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Recommendation for an Ambient Air Quality Standard for Ozone

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California Environmental Protection Agency

The energy challenge facing California is real. Every Californian needs to take immediate action to reduce energy consumption.

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7. OEHHA Recommendation for Standard

This chapter presents the OEHHA recommendations for ozone ambient air quality standards (AAQSs) for California for the Board's consideration. The section begins with findings on the overall adequacy of the current standards for ozone with respect to protecting the health of the public, including infants and children. It continues with recommendations for the pollution indicators, averaging times, forms, and concentrations adequate to protect public health.

The recommended concentrations for the ozone standard should be based on scientific information about the health risks associated with ozone, recognizing the uncertainties in these data. With this in mind, the numerous human chamber and epidemiologic studies of ozone-associated morbidity and mortality indicate that, within the concentration ranges reported, there is no identified "bright line" or threshold ozone concentration below which health effects would not occur in at least some individuals. However, the Children's Environmental Health Protection Act [Senate Bill 25, Escutia; Stats. 1999, Ch. 731, specifically California Health & Safety Code Section 39606(d)(2)] requires a standard that "adequately protects the health of the public, including infants and children, with an adequate margin of safety." In the development of standards, SB25 called for, to the extent that information is available, that the following information be assessed:

1. Exposure patterns among infants and children that are likely to result in disproportionately high exposures relative to the general population

2. Special susceptibility of infants and children to ambient air pollution relative to the general population

3. The effects on infants and children of exposure to ambient air pollution and other substances that have common mechanisms of toxicity

4. The interaction of multiple air pollutants on infants and children, including between criteria air pollutants and toxic air contaminants.

The governing statutory language indicates that California's ambient air quality standards should also protect other vulnerable populations, in addition to infants and children, and the general public [(H&SC sections 39606(d)(2) and 39606(d)(3)]. This legislative directive is consistent with historical practice in California, where ambient air quality standards have been formulated to protect identifiable susceptible subgroups, as well as the general population. For instance, the one-hour sulfur dioxide standard was developed in order to protect the most sensitive recognized subgroup, exercising asthmatics. Nonetheless, even with standards tailored to shield vulnerable populations, there may be exquisitely sensitive individuals remaining outside the ambit of protection.

Although both the California Health & Safety Code (section 39606) and the federal Clean Air Act (section 109) refer to an adequate margin of safety, no specific legislative definition of “adequate” is provided. This judgment is left to the responsible regulatory agencies. As described in the preceding chapters, data from controlled exposure studies demonstrate that some individuals experience ozone-associated toxicity at relatively low concentrations, while several epidemiologic studies suggest a fairly linear relationships between adverse health outcomes and ambient ozone concentrations, with no clear demarcation of a “threshold” level of ozone exposure below which no adverse health effects would ever be expected to occur. The incorporation of a safety margin has been recognized by the California Supreme Court as integral to the process of promulgating ambient air quality standards [Western Oil and Gas Association v. Air Resources Board, 22 ERC 1178, 1184 (1984)]. To the extent that health effects associated with ambient ozone occur at low levels of exposure, and that there is substantial inter-individual variability in response to environmental insults, it is unlikely that any ozone standard will provide universal protection for every individual against all possible ozone-related effects. Thus, in this instance, applying the notion of an “adequate margin of safety” for ozone standards becomes somewhat challenging. Nevertheless, taking into account the limitations of the scientific data, we have operationalized the concept of an adequate margin of safety by recommending standards that, when attained, should protect nearly all of the California population, including infants and children, against ozone-associated effects throughout the year.

The Children’s Environmental Health Protection Act required the ARB and OEHHA to review all health-based ambient air quality standards to determine whether the standards were protective of the health of the public, including infants and children, with an adequate margin of safety. The Act also required that, depending on the outcome of these reviews, the various ambient air quality standards be prioritized for full review and possible revision. Five factors were considered in assessing the health protectiveness of each ambient air quality standard during the prioritization process:

1) The extent of the evidence of effects reported to occur at or near the existing ambient air quality standard.
2) The nature and severity of those effects.
3) The magnitude of risk of effects anticipated when ambient (outdoor) levels are at or near the level of the existing standard.
4) Any evidence indicating that children may be more susceptible to effects than adults.
5) The degree of outdoor exposure in California relative to the level of the standard.

Following these reviews, the various ambient air quality standards were prioritized for full review (California Air Resources Board and Office of Environmental Health Hazard Assessment 2000). The standard for ozone was prioritized to undergo full review after the standards for particulate matter and sulfates. The SB25 review found that several clinical and epidemiological studies suggested effects of ozone exposure on lung

function, asthma exacerbation, and other indices of acute respiratory morbidity in children and adults at concentrations at or below that of the current State standard of 0.09 ppm, averaged over one hour. Such evidence could indicate the need for a more stringent standard, an averaging time different from the current one-hour average, or both.

7.1 Defining an Adverse Effect

A key issue in evaluating the public health consequences of ozone exposure is consideration of the definition of an “adverse health effect”. The term “adverse health effect” is incorporated in the legislative background of the Federal Clean Air Act, as well as the California Health and Safety Code, although neither provides a definition for the term. Because it is helpful to the standard review process to consider the available scientific literature in the context of guidelines as to what is meant by the term, we have used guidelines published by the Scientific Assembly for Environmental and Occupational Health of the American Thoracic Society, which developed the most commonly used guidelines in the US (American Thoracic Society 1985; American Thoracic Society 2000)). Both USEPA and ARB have referred to these guidelines over the intervening years in assessing the significance of pollutant-associated physiological, biological or pathological changes.

It is important to keep in mind the differences between statistical significance and medical or biological significance when considering what constitutes an adverse health effect. The 1985 ATS statement defined “adverse respiratory health effects” as medically significant physiologic or pathologic changes generally evidenced by one or more of the following: (1) interference with the normal activity of the affected person or persons, (2) episodic respiratory illness, (3) incapacitating illness, (4) permanent respiratory injury, and/or, (5) progressive respiratory dysfunction. The 2000 ATS statement expanded on the 1985 statement to include consideration of biomarkers, quality of life, physiological impact, symptoms, clinical outcomes, mortality, and population health versus individual risk when evaluating whether or not a change should be designated as an adverse health effect. The 2000 ATS review committee’s recommendations are summarized here:

1. *Biomarkers:* These should be considered, however it must be kept in mind that few biomarkers have been validated sufficiently to establish their use for defining a point at which a response becomes adverse, consequently, not all changes in biomarkers should necessarily be considered adverse.
2. *Quality of life*: In recent years, decreased health-related quality of life has become widely accepted as an adverse health effect. The review committee concluded that reduction in quality of life, whether in healthy persons or persons with chronic respiratory disease, should be considered as an adverse effect.
3. *Physiological impact*: The committee recommended that small, transient reductions in pulmonary function should not necessarily be regarded as adverse, although

permanent loss of lung function should be considered adverse. The committee also recommended that reversible loss of lung function in conjunction with symptoms should be considered adverse.

4. *Symptoms*: Air pollution-related symptoms associated with reduced quality of life or with a change in clinical status (i.e., requiring medical care or a change in medications) should be considered adverse at the individual level. At the population level, the committee suggested that any detectable increase in symptom frequency should be considered adverse.
5. *Clinical outcomes:* Detectable effects of air pollution on clinical measures should be considered adverse. More specifically, the ATS committee cited as examples increases in emergency department visits for asthma or hospitalizations for pneumonia, at the population level, or an increased need to use bronchodilator medication, at the individual level. The committee recommended that: "no level of effect of air pollution on population-level clinical indicators can be considered acceptable."
6. *Mortality:* Increased mortality should clearly be judged as adverse.
7. *Population health versus individual risk*: The committee concluded that a shift in risk factor distribution, and hence the risk profile of an exposed population, should be considered adverse when the relationship between the risk factor and the disease is causal, even if there is no immediate occurrence of obvious illness.

Based on these recommendations, many health outcomes found to be associated with ozone could be considered adverse including pulmonary function changes accompanied by symptoms, pulmonary function changes and respiratory symptoms that reduce quality of life, large changes in pulmonary function, clinical outcomes such as emergency department visits for asthma, hospitalization for respiratory and cardiovascular disease, and mortality. In additions, outcomes such as increase in airway reactivity and inflammation may be considered adverse if they signify increases in the potential risk profile of the population.

7.2 Summary of the Scientific Evidence

7.2.1. Summary of Findings from Chamber Studies

7.2.1.1. Exposure protocol and effective dose

Acute respiratory responses to inhaled ozone are roughly proportional to the "effective dose" (ED) of inhaled ozone. ED is defined as the simple product of ozone concentration, ventilation rate and duration of exposure. The concept has been refined to indicate that ozone concentration is the most significant of the three factors, explaining the largest share of the variance in responses. Ventilation rate explained the

second largest portion, followed by exposure duration. Subsequent investigations revealed that increased ventilation rate accentuated the observed pulmonary response at any given ozone concentration, and lowered the minimum ozone concentration at which significant pulmonary responses were evident. Further, there is a positive correlation between ozone concentration and the rate at which adverse responses develop: the higher the ozone concentration, the more rapidly adverse effects become apparent. Consequently, a large number of exposure scenarios, based on varied ozone concentrations, ventilation rates, and durations, could be developed that are likely to induce adverse health effects. An exposure scenario that has been used repeatedly in chamber studies over the last decade, involves multi-hour exposure durations of 6.6 to 8 hours to a constant level of ozone.

