic-related PM, particularly smaller particles (ambient PM_{10} and $PM_{2.5}$, lab-generated diesel and gasoline exhaust particles were tested). In rats, the effects of combined particle and O_3 exposures on production of vasoactive endothelin peptides are mixed and may be additive or antagonistic depending on the particular endothelin or tissue being examined (Thomson et al., 2005, 2006, 2007). Synergistic toxicological effects between the copollutants O_3 and 1-Nitronaphthalene (1-NN) have been observed in the rat lung (Schmelzer et al., 2006; Wheelock et al., 2005), whereas a subsequent study showed that pre-exposure to O_3 actually protected against 1-NN mediated damage in certain areas of the nose, particularly those in which O_3 had caused goblet cell metaplasia and mild hyperplasia (Lee et al., 2008).

4.4. Susceptible and Vulnerable Populations

Information concerning susceptibility and vulnerability gleaned from toxicological studies is distributed throughout Chapters 4 and 5 in the 2006 O_3 AQCD, which concluded that genetic factors,

age, gender, pregnancy, preexisting pulmonary disease (allergic or otherwise), and copollutant exposures can all contribute to susceptibility. More recent studies continue to show that a preexisting asthmatic phenotype confers susceptibility to O_3 in animals (Funabashi et al., 2004; Wagner et al., 2007), as do preexisting fibrotic lung disease and hyperthyroidism (Huffman et al., 2006; Oyarzun et al., 2005). New studies also support previous findings of greater susceptibility in immature and senescent animals. Susceptible genotypes previously identified in humans have been examined in two recent studies in mice. Voynow et al. (2008) have shown that NAD(P)H quinone oxidoreductase 1 (NQO1) deficient mice, like their human counterparts, are resistant to O_3 induced AHR and inflammation. In humans, an association between inflammatory conditions including asthma and increased *TNF-α* production due to a TNF polymorphism has been observed. The role of *TNF-α* in O_3-induced responses has been previously established through depletion experiments, but a more recent study investigated the effects of combined O_3 and PM exposure in transgenic TNF overexpressing mice. Kumarathasan et al. (2005) found that subtle effects of these pollutants were difficult to identify in the midst of the severe pathological changes caused by constitutive *TNF-α* overexpression. However, there was evidence that TNF transgenic mice were more susceptible to O_3/PM-induced oxidative stress, and they exhibited elevation of a serum creatine kinase after pollutant exposure, which may suggest potential systemic or cardiac related effects.

5. ECOLOGICAL AND VEGETATION STUDIES

Numerous studies of the effects of O_3 on vegetation and ecosystems were reviewed in the 2006 O_3 AQCD. That document concluded that the effects of O_3 on vegetation and ecosystems appear to be widespread across the US, and experimental studies demonstrated plausible mechanisms for these effects. Many exposure studies were conducted at the species level, in field chambers. However, there were emerging studies at larger-scales, including ecosystem levels, which supported the results of the field chamber studies. The 2006 O_3 AQCD also concluded O_3 effects in plants are cumulative and metrics that accumulate hourly O_3 concentrations while positively weighting the higher concentrations have a better statistical fit to growth and yield response than do mean or peak indices.

EPA has surveyed and screened the recent vegetation and ecological literature and identified a number of studies on effects associated with O_3 exposure that were published since the 2006 O_3 AQCD. This provisional assessment is limited to studies of vegetation and ecosystems that occur in the US and report endpoints most relevant to the review of the secondary standard. The following section summarizes the results of the provisional review for a range of issues related to the effect of O_3 on vegetation and ecosystems.

5.1. Meta-Analyses of Vegetation Effects

Recently published meta-analyses have quantitatively compiled peer reviewed studies from the past 40 yr on the effect of current and future O_3 exposures on the physiology and growth of forest and crop species (Feng et al., 2008; Wittig et al., 2007; Wittig et al., 2008). In compiling more than 55 studies, Wittig et al. (2007) reported that current O_3 concentrations in the northern hemisphere are decreasing photosynthesis (-11%) and stomatal conductance (-13%) across tree species. They also found that younger trees (<4 yr) were affected less by O_3 than older trees. Further, the authors also found that damage to photosynthesis is consistent with the cumulative uptake of O_3 into the leaf (Wittig et al., 2007). In another meta-analysis, Wittig et al. (2008) reported that current ambient O_3 concentrations (~40ppb) significantly decreased annual total biomass growth (-7%) across 263 studies. However, this effect could be greater (-11 to -17%) in areas that have higher O_3 concentrations and as background O_3 increases in the future (Wittig et al., 2008). In a meta-analysis of 52 studies of wheat, Feng et al. (2008) reported that current ambient O_3 concentrations may be decreasing yield by an average of 17.5%. The authors also found that O_3-induced decreases in yield

were greater in wheat grown in the field than grown in the in pots. Together these meta-analyses demonstrate the coherence of O_3 effects across numerous studies and species using a variety of experimental techniques.