Ozone concentrations are highest outdoors, since there are few indoor sources of ozone, with varying penetration (20 to 80%) to indoor environments. Greater penetration occurs with open windows and doors and in the absence of air conditioning. Consequently, individuals at greatest risk of experiencing adverse health consequences from ozone exposure are those who spend prolonged periods of time outdoors while participating in activities that increase the breathing rate. This group is comprised primarily of children, outdoor workers and recreational and professional athletes. Thus, in order to emulate these likely exposure patterns, participants in most chamber studies have included healthy, exercising young adults (ages approximately 18 to 35) as part of the experimental protocol.

At this time, the susceptibility of certain subgroups, such as asthmatics, although not clearly demonstrated in experimental settings, can be inferred from results of both chamber studies and epidemiological studies. The range of responses to ozone exposure in people with compromised health status is largely unknown, although there is a growing body of literature addressing the responses of mild to moderate asthmatics. At near-ambient ozone concentrations, the asthmatics studied have typically had changes in symptoms and lung function in the same ranges as nonasthmatics. However, some studies have shown that asthmatics have experienced larger increases in airway reactivity and inflammation than healthy, nonasthmatic people. These ozone-associated changes are superimposed on pre-existing chronic airway inflammation and elevated airway responsiveness that are hallmarks of asthma. Furthermore, significant decrements in FEV1 in an asthmatic would lead to increased medication use including inhaled steroids (National Asthma Education and Prevention Program 2002). This would qualify as an adverse effect based on ATS and suggests that asthmatics may represent a sensitive subpopulation for ozone.

Because of ethical and major logistical considerations, there are few studies of individuals with cardiovascular disease or COPD. However, since seriously impaired individuals are unlikely to spend significant periods of time outdoors working or exercising, their response to ozone is unlikely to be well characterized in the multi-hour chamber studies. (However, some epidemiological studies are likely to include these potentially sensitive individuals.) Therefore, the findings derived from the clinical

literature are likely representative of people who are physically able to perform moderate exertion for several hours, and by extension, likely to experience the greatest ozone exposures from active outdoor work or play for multi-hour periods.

7.2.1.2. Changes in Pulmonary Function

Collectively, the available literature exploring the responses of primarily healthy, young human subjects exposed to controlled concentrations of ozone indicates that one- to three-hr exposures to ozone concentrations as low as 0.12 ppm with moderate to heavy exercise can induce decrements in pulmonary function and increases in respiratory symptoms for some subjects. Statistically significant group mean decrements in lung function have been reported at ozone concentrations of 0.12 ppm, but there are no studies that show group mean differences below this level. For example, Horstman et al. (1990) and McDonnell et al. (1991) reported no statistically significant change in FEV_1 after a 1-hour exposure to 0.10 ppm (as part of a multi-hour exposure). The group mean responses with short exposures to 0.12 ppm ozone have been relatively small – about a 3 to 5 percent decrement in FEV_1. However, the studies at 0.12 indicate that some individuals responded with large reductions in lung function. For example, as reported by McDonnell et al. (1983), McDonnell et al. (1985b) and Gong et al. (1986), the maximum individual decrements were 16, 21, and 29%, respectively.

These results illustrate that, in the controlled exposure studies, a modest to moderate percentage of volunteer subjects experience decrements in lung function (often accompanied by increases in symptoms) that are markedly greater than the rest of the study populations (McDonnell et al. 1983; McDonnell et al. 1991). While the notion of ozone “responders” and “nonresponders” has existed for many years, the constitutional factors that determine such responsiveness are largely unknown, except that increasing age among adults is associated with decreasing functional and symptomatic responses to ozone. Repeated exposures of the same individuals at intervals of up to a year or more indicate that ozone responsiveness is an intrinsic individual characteristic, which is likely related to genetic polymorphisms, possibly those involved in anti-oxidant defenses. In the 1987 review of the ozone standard, the Department of Health Services stated that such responders, although they could not yet be identified a priori, represented a subpopulation warranting protection by the ozone AAQS (California Department of Health Services 1987)

Concern about the impacts of longer averaging times led to studies in healthy adults who performed a protocol simulating a day of active outdoor work or play. These studies demonstrate that statistically significant group mean decrements in FEV1 occur at 6.6 to 8-hour ozone concentrations as low as 0.08 ppm. The importance of multi-hour exposures was discussed in the review of the chamber studies, which clearly indicate an increasing response after the third hour of exposure. Except for one unpublished study, ozone concentrations between 0.04 and 0.08 ppm have not been investigated with multi-hour exposure protocols. Although the group mean effect on FEV_1 is relatively small in these studies of multi-hour exposures at 0.08 ppm (from approximately 2 to 8%

with a median decrement of 3.5%), the evidence indicates that some individuals experience large changes. For example, as indicated by Folinsbee et al. (1991), 26% of the subjects had FEV1 decrements greater than 10% while about 10% had decrements greater than 30%. These data demonstrate that significant lung function decrements coupled with increased reporting of symptoms such as cough or pain upon deep inspiration can occur in certain individuals when they undergo multi-hour exposures to 0.08 ppm ozone. Thus, based on the recommendations of ATS, these outcomes should be labeled as adverse. In addition, further decrements in those with already compromised lung function, such as asthmatics, should be considered adverse. Finally, Adams (1998) tested 30 subjects at 6.6 hours exposure to 0.06 ppm. At this concentration, the changes in FEV_1 or symptoms were not statistically different relative to clean air, though some differences in group response were observed. However, five of the 30 subjects had FEV_1 decrements greater than 10%. The paper did not report whether these same individuals experienced symptoms or not so it is not clear whether these outcomes should be labeled as adverse, based on ATS recommendations.

7.2.1.3. Symptoms

Significantly increased symptoms of respiratory irritation have been reported with 1 to 3 hr exposures with moderate exercise at ozone concentrations as low as 0.12 ppm in healthy adults. Specifically, McDonnell et al. (1983) reported associations with cough at 0.12 ppm, and with shortness of breath and pain upon deep inspiration at 0.24 ppm, while Seal et al. (1993) reported increased cough at 0.18 ppm, but not lower. At 6.6 hours of exposure to 0.08 ppm ozone with moderate exercise, increases in cough, shortness of breath and pain on deep breath (McDonnell et al. 1991) and increases in total symptom score (but not pain on deep breath) (Adams 2002) were reported.

7.2.1.4. Nonspecific Airway Responsiveness

Increased nonspecific airway responsiveness, referring to the tendency of the airways to constrict in reaction to exposure to irritant chemicals, pharmaceutical spasmogens, or physical stimuli such as cold air, has been reported with one- to three- hr exposures to 0.40, but not 0.20 ppm ozone at rest. The lowest short-term ozone concentration at which an increase in nonspecific airway responsiveness has been reported in exercising subjects is 0.18 ppm, but there was no change at 0.12 ppm compared to FA exposure. Exposures to ozone concentrations as low as 0.08 ppm for 6.6 hr can increase nonspecific airway hyperresponsiveness.

7.2.1.5. Airway Inflammation

Increased levels of cellular (i.e., neutrophils) and various biochemical (i.e., lactate dehydrogenase and other proteins) indicators of airway inflammation have been observed following 1 to 3 hr exposures of healthy adults to 0.20, 0.30 and 0.40 ppm ozone with heavy exercise. There are no studies that have investigated airway

inflammation after 1 to 3 hr exposures at ozone concentrations lower than 0.20 ppm. Analysis of BALF after 6.6-hr exposures with moderate exercise to 0.08 and 0.10 ppm ozone has demonstrated both cellular and biochemical evidence for airway inflammation. Possible inflammatory effects of ozone concentrations lower than 0.08 ppm for 6.6 hr or longer have not been investigated.

Exposure to 0.08 ppm ozone for 6.6 hours decreases the ability of alveolar macrophages to phagocytose microorganisms via the complement receptor, potentially reducing the effectiveness of immune responses in the lung. The data also suggest that ozone exposures that induce airway inflammation could lead to fibrotic changes in the lung tissues, based on the increased fibronectin and protein recovered following 6.6 hr exposure to 0.10 ppm ozone. There was a considerable range in response magnitude between individual subjects in the changes in the cellular and biochemical markers measured, suggesting that there is a fraction of the population that is very sensitive to the inflammatory effects of ozone.

7.2.1.6. Pollutant Mixtures

Although there are isolated findings to the contrary, the published data do not support the likelihood of clinically meaningful interactions in human subjects between ozone and gaseous nitrogen-based air pollutants, SO_2 or H_2SO_4 aerosols at concentrations in the ambient range. Observed responses at the pollutant concentrations studied to date appear to be attributable to the O_3 in the mixture. Research also suggests that pre-exposure to fog (water or nitric acid) may mitigate the effects of subsequent ozone exposure, although inhalation of nitric acid gas had no effect on responses to ozone. There is evidence that concurrent exposures to high concentrations of PAN and ozone result in pulmonary function and symptom responses somewhat larger than those observed following exposure to the same concentration of O_3 alone. However, typical ambient PAN concentrations are considerably lower than those utilized in these studies. Consequently, even if ozone and PAN do interact in their effects on pulmonary function at high concentrations, it is unlikely that PAN contributes significantly to adverse health effects in healthy young and older adults at concentrations in the ambient range. There have been few human exposure studies on mixtures of ozone with particulate matter, with the exception of H_2SO_4 aerosol.

An early report demonstrated that ozone exposure at 0.12 ppm at rest for one hour resulted in an increase in allergic asthmatics' sensitivity to the effects of subsequent exposure to allergen. Although two separate studies failed to replicate these results, other studies suggest that higher exposure concentrations (i.e., above 0.20 ppm) can result in allergic asthmatics' requiring a lower dose of allergen to produce a given degree of airway hyperresponsiveness.

7.2.1.7. Effect Modifiers

It is unresolved at this time whether there is a difference in the responsiveness of males and females to ozone exposure. The conclusion reached with available data varies

depending on whether or how the inhaled doses of ozone are normalized, and at present there is no basis to recommend one approach over another.

Data addressing the issue of age-related responsiveness to ozone are limited to studies that investigated pulmonary function and symptoms. The few data available do not identify children or adolescents as being either more or less responsive than young adults who have undergone similar exposure protocols, although children tend to report fewer symptoms (McDonnell et al. 1985a). The lack of symptoms reported by children suggests a lower level of somatic awareness of pain/discomfort among children, which might result in their failure to curtail exposure in real-life situations. In contrast, after about age 30 pulmonary function changes due to ozone exposure become progressively smaller (Drechsler-Parks et al. 1987; Drechsler-Parks et al. 1989; Seal et al. 1993). Middle-aged and older adults also tend to report few symptoms, even with exposure to ozone concentrations in excess of 0.4 ppm, while young adults are symptomatic following exposures at that level. Although children and adolescents do not appear to experience greater adverse responses than adults who complete similar exposures, they are among those most likely to spend significant periods of time outdoors while engaged in exercise, putting them at increased risk of adverse responses. There is no information available on other endpoints, such as airway inflammation or airway hyperreactivity, other than for young adults.

There are insufficient data available to draw a conclusion as to whether there is a difference in the ozone responsiveness of various socioeconomic groups (one study) or African-Americans (one study) compared to Caucasians. There are no data available on other ethnic or racial groups.

Though a variety of factors have been examined to explain differences in responsiveness to acute ozone exposure, only current smoking and increasing age have been linked with airway responsiveness, both in an inverse direction. This reduced responsiveness in smokers may wane after smoking cessation (Emmons and Foster 1991).

7.2.1.8. Relationship between Short-Term Effects and Long-Term Outcomes

The results of controlled human exposure studies utilizing ozone exposures up to about eight hr have clearly established that ozone induces acute responses that qualify as adverse and raise concern that residual effects from repeated acute exposures could accumulate over time and lead to chronic effects or disease. However, practical and logistic considerations are such that controlled human exposure studies are unable to shed light on the impact of long-term exposures to ozone. What is known about long-term exposures comes from results of both epidemiological and animal studies. There are limitations to both of these bodies of literature that cannot be fully overcome, but they do provide some guidance into evaluating the likelihood for chronic effects from ozone exposure. Only a few epidemiological studies have followed a cohort over a long period of time (i.e., several years). In addition, it is difficult to characterize long-term exposure to ozone because of the lack of high penetration rates into the indoor

environment. Therefore, results from these studies of long-term exposure could be reviewed as suggestive. Animal toxicology studies are limited by incomplete knowledge of species sensitivity and dosimetry patterns compared to humans, although they can offer controlled experimental conditions for chronic exposures, provide evidence of causal relationships, and also allow investigation of endpoints not possible to study in humans.

7.2.1.9. Concentrations where adverse effects have been observed

Taken together and using the ATS criteria for adverse health effects, many health outcomes found to be associated with ozone in chamber studies could be considered adverse including pulmonary function changes accompanied by symptoms, pulmonary function decrements and respiratory symptoms that reduce quality of life, and large changes in pulmonary function. In addition, outcomes such as increase in airway reactivity and inflammation may be considered adverse if they signify increases in the potential risk profile of the population exposure to ozone. These adverse outcomes are demonstrated among exercising individuals exposed to a 1-hour ozone concentration of 0.12 ppm and an 8-hour concentration of 0.08 ppm. At multi-hour exposures to 0.08 ppm, some individuals experienced both large changes in lung function and increases in respiratory symptoms. For asthmatics, a repeated decrease in FEV_1 of 20 to 30% could necessitate medical intervention through low-dose inhaled corticosteroids (National Asthma Education and Prevention Program 2002), which clearly qualifies as an adverse effect.

7.2.2. Summary of Findings from Toxicological Studies

Animal toxicological studies have shown that chronic ozone exposure can induce morphological changes throughout the respiratory tract, particularly at the junction of the conducting airways and the gas exchange zone in the deep lung. The morphological changes found in animals following chronic ozone exposures are similar to those characteristic of respiratory bronchiolitis, which may progress to fibrotic lung disease (Last et al. 1994; Reiser et al. 1987). The exposure concentrations that have caused morphological changes in these animal studies are typically considerably higher than ambient levels; however, uncertainties about low-dose extrapolation and animal-to-human extrapolation of the results make it unclear whether similar tissue changes also occur in humans with chronic exposures to ambient concentrations of ozone. Interestingly, morphological damage has been reported in rats exposed to 0.50 and 1.0 ppm ozone for 20 months, but not 0.12 ppm, while there were no alterations in pulmonary function with any exposure (Catalano et al. 1995; Pinkerton et al. 1998; Pinkerton et al. 1995; Szarek et al. 1995). Studies on monkeys exposed to ozone at 0.15 ppm for 8 hr/d for 6 to 90 days showed significant distal airway remodeling, with the morphological changes consistent with incipient peribronchiolar fibrogenesis (Harkema et al. 1993). There is some evidence from primate studies that intermittent

challenge with a pattern of ozone exposure designed to simulate seasonal episodes, with extended periods of clean air in between extended periods of ozone exposure led to greater injury than regular exposures to similar conditions (Tyler et al. 1988).

A series of studies in monkeys has demonstrated that cyclic multi-day exposures to relatively high ozone concentrations (0.5 ppm) can impact development of the lung. Cyclic exposure to ozone and to ozone plus house dust mite allergen (HDMA) alters the development of the tracheal basement membrane zone (BMZ) (Evans et al. 2003). The BMZ is important to the tracheal epithelial functioning as it serves as the attachment point for the epithelial cells, functions as a barrier to foreign substances, and is intimately involved in cell-to-cell communication. The BMZ is important to normal growth and development of the airway including storage and release of growth factors. (Schelegle et al. 2003) also noted that ozone in combination with airborne allergen (dust mite allergen, HDMA) can amplify the immune response to allergens in sensitized infants, resulting in an allergic phenotype airway. This phenotype was characterized by increased HDMA-induced histamine release as measured by serum histamine, elevated BAL eosinophils, and increased airway resistance and reactivity. The increased levels of serum HDMA-specific IgE is consistent with the concept that ozone may prime the developing immune system towards a Th2-type response.

Also of import is the recent publication from this study of changes in airway epithelial innervation induced in the developing rhesus monkey by exposure to ozone and to ozone plus HDMA (Larson et al. 2004). The changes noted included significant decreases in the density of epithelial nerves in the midlevel airways (between the sixth and seventh intrapulmonary airway generations) accompanied by the appearance of abnormal streaks and clusters of nerve cells in the airways just proximal to the midlevel generations. The authors conclude that these effects represent either neural regression or stunted nerve development in the airway.

The animal data provide a biologically plausible basis for considering that repeated inflammation associated with exposure to ozone over a lifetime may result in sufficient damage to the respiratory tissue such that individuals may experience some degree of chronic lung injury. However, uncertainties in interspecies extrapolation, and the use of high ozone concentrations in the animal studies compared to current ambient concentrations, pose difficulties in developing a quantitative relationship for chronic effects.

7.2.3. Summary of Findings from Epidemiologic Studies

The experimental studies such as the chamber studies reported in this document provide valuable information about the acute effects of ozone exposure in humans under controlled conditions. Epidemiologic studies have added to that evidence by evaluating short-term effects of ozone on lung function and respiratory symptoms in free-living populations. As such, epidemiologic studies are able to examine a wide

range of individuals, behaviors, subgroups, and exposure conditions. The studies have been able to provide information on the effects of short-term ozone exposure on acute mortality, emergency department visits and hospitalizations. In addition, epidemiologic studies supply evidence of associations between adverse health outcomes and longer-term (i.e., a year or more) exposures to ozone.