5.2. Field Studies of Forest Ecosystems

Two companion papers (McLaughlin et al., 2007a, 2007b) investigated the effects of ambient O_3 on tree growth and hydrology at forest sites in the southern Appalachian Mountains. The authors reported the cumulative effects of ambient levels of O_3 decreased seasonal stem growth by 30-50% for most trees species in a high O_3 year in comparison to a low O_3 year (McLaughlin et al., 2007a). The authors also report that high ambient O_3 concentrations can disrupt whole tree water use and in turn reduce late-season stream-flow (McLaughlin et al., 2007b). The finding that O_3 exposures disrupt tree water use is consistent with several recent studies that report O_3 exposure resulting in loss of stomatal control, incomplete stomatal closure at night and a decoupling of photosynthesis and stomatal conductance (Gregg et al., 2006; Grulke et al., 2007a, 2007b).

Since the 2006 O_3 AQCD several new studies were published based on the Aspen FACE "free air" O_3 and carbon dioxide exposure experiment in a forest in Wisconsin (Darbah et al., 2007, 2008; Hillstrom and Lindroth, 2008; Kubiske et al., 2006a, 2006b; Liu et al., 2007; Percy et al., 2007; Zak et al., 2007). Kubiske et al. (2006b) reported that elevated O_3 may change the intra- and inter-species competition. For example, O_3 treatments increased the rate of conversion from a mixed aspen-birch community to a birch dominated community. Darbah et al. (2007, 2008) reported that O_3 treatments decreased paper birch seed weight and seed germination and that this would likely lead to a negative impact of regeneration for that species. Hillstrom and Lindroth (2008) found that elevated O_3 treatments significantly affected insect community composition. In another study at this site, Percy et al. (2007) showed that negative growth effects were seen below the previous 8-h O_3 standard level of 0.084 ppm. The authors also attempted to compare different O_3 metrics to predict effects on tree growth by using trees repeatedly measured over 5 yr. The authors suggested that 4th highest maximum metric was a strong predictor of effects, but they did not include the 3-mo 12-h W126 in their analysis. Overall, the studies at the Aspen FACE experiment are consistent with many of the open-top chamber studies that were the foundation of previous O_3 NAAQS reviews. These results strengthen our understanding of O_3 effects on forests and demonstrate the relevance of the knowledge gained from trees grown in open-top chamber studies.

5.3. Visible Foliar Injury

Several new studies have been published on the incidence of foliar injury in the field due to ambient O_3 concentrations (Campbell et al., 2007; Chappelka et al., 2007; Davis, 2007a, 2007b; Davis and Orendovici, 2006; Kohut, 2007). Kohut (2007) presented a foliar injury assessment for 244 National parks over 5 yr. The author reported that risk of foliar injury was high in 65 parks, moderate in 46 parks, and low in 131 parks. Chappelka et al. (2007) reported that the average incidence of O_3-induced foliar injury was 73% on milkweed in the Great Smokey Mountain National Park in the years 1992-1996. Three papers (Davis, 2007a, 2007b; Davis and Orendovici, 2006) reported O_3-induced foliar injury in several plants species in National Wildlife Refuges in Maine, Michigan and New Jersey. In a study of the west coast of the U.S, Campbell et al. (2007) reported ozone injury in 25-37% of biosites in California forested ecosystems from 2000-2005.

5.4. Agricultural Crops

The effect of O_3 on crop health and productivity is an important area of research, and several studies have been published on this topic since the 2006 AQCD. For example, in a study of peanuts in North Carolina, near ambient and elevated exposures of O_3 reduced photosynthesis and yield compared to very low O_3 conditions (Burkey et al., 2007; Booker et al., 2007). In another study, Grantz and Vu (2009) reported that sugarcane biomass growth significantly declined under O_3 exposure. This result is important because sugarcane is being considered as a bioenergy crop to be grown in the San Joaquin Valley of California, an area with high levels of ambient O_3.

5.5. Carbon Sequestration

In a large-scale modeling analysis, Sitch et al. (2007) suggested that increasing ambient O_3 concentrations across the globe suppress the land carbon sink due to decreased plant productivity. A consequence of the diminishing carbon sink would be increased CO_2 accumulation in the atmosphere. The authors suggest that the radiative forcing of this extra CO_2 is greater than the direct radiative forcing of O_3 as a greenhouse gas alone.

Another modeling study considered how the changes in climate, CO_2 concentration and O_3 pollution have affected carbon storage in the Great Smokey Mountain National Park in the years 1971-2001 (Zhang et al., 2007). The authors reported that rising CO_2 concentrations had significantly stimulated carbon storage, but ambient O_3 concentrations reduced the potential carbon storage by approximately 50%.

6. SUMMARY

EPA emphasizes that this is a provisional evaluation of the recent literature, and it is not intended to serve as a supplement to the 2006 O_3 AQCD. This summary of recent studies has not undergone the detailed and extensive review process entailed in the development of a Criteria Document or Integrated Science Assessment, and it has not been reviewed by CASAC.

Overall, the recent study results support and expand upon findings in the 2006 O_3 AQCD; these results do not materially change any of the broad scientific conclusions regarding the health effects of O_3 exposure made in the 2006 O_3 AQCD. Briefly:

Recent controlled human exposure studies strengthen evidence for lung function decrements in healthy young adults during exposures to O_3 concentrations below 80 ppb.

The epidemiologic evidence from recent publications provides further evidence that short-term exposure to O_3 is associated with effects on the respiratory system, and also report associations with mortality.

Many new toxicological studies are available on respiratory or allergic effects; in addition, some have suggested systemic effects of O_3 on the cardiovascular or neurological systems.

New ecological analyses expand the already large body of evidence indicating that O_3 exposure causes injury to plants.

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