There are some limitations to epidemiologic studies. Firstly, it is not possible to characterize exposure in a precise manner similar to that of a chamber study. Most of the epidemiologic studies rely on regional air pollution monitors, which may not reflect the true exposures at the residences of the study subjects. For ozone and other gases this may be an issue of significant exposure mismeasurement since some limited evidence suggests a low correlation between personal exposure and ambient concentrations of ozone (Sarnat et al. 2001). This finding is contradicted, however, by evidence from Linn et al. (1996) which reported a relatively high correlation ($r = 0.61$) between ozone measured from a personal badge and from a fixed site monitor in a study in Southern California. In addition, study subjects move around from place to place during the day, so one measurement will not adequately reflect overall exposure. Secondly, epidemiologic studies may be subject to bias from uncontrolled or poorly controlled confounders such as seasonality, weather and co-pollutants. However, time series studies which examine the association between health and air pollution at a given site over a designated period of time (from several months to years) have employed sophisticated modeling techniques including non-parametric and parametric smoothing in an attempt to control for these potential confounders. However, ozone presents a particular challenge because of its seasonal nature and high correlation with temperature. More recent studies appear to be successful in addressing some of these limitations. Thirdly, the epidemiologic studies in this review used different averaging times of ozone for their exposure measurements. Many used a 1-hour maximum while others reported results for 8-hour or 24-hour average levels. Since these metrics tend to be highly correlated, if there is a positive association between ozone and a given health effect, it is difficult to attribute the effect to a precise averaging time.

Despite these limitations, a large number of studies published in the last several years have shown positive associations between ozone levels and several health effects including overall mortality, cardiopulmonary mortality, decreased lung function, respiratory symptoms, and emergency visits for asthma. The overall findings from these studies are supported by the consistency of effects, many of which are seen in the summer season only, the biological plausibility obtained from animal studies, and the finding of a concentration-response relationship in many of the studies. Thus, it is difficult to use these studies to determine a low or no effects level useful for standard setting. However, these studies often provide useful information on the type and magnitude of health effects associated with exposure to ozone and provide information on concentration-response relationships. As such, they contribute to important considerations of margin of safety and to the calculations of the potential benefits of controlling ozone. While any given epidemiologic study may have some limitations, taken together these studies provide a strong case for a causal relationship between

ambient ozone and a suite of adverse health outcomes. A summary of the most important findings is presented here.

7.2.3.1. Field Studies Addressing Acute Respiratory Effects of Ozone

Nine of 11 newer studies presented in this document that tested for effects of ozone on lung function reported significant associations, although there were several inconsistent findings. In another particularly relevant study, investigators measured lung function before and after outdoor summer work shifts on a group of 58 berry pickers, ages 10 to 69, in Fraser Valley, British Columbia (Brauer et al. 1996). These workers had an extended exposure period outdoors and elevated levels of exertion throughout exposure. Statistically significant changes in several measures of lung function were reported. Thus, this study suggests that, as demonstrated in the chamber studies, multi-hour exposures to ozone combined with exercise can generate enhanced response to ozone. There is some possibility of greater responsiveness in this cohort due to a generally less advantaged health and social status.

Among the 12 studies reporting results for daily symptoms, seven reported associations with ozone that appear fairly robust; two of those seven were conducted in the United States. One of the largest and best conducted studies was that of Gent and colleagues (Gent et al. 2003), where 271 asthmatic children under age 12 living in southern New England were each followed over six months (April through September) for daily symptoms. Significant effects of lag 1 daily maximum 1-hour and 8-hour ozone were observed for a variety of respiratory symptoms, including chest tightness and shortness of breath, in the group who used maintenance asthma medications (n=130). The effects of ozone, but not PM2.5, remained significant and even increased in two-pollutant models. Significant associations, such as with chest tightness were observed at 52 ppb or higher for both the 1- and 8-hour averages of ozone. However, there was no measurement of sulfate, which may have high temporal correlation with ozone in this region.

Absence from school was associated with ozone concentrations in a study of 1,933 fourth grade students from 12 southern California communities participating in the Children's Health Study (Gilliland et al. 2001). They found an 83% increase for absences due to respiratory disease and a 37% increase for non-respiratory causes per 20 ppb rise in 10am-6pm ozone concentrations. A wide range of exposures were captured while staying below the highest levels observed in the summer season.

7.2.3.2. Effects of Ozone on Daily Hospital Admissions and Emergency Department visits

Large, multi-city studies of hospital admissions have reported significant ozone associations with total respiratory hospitalizations (Burnett et al. 1997) and chronic

obstructive pulmonary disease (Anderson et al. 1997). The largest such study to date was carried out using all-age respiratory hospital admissions from 16 Canadian cities from 1981-1991 (Burnett et al. 1997). Pooling the 16 cities, a significant positive association was observed between respiratory hospital admissions and lag 1 daily 1-hour maximum ozone concentration in spring and summer. There was no evidence of an ozone effect in the winter season. Other ozone metrics were also evaluated. However, the 1-hour maximum had the strongest associations with admissions. Other studies, such as the analysis of six European cities (Anderson et al. 1997) have found stronger effects in the summer or warm seasons. Many of the individual city studies have reported associations with total respiratory admissions and a few with asthma. In the case of emergency department (ED) studies, asthma has been studied most often, with variable results. An important consideration in determining whether a safe level of ozone can be identified is whether the concentration-response (C-R) relationship is linear across the full concentration range or instead shows evidence of a threshold. Several studies on ED visits for asthma that have examined the impacts of increasing intervals of exposure report a non-linear response consistent with a potential threshold. The lowest effect level appears to be somewhere between 75 and 110 ppb 1-hour ozone. This range corresponds roughly with an 8-hour concentration of 90 to 130 ppb. The one study of emergency room visits that used 8-hour ozone (Tolbert et al. 2000) reported elevated (but not statistically significant) risks for concentrations starting in the interval of 70 to 80 ppb, with a more consistent response in the interval from 90 to 100 ppb, and statistical significance attained for the interval between 100 and 113 ppb 8-hour ozone. As noted above, due to the high correlation among ozone concentrations at varying averaging times, it is difficult to ascribe an effect solely to a one-hour or 8 hour ozone exposure.

7.2.3.3. Ozone and Acute Mortality

Though limited in some ways, a large and growing body of data now exists examining the association between daily mortality and ozone concentrations. These data support a preliminary conclusion that warm season ozone concentrations represent an independent risk factor for premature mortality, controlling for weather effects and other air pollutants. The most robust data on ozone effects on mortality come from the National Mortality and Morbidity Air Pollution Study (NMMAPS), a study of mortality in the largest 90 cities in the U.S. which was reanalyzed in 2003 using non-GAM methods (Dominici, 2003). Several other studies conducted both within the U.S. (Moolgavkar et al. 1997) and outside of the U.S. (Hoek et al. 2000; Simpson et al. 1997; Goldberg et al. 2003; Goldberg MS 2003; Vedal et al. 2003) reported larger excess mortality risks in the warm (or summer) season than in the cool (or winter) season. While there is a real potential for the occurrence of these outcomes, based on the inflammatory response generated from ozone exposure, additional studies need to be conducted to ensure that: (1) ozone is not confounded by other pollutants including particulate matter (PM10 and PM2.5); (2) ozone is not confounded by temperature and season using parametric (versus non-parametric) generalized linear models; and (3) personal exposure to ozone

is sufficiently related to ambient concentrations of ozone. Finally, the ozone-specific models need to undergo the thorough sensitivity analysis of their results similar to that undertaken for studies on particulate matter.

7.2.3.2 Effects of Long-Term Ozone Exposures

Epidemiology has a key role to play in addressing the health impacts of long-term ozone exposures in humans, since it is impractical to study these effects using controlled human exposure studies. In recent years the following outcomes have been evaluated with respect to long-term ozone exposure: respiratory inflammation, lung function and respiratory symptoms, long-term mortality risks, growth or decline of lung function over many years, and asthma prevalence.

For example, Kinney et al. (1996) found greater cell damage, measured in bronchoalveolar lavage (BAL) fluids collected in summer compared with those collected in winter among adult joggers. Kinney and Lippmann (2000) found a larger decline in FEV_1 among subjects who had trained in high versus moderate ozone regions.

The results of studies of lung function and long-term ozone exposure have been variable. For example, Peters et al. (1999) found evidence for lung function declines in females but not males living in high ozone cities. In a longitudinal analysis of lung function growth in the fourth grade, decrements in lung function growth were associated with particulate matter and NO_2, but not with ozone (Gauderman et al. 2000). Finally, studies of college students have shown decrements in lung function among students who had lived in areas with higher ozone (Galizia and Kinney 1999; Tager et al. 1998; Kunzli et al. 1997).

Two recent reports from longitudinal cohort studies have reported associations between the onset of asthma and long-term ozone exposures (Abbey et al. 1999; McConnell et al. 2002).

Finally, there is inconsistent and inconclusive evidence for a relationship between long-term ozone exposure and increased mortality risk (Abbey et al. 1999; Pope et al. 2002). However the Pope study of 500,000 members of the American Cancer Society cohort did find that the association between cardiopulmonary mortality and July-September daily 1-hour maximum ozone was positive and nearly significant.

7.3. Consideration of Infants and Children

As noted earlier, SB25 specifically asks that OEHHA assess the proposed standard in light of four factors related to infants and children, to the extent that information is available.

1. Exposure patterns among infants and children that are likely to result in disproportionately high exposures relative to the general population

As indicated above, children who are outdoors for extended periods of time, particularly while engaged in physical activity that increases their breathing rate, should be considered as a potentially susceptible subpopulation. Under these circumstances, their effective dose of ozone would be disproportionately high relative to the general population. Infants and children inhale more air per unit body weight than adults, even at rest. Thus, young children and infants experience a greater exposure per lung surface area than adults

2. Special susceptibility of infants and children to ambient air pollution relative to the general population

A number of animal studies have indicated that the developing lung is altered by multi-day exposure to ozone at relatively high concentrations (0.5 ppm) and also to ozone plus airborne allergen. Studies in primates have shown altered structural development of the tracheal epithelium, including areas where the tracheal epithelial basement membrane is incompletely developed (Schelegle et al. 2003; Evans et al. 2003). In addition, ozone alters neuronal distribution in the midlevel airways, resulting in decreased neuronal density in the midlevel airways and abnormal clumping of neurons in larger airways (Larson et al. 2004). Ozone exposure enhances the allergic response of the developing primate infant lung to airborne allergens, promoting the development of an allergic airway (Schelegle et al. 2003). In addition, there is epidemiological evidence of lower lung function in 18 to 21 year-old males raised in areas with high ozone in the U.S (Kunzli et al. 1997; Galizia and Kinney 1999). Finally, one longitudinal epidemiological study found a consistent association between elevated long-term ozone concentrations and new-onset asthma in children playing outdoor team sports (McConnell et al. 2002). Thus, children may be more susceptible to the effects of ozone than the general population due to effects on the developing lung. The standard setting takes this into consideration.

3. The effects on infants and children of exposure to ambient air pollution and other substances that have common mechanisms of toxicity.

There are no data that can be used to assess the combined effects of oxidant chemicals in the ambient air on children's health. However, in considering the epidemiological studies (including field studies), it should be noted that exposures to highly correlated oxidant chemicals in the ambient air are inherently included in the evaluation. In

addition, notwithstanding isolated findings to the contrary, the majority of controlled exposure studies with ozone in combination with nitrogen oxides or sulfur oxides indicated that there was little to no difference in symptoms and lung function changes for the combined exposures relative to ozone alone.

4. The interaction of multiple air pollutants on infants and children, including between criteria air pollutants and toxic air contaminants.

There are some studies that shed light on interactions of ozone and other criteria air pollutants. Current evidence from both chamber studies and the epidemiological literature for the most part indicates that other criteria air pollutants have little or no modification of the effects attributed to ozone such as decreased lung function and respiratory symptoms. There are no studies evaluating the interaction of ozone and toxic air contaminants.

7.4. Recommended Pollutant Indicator

OEHHA recommends that ozone continue to be the indicator for oxidant air pollutants. It is generally recognized that control of ambient ozone levels provides the most effective means of controlling harmful photochemical oxidants. Furthermore, available health-related data suggest that, at current ambient levels of photochemical oxidants, only ozone is likely to play an important role in the genesis of adverse health effects. Thus, OEHHA recommends that ozone remain the sole pollutant indicator for protection of public health from exposure to all photochemical oxidants found in ambient air.

7.5. Recommended Averaging Times and Forms

The current California ambient air quality standard for ozone has a 1-hr averaging time. Selection of this averaging period was based on the desire to protect the public against health effects associated with 1-hr exposures to ozone, based on typical ozone monitoring patterns in the South Coast Air Basin, and for historical reasons, in that the State standard has had a 1-hr averaging time since its inception. It was recognized in 1987 that multi-hour ozone exposures were likely associated with adverse health effects as well, but there were virtually no published data available at that time to support a longer averaging time. It was also recognized that a stringent 1-hr ozone standard would serve to drive multi-hour term average ozone concentrations down, and thereby also provide protection against health effects associated with exposures longer than one hr. The studies on which the 1-hr standard was based indicated that exposures to ozone as low as 0.12 ppm for 1-2 hr induced decrements in lung function and increased symptoms in exercising subjects. Other chamber studies have show increased airway resistance at 0.18 ppm. Airway inflammation has been noted at 0.20 ppm, but has not been studied at lower concentrations in 1 to 3 hr protocols.

Dozens of epidemiological studies also demonstrate an association between 1-hour daily maximum concentrations of ozone and a wide range of adverse health effects, including premature mortality, hospitalizations, emergency rooms visits, asthma exacerbation, and respiratory symptoms. Some of these studies have the potential to be confounded by season, weather and co-pollutants. In addition, some of the effects may be likely due to multi-hour exposures to ozone, which are highly correlated with one-hour averages. In other words, it is not possible to ascribe the measured health effects solely to one-hour ambient peak concentrations rather longer term exposures. However, short-term exposures still may be of concern given the nature of some of the health effects (i.e., cardiovascular mortality among the elderly and emergency room visits for infants), It is possible that at least some of the important exposures may be relatively short-term in nature (i.e., less than 2 hours), since these subgroups are unlikely to be engaged in multi-hour periods of moderate or heavy exercise. Therefore, OEHHA recommends that a short-term 1-hour standard be retained to protect against these possible effects. Further, OEHHA recommends that a substantial margin of safety be used in setting the 1-hour standard to account for the possibility of significant adverse health effects, as suggested by the epidemiologic studies.

Since the 1987 review of the California AAQS for ozone, a series of controlled human exposure studies have appeared that used a 6.6 to 8 hr protocol, in simulation of a full day of outdoor work, recreation or play. These studies indicated that multi-hour exposures to ozone concentrations as low as 0.08 ppm could induce statistically significant decrements in group mean lung function and respiratory symptoms, and increases in airway hyperreactivity and markers of airway inflammation. These studies, in concert with observations of a broad, low peak level pattern to ozone concentration profiles in much of the US led the US EPA to select an averaging time of 8 hr in its ozone standard recommendation in 1996. In California, different regions exhibit varying relationships between the 1- and 8-hour averages. Some exhibit narrow, high peaks (and relatively high ratios of 1 to 8-hour averages) while other exhibit a wide afternoon peak concentration and a relatively low ratio of 1- to 8-hour averages.

We analyzed the relationship between high 1-hour and high 8-hour ozone averages for the years 2000 - 2002 using the California Design Value approach, also known as the Expected Peak Day Concentration (EPDC). As discussed earlier in this Staff Paper, this procedure is used to determine “design values,” which are concentrations that play the primary role in determining the attainment status of regions with respect to California's state standards. California Design Values are calculated values for which one exceedance per year is expected. The "one expected exceedance" criterion and the calculation procedure are applied to all pollutants, including ozone, with short-term standards of 24 hours or less. The procedure is based on a statistical model of the highest 20% of the daily maximum 1-hour or 8-hour values from the previous three years. The resulting design values are relatively robust to fluctuations in daily meteorological conditions and are not unduly influenced by any single day. State regulations permit exceptional events, such as forest or urban fires, to be excluded from

the calculation. Based on 2000 - 2002 data, we compared the California Design Values for 1-hour and 8-hour ozone levels at each ozone monitoring site in the state.

We first calculated the projected 1-hr design value for alternative 8-hr targets using a simple rollback model. In this model, the ratio between the 8-hour target concentration (e.g., 0.08 ppm) and the current 8-hour maximum at each design monitor is calculated. This ratio is then applied to the current 1-hour maximum value at that monitor location to determine the projected 1-hour design value. These results indicate that, using the design monitors, an 8-hr average of 0.080 ppm is associated with 1-hour values greater than 0.09 at several sites (see Table 7.1). For example, a rollback to the 8-hour average of 0.08 ppm is associated with a 1-hour maximum of 0.111 ppm at the Calexico site, 0.102 ppm at the Livermore (Old First St.) site, 0.097 ppm at the Gilroy site, and 0.095 ppm at the Santa Clarita site. A rollback to a 0.75 8-hour average is associated with 1-hour averages of 0.102, 0.094, 0.090 and 0.088 ppm, respectively, at these four sites. Thus, these multi-hour exposures could co-exist with 1-hour exposures greater than 0.09 ppm; this suggests the need for standards with both averaging times.

We also examined the 8-hour EPDC assuming that each site is rolled back to meet the current state 1-hour standard of 0.09 ppm. As indicated in Table 7.2, 6 of the 84 design monitor sites would have 8-hour averages above 0.08, 27 sites (~32%) would still have an EPDC 8-hour average above 0.075 ppm, and 78 (~93%) would have an EPDC 8-hour average above 0.070 ppm. Thus, a simple rollback model indicates that even after attainment of a 1-hour maximum of 0.09 ppm, significantly elevated 8-hour averages could remain.

Therefore, based on both the evidence from the studies examining the concentrations of ozone at which adverse health effects have been observed and on the existing relation between 1- and 8-hour averages at existing monitoring sites, it is reasonable to recommend standards for both 1- and 8-hour averages. Such standards would ensure that the public is protected from both single and multi-hour concentrations of concern. We recommend that the form of the standard continue as “not to be exceeded.”

7.6. Recommended Concentrations

7.6.1. Considerations for the Margin of Safety

Both the California Health & Safety Code (section 39606) and the federal Clean Air Act (section 109) refer to an adequate margin of safety, although neither includes a specific legislative definition of this term. The Children’s Environmental Health Protection Act [Senate Bill 25, Escutia; Stats. 1999, Ch731, sec. 3; Health & Safety Code section 39404(d)(2)] requires a standard that “*adequately* protects the health of the public, including infants and children, *with an adequate margin of safety*.” (emphasis added) Given the current state of the science, which is limited by uncertainties in the existing data sets and methods available to analyze the impacts of low-level exposures, it is not possible to set standards for ozone that absolutely protect all individuals.

The governing statutory language indicates that California's ambient air quality standards should also protect other vulnerable populations, in addition to infants and children, and the general public [(Health & Safety Code sections 39606 (d)(2) and 39606 (d)(3)]. This legislative directive is consistent with historical practice in California, where ambient air quality standards have been formulated to protect identifiable susceptible subgroups, as well as the general population. Nonetheless, even with standards tailored to protect vulnerable populations, there may be exquisitely sensitive individuals who still have adverse responses.

As a result, OEHHA has recommended ozone standards that are somewhat below the lowest levels reported for statistically significant group mean decrements in lung functions as observed in the chamber studies. These studies have been given primary focus since both the dose and response are well characterized. A margin of safety was developed based on the following evidence: (1) chamber studies indicating variability in human response and the existence of particularly large individual responses; (2) chamber studies indicating, at higher ozone levels, both bronchial responsiveness and pulmonary inflammation; (3) animal toxicology studies supporting many of these findings and also suggesting the possibility of decreases in lung defense mechanism; and (4) epidemiologic studies reporting associations between ambient ozone and a suite of adverse outcomes including premature mortality, hospitalization, emergency room visits, school loss, respiratory symptoms and changes lung function. While it is difficult to use all of the latter set of studies quantitatively in developing a standard, the significant potential of adverse effects clearly should factor into the margin of safety considerations. Below, we provide the scientific rationale for the 1- and 8-hour standards.

7.6.2. One-hour average

We recommend that the current standard of 0.09 ppm, not to be exceeded, be retained. While there have been no new controlled chamber studies to indicate group-level effects at concentrations below 0.12 ppm for short (one to three hours) durations of exposure, the OEHHA recommendation is based on several factors.

First, at 0.12 ppm, in several studies 10 - 25% of the subjects experienced a decline of 10% of more in FEV1. In one study, these lung function changes were accompanied by increases in cough. At 0.24 ppm, increases were also observed in shortness of breath and pain on deep breath. These lung function and symptom outcomes have been demonstrated and replicated in several carefully controlled human exposure studies. The population at risk for these effects includes children engaged in active outdoor exercise and workers engaged in physical labor outdoors. Thus, a margin of safety is necessary to account for variability in human responses. In addition, the chamber studies, by design, do not include especially vulnerable populations (e.g., people with moderate to severe asthma, COPD, and heart disease), which may be incorporated in the epidemiologic studies.

Second, chamber studies indicate that bronchial responsiveness and pulmonary inflammation occur at 1-hour exposure to 0.18 to 0.20 ppm. The bronchial responsiveness is capable of aggravating pre-existing chronic respiratory disease. The ultimate impact of the inflammatory response is unclear but repeated exposures to high ozone levels may result in restructuring of the airways, fibrosis, and possibly permanent respiratory injury. These latter outcomes are supported by animal toxicology studies which also suggest the possibility of decreases in lung defense mechanism.

Third, there have been a plethora of epidemiological studies completed over the last 10 years indicating the potential for severe adverse health outcomes including premature mortality, hospitalizations, and emergency room visits. These studies include concentrations to which the public is currently being exposed. Some of the epidemiological associations have been reported for outcomes including cardiovascular mortality (likely to be observed among older individuals with pre-existing heart or lung disease) and hospital visits for children less than age two. Thus, it is possible that some of these associations are due to relatively short-term exposures of less than two hours in duration since these subgroups are unlikely to be engaged in multi-hour periods of moderate or heavy exercise outdoors. However, it is difficult to attribute these adverse outcomes to a specific ozone concentration or time. Likewise, because of the high temporal correlation of 1-, 8-, and 24-hour average ozone, the averaging time of concern cannot be discerned from these studies. Most of the studies used linear non-threshold models and did not explicitly test for thresholds. In addition, certain models, such as the time-series studies of mortality and hospitalization, suffer from problems of confounding from seasonal and weather factors and possibly co-pollutants. However, several of the studies of short-term exposure on mortality demonstrate effects only in the warmer months when ozone concentrations are highest. This suggests either the importance of outdoor exposure, the possibility of thresholds (i.e., non-linear concentration-response functions, or both. These studies have annual averages for 1-hour daily maximum ozone of between 20 and 70 ppb (see Table 7.3).

Additional uncertainties with these studies exist due to issues related to measurement of exposure and biological mechanisms. Concerning exposure assessment, Sarnat et al (Sarnat et al. 2001) demonstrated a very low and statistically non-significant association between personal exposure to ozone and ambient ozone in Baltimore. In addition, evidence clearly indicates only low to moderate levels of indoor ozone associated with outdoor ozone. Finally, the limited number of chamber studies to date indicate that individuals with asthma, COPD or hypertension do not, in general, have proportionately greater responses to short-term exposures to ozone than healthy individuals. However, since such individuals' baseline health status is already compromised to some extent, on an absolute basis some ozone-associated effects would likely carry more significant clinical implications for this group. Therefore, the mortality effects should be viewed as suggestive until additional epidemiologic studies are undertaken that carefully control for season, weather and confounding by other pollutants, most importantly, particulate matter. Additional research on potential biological mechanisms is required, as well as some further reconciliation of the longer-term impacts of repeated ozone-induced inflammation. However, the existing evidence from the chamber and epidemiologic

studies clearly argue for a significant margin of safety below the effect level of 0.12 ppm level of effect observed in the 1-hour chamber studies.

Only one set of epidemiological studies, those time-series studies examining emergency room visits for asthma, has more systematically examined the shape of the concentration-response function for possible non-linearities and thresholds. We have reviewed these studies and attempted to determine the likely interval of concentrations in each study where associations are clearly demonstrable (Figure 7.1). Taken together these studies suggest that the low end of the interval has a range of 0.060 to 0.115 ppm ozone averaged over one hour. The lowest value comes from the study of (Weisel et al. 1995) which did not include any analysis of daily PM10, PM2.5 or sulfate, all of which have been demonstrated to exacerbate asthma. Thus it is difficult to attribute the results strictly to ozone. Dropping this study suggests a lower bound of the interval of 0.075 ppm. However, this is not the same as a “lowest observable effects level” since the actual concentrations at which statistically significant associations emerge are between 0.075 ppm and 0.16 ppm. In fact, three of the studies suggest that significant associations occur at around 0.11 ppm 1-hour ozone. We also can make some inferences about no effects levels from negative studies which rarely have values above 1-hour concentrations of 0.080 ppm. Again, it is difficult to determine the actual averaging time of concern from these studies given their high correlations. In addition, emergency room visits for asthma are a fairly serious indicator of ozone toxicity and other less severe outcomes may have lower thresholds, if any. Thus, the evidence suggesting associations between emergency room visits and 1-hour ozone concentrations at or below 0.11 ppm needs to be incorporated into the margin of safety.

Finally, a large margin of safety (relative to the 1-hour 0.12 ppm from the chamber studies) may be necessary to account for the possibility of adverse impacts of long-term (i.e., one year or more) exposures to ozone. For example, modest associations have been reported between long-term summertime exposure to ozone and cardiovascular mortality (Pope et al. 2002). Also, long-term exposure to ozone, particularly prior to age 6 has been associated with impairment of the small airways (Kunzli et al. 1997; Galizia and Kinney 1999). The application of a safety margin reducing the standard below the level of effect of 0.12 ppm observed in the chamber studies to a concentration of 0.09 ppm would succeed in lowering the entire distribution of daily exposures at all durations. Therefore, this standard will afford some increased degree of protection from longer-term exposures. Specifically, our analysis indicates that when a 1-hour standard of 0.09 is attained, the annual mean of daily 1-hour maxima for the years 1999 - 2001for monitors in California cites with populations above 100,000 will range from 0.023 to 0.052 ppm, with most of the cities in the range of 0.033 to 0.048 ppm, with an average of around 0.04 ppm (see Table 7.3).

In 1987, the Department of Health Services recommended a 1 hour standard of 0.08 ppm. The primary basis of the 1987 DHS recommendation were the chamber studies conducted for 1-2 hours in humans which showed effects on the group mean decrements in lung function and symptoms measurements in healthy young exercising adults at an ozone concentration of 0.12 ppm. At the time, there was little information on the effects of repeated or prolonged exposures to ozone. Experimental evidence in

animals indicated concern for repeated or prolonged ozone exposure. Thus, DHS recommended a 1-hour standard of 0.08 ppm in order to incorporate some margin of safety from the chamber studies in humans. This was the only averaging time for which a standard was recommended.

Viewing all of the evidence, OEHHA recommends a retention of the 1-hour standard of 0.09 ppm, not to be exceeded, as being protective of public health with an adequate margin of safety. Our current recommendation is made in conjunction with an 8 hour standard which together with the 1-hour standard provides an adequate protection of public health. However, if the Board does not adopt the 8-hour standard then OEHHA recommends a 1-hour standard of 0.08, not to be exceeded, in consideration of the concern regarding repeated or prolonged exposures to ozone.

7.6.3. Eight-hour standard

We recommend an 8-hour standard of 0.070 ppm, not to be exceeded. Our recommendation for the 8-hour standard is based primarily on the chamber studies that have been conducted over the last 15 years, supported by the important health outcomes reported in many of the epidemiologic studies. At a 6.6 -to 8-hour concentration of 0.08 ppm, several studies have reported statistically significant group effects on lung function changes, respiratory symptoms, and airway hyperresponsiveness among healthy, exercising individuals. A substantial fraction of subjects in these studies exhibited particularly marked responses in lung function and symptoms, effects that are labeled as “adverse” by ATS. As a result, a concentration of 0.08 ppm ozone for an 8 hour averaging time is not sufficiently protective of public health. The one published multi-hour study investigating a concentration below 0.08 ppm showed no statistically significant group mean decrement in lung function or symptoms at 0.04 ppm compared to a baseline of clear air. In addition, all subjects had changes in FEV_1 of less than 10%. One unpublished multi-hour study at 0.06 ppm (Adams 1998) reported no statistically significant group mean changes, relative to clean air, in either lung function or symptoms including pain on deep inspiration and total symptom score. Therefore, OEHHA has recommended an 8-hour level of 0.070 ppm, not to be exceeded, to ensure a minimal number of days of ozone-related, significant respiratory effects for children and adults.

Many of the studies, and issues and concerns associated with the epidemiological studies listed above concerning the 1-hour standard are also relevant to the 8-hour standard. As discussed above, it may be that these health effects, often correlated with 1-hour exposures in the epidemiologic studies, are actually associated with 8-hour (or other) average exposures. Evidence for this possibility is provided by the stronger response, in terms of effects on both lung function and symptoms, observed in multi-hour exposures at concentrations that do not elicit responses after only 1-hour exposures. Therefore, these epidemiologic studies need to be reflected in the margin of safety for the 8-hour average.

Regarding the level of effect from the studies of emergency room visits for asthma, the lower bound of 0.11 1-hour is generally associated with an 8-hour concentration of 0.09 ppm (using a general ratio of 1-hour to 8-hour of 1.20 in California). The one study of emergency room visits using the exposure intervals that examined 8-hour ozone (Tolbert et al. 2000) reported elevated risks within the interval of 0.070 to 0.10 ppm with a more consistent response in the interval from 0.90 to 0.10 ppm and statistical significance attained for the interval between 0.10 and 0.113 8-hour ozone.

Finally, as discussed concerning the 1-hour standard above, our recommendation recognizes that attainment of an 8-hour standard of 0.070 ppm would significantly reduce the entire distribution of daily ozone concentrations (Table 7.3). Based on information on current distributions of daily 8-hour averages, we would expect to see relatively few days in the 0.060 to 0.70 ppm 8-hour range in most major cities in California. Thus, we would expect to find few days were sensitive individuals would experience large changes in lung function.

7.6.4. Consideration of Infants and Children in Recommending the Ozone Standards

As noted above, children breathe more per body weight at rest and when active than adults, and tend to be outside more and more active than adults. Thus, by virtue of physiology and behavior, they are likely to be disproportionately more highly exposed than the general population. However, the chamber studies of exercising children suggest that they have responses generally similar to adults. Similarly, those epidemiologic studies that have been able to examine both children and adults do not show clear evidence for greater sensitivity in children. Studies in animals at high exposure concentrations (0.5 ppm and higher, 8 hrs/day for several consecutive days) indicate that developing lungs of infant animals are adversely affected by ozone. The recommended standards are well below that level of exposure. Two studies have shown evidence of lower lung function in young adults raised in high ozone areas (Kunzli et al. 1997; Galizia and Kinney 1999). For the study by Kunzli et al. (1997), exposure to ozone prior to age 6 was an important variable. Examination of data for the Los Angeles basin from the early 1980s, show summer averages of the 1-hour maximum to be above 0.10 ppm. This is considerably above present levels and above the recommended one hour standard. There is also evidence that children who play three or more sports are at higher risk of developing asthma if they also live in high ozone communities in Southern California. This study needs to be repeated before the effect can be attributed to ozone exposure with greater certainty, but the finding is of concern. The warm season daily 8-hour maximum concentrations of ozone measured in these high ozone areas, over the four years of study, was 0.084 ppm. The proposed 8-hour standard of 0.070 ppm, therefore, should protect most children from asthma induction associated with exposure to ozone.

7.7. Summary of OEHHA Recommendation:

1) Ozone continues to be the indicator for oxidant air pollutants.

2) An averaging time for standards of both 1- and 8-hours.

3) Retain the 1-hour average standard of 0.09 ppm, not to be exceeded and add an 8-hour standard of 0.070 ppm, not to be exceeded. If the Board does not adopt an 8-hour standard, then the 1-hour standard should be lowered to 0.08 ppm, not to be exceeded. Such a standard would protect against both 1-hour concentrations and repeated or multi-hour exposures to ozone.

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Table 7.1. Predicted values of daily maximum 1-hour ozone at a time in the future when an 8-hour standard of 0.080 ppm is attained statewide at selected monitor sites.

SITE	COUNTY	BASIN	DISTRICT	1-hr EPDC
Calexico-Ethel Street	IMP	SS	IMP	0.111
Livermore-Old 1st Street	ALA	SFB	BA	0.102
Concord-2975 Treat Blvd	CC	SFB	BA	0.098
Westmorland-W 1st Street	IMP	SS	IMP	0.097
Gilroy-9th Street	SCL	SFB	BA	0.097
Calexico-Grant Street	IMP	SS	IMP	0.095
Santa Clarita	LA	SC	SC	0.095
Livermore-793 Rincon Avenue	ALA	SFB	BA	0.094
El Centro-9th Street	IMP	SS	IMP	0.094
Parlier	FRE	SJV	SJV	0.093
Cool-Highway 193	ED	MC	ED	0.093
San Martin-Murphy Avenue	SCL	SFB	BA	0.093
Pinnacles National Monument	SBT	NCC	MBU	0.093
Calexico-East	IMP	SS	IMP	0.092
Clovis-N Villa Avenue	FRE	SJV	SJV	0.091
Palm Springs-Fire Station	RIV	SS	SC	0.091
Simi Valley-Cochran Street	VEN	SCC	VEN	0.090
Sloughhouse	SAC	SV	SAC	0.090
Fremont-Chapel Way	ALA	SFB	BA	0.089
Folsom-Natoma Street	SAC	SV	SAC	0.089
Echo Summit	ED	LT	ED	0.089
Phelan-Beekley Road & Phelan Road	SBD	MD	MD	0.089
South Lake Tahoe-Sandy Way	ED	LT	ED	0.088
Lancaster-W Pondera Street	LA	MD	AV	0.088
Edison	KER	SJV	SJV	0.088
Bethel Island Road	CC	SFB	BA	0.088
Fairfield-Bay Area AQMD	SOL	SFB	BA	0.088
Alpine-Victoria Drive	SD	SD	SD	0.088
Arvin-Bear Mountain Blvd	KER	SJV	SJV	0.087

Table 7.2. Predicted 8-hour EPDC after rollback to 1-hour maximum of 0.09 ppm at design monitors throughout the state.

SITE NAME	8-hour EPDC
Mammoth Lakes-Gateway HC	0.087
Echo Summit	0.083
Alpine-Victoria Drive	0.082
Simi Valley-Cochran Street	0.082
Death Valley Natl Monument	0.082
Crestline	0.081
Cool-Highway 193	0.080
Livermore-Old 1st Street	0.080
Pinnacles National Monument	0.080
Fresno-Sierra Skypark #2	0.079
Redlands-Dearborn	0.079
Folsom-Natoma Street	0.078
Phelan-Beekley Road & Phelan Road	0.078
Clovis-N Villa Avenue	0.078
Arvin-Bear Mountain Blvd	0.077
San Bernardino-4th Street	0.077
Parlier	0.077
Upland	0.077
South Lake Tahoe-Sandy Way	0.077
Hesperia-Olive Street	0.077
Santa Clarita	0.077
Gilroy-9th Street	0.077
Ojai-Ojai Avenue	0.076
Placerville-Gold Nugget Way	0.076
Grass Valley-Litton Building	0.076
White Cloud Mountain	0.076
Lancaster-W Pondera Street	0.076
Fresno-1st Street	0.075
Fontana-Arrow Highway	0.075

Auburn-Dewitt-C Avenue	0.075
Perris	0.075
Piru-3301 Pacific Avenue	0.075
Palm Springs-Fire Station	0.075
Edison	0.075
Mojave-923 Poole Street	0.075
Sequoia & Kings Canyon Np	0.075
Westmorland-W 1st Street	0.075
Jerseydale - 6440 Jerseydale	0.074
Merced-S Coffee Avenue	0.074
Healdsburg-Municipal Airport	0.074
Glendora-Laurel	0.074
Calexico-Ethel Street	0.074
Bakersfield-5558 California Avenue	0.074
Sloughhouse	0.073
San Martin-Murphy Avenue	0.073
San Andreas-Gold Strike Road	0.073
Jackson-Clinton Road	0.073
Five Mile Learning Center	0.073
Riverside-Rubidoux	0.073
Ventura County-W Casitas Pass Road	0.073
Hanford-S Irwin Street	0.073
Camp Pendleton	0.073
Tuscan Butte	0.073
Joshua Tree-National Monument	0.073
Lakeport-Lakeport Blvd	0.073
Hollister-Fairview Road	0.072
Sequoia National Park-Lookout Point	0.072
Rocklin-Rocklin Road	0.072
Victorville-14306 Park Avenue	0.072
Twentynine Palms-Adobe Road #2	0.072
Sacramento-Del Paso Manor	0.072
Banning Airport	0.072
Roseville-N Sunrise Blvd	0.072

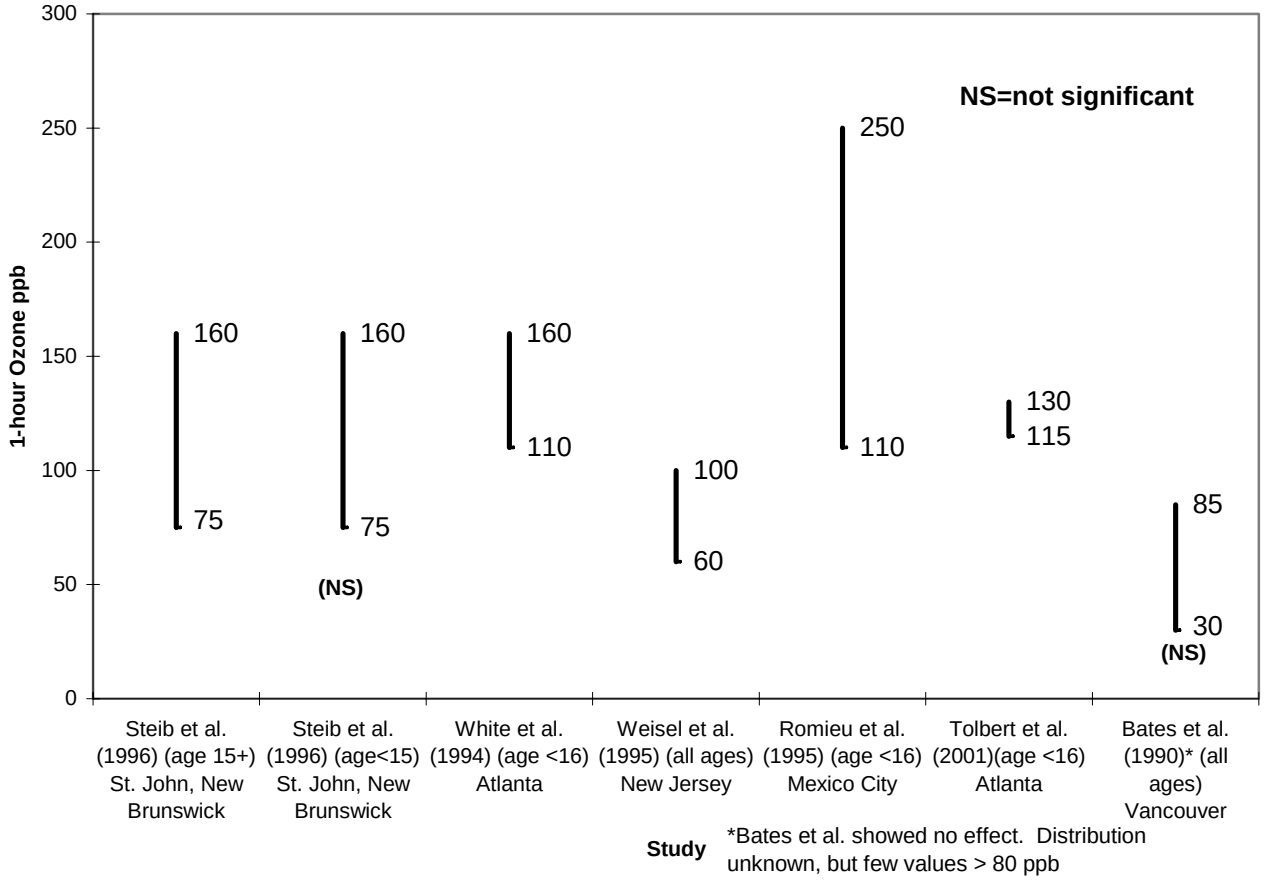
Maricopa-Stanislaus Street	0.072
Azusa	0.072
Livermore-793 Rincon Avenue	0.072
Fresno-Drummond Street	0.072
Concord-2975 Treat Blvd	0.072
Escondido-E Valley Parkway	0.072
Shafter-Walker Street	0.071
Barstow	0.071
Oildale-3311 Manor Street	0.071
Bethel Island Road	0.071
Fairfield-Bay Area AQMD	0.071
Visalia-N Church Street	0.071
San Diego-Overland Avenue	0.071
Lake Elsinore-W Flint Street	0.071
Calexico-East	0.071
Shaver Lake - Perimeter Road	0.070
Yosemite Natl Park-Turtleback Dome	0.070
Thousand Oaks-Moorpark Road	0.070
Los Gatos	0.070
North Highlands-Blackfoot Way	0.070
Calexico-Grant Street	0.070

Table 7.3 Annual mean of daily 1-hour maximum for 1999-2001 associated with attainment of 0.09 ppm 1-hour ozone for monitors in cities greater than 100,000 population.

City – Monitoring Site	2000 Population	Annual mean of daily 1-hr maximum for 1999-2001
Los Angeles-651 Mott St	3,694,820	0.0393
Los Angeles-North Main St	3,694,820	0.0374
San Diego-12th Ave	1,223,400	0.0408
San Diego-Logan Ave	1,223,400	0.0369
San Diego-Overland Ave	1,223,400	0.0437
San Jose-4th St	894,943	0.0323
San Jose-935 Piedmont Rd	894,943	0.0349
San Francisco-Arkansas St	776,733	0.0295
North Long Beach	461,522	0.0359
Fresno-1st St	427,652	0.0471
Fresno-Drummond St	427,652	0.0461
Fresno-Sierra Skypark #2	427,652	0.0524
Sacramento-3801 Airport Rd	407,018	0.0409
Sacramento-Del Paso Manor	407,018	0.0427
Sacramento-T St	407,018	0.0382
Oakland-Alice St	399,484	0.0242
Oakland-6701 Intern Blvd	399,484	0.0228
Anaheim-Harbor Blvd	328,014	0.0380
Riverside-Rubidoux	255,166	0.0446
Bakersfield-5558 Cal. Ave	247,057	0.0485
Bakersfield-GS Hway	247,057	0.0463
Stockton-E Mariposa	243,771	0.0436
Stockton-Hazelton St	243,771	0.0369
Fremont-Chapel Way	203,413	0.0349
Modesto-14th St	188,856	0.0407
San Bernardino-4th St	185,401	0.0446
Chula Vista	173,556	0.0453
Oceanside-Mission Ave	161,029	0.0423
Santa Clarita	151,088	0.0489

Santa Clarita-Cnty Fire Stat	151,088	0.0417
Salinas-High School	151,060	0.0380
Salinas-Natividad Road #2	151,060	0.0357
Pomona	149,473	0.0336
Santa Rosa Island	147,595	0.0427
Santa Rosa-5th St	147,595	0.0328
Hayward-La Mesa	140,030	0.0385
Pasadena-S Wilson Ave	133,936	0.0398
Sunnyvale-910 Ticonderoga	131,760	0.0304
Fontana-Arrow Highway	128,929	0.0413
Concord-2975 Treat Blvd	121,780	0.0388
Lancaster-43301 Division St	118,718	0.0368
Lancaster-W Pondera St	118,718	0.0481
Thousand Oaks-Moorpark Rd	117,005	0.0475
Vallejo-304 Tuolumne St	116,760	0.0326
Simi Valley-Cochran St	111,351	0.0508
Burbank-W Palm Ave	100,316	0.0400

Figure 7.1 Intervals of 1-hr Ozone Indicating Likely Effect Levels for Emergency Room Visits for Asthma



*Bates et al. showed no effect. Distribution unknown, but few values > 80 ppb