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**Comments of the American Lung Association on
U.S. EPA's Air Quality Criteria for Ozone and Related
Photochemical Oxidants
(First External Review Draft)
EPA/600/R-05/005aA
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I. Introduction

Ozone is a powerful oxidizing agent that damages lung tissue. Recent research with laboratory animals, clinical subjects, and human populations has identified a cascade of adverse health effects from ozone at levels common in the U.S. Effects include increased respiratory symptoms, damage to cells of the respiratory tract, pulmonary inflammation, declines in lung function, increased susceptibility to respiratory infections, and increased risk of hospitalization and early death.

Four groups of people are especially sensitive to ozone: infants and children, people with chronic obstructive respiratory disease (chronic bronchitis and emphysema) and asthma, persons who exercise or work outdoors, and people who are more sensitive to the physiologic effects of ozone. Under the Clean Air Act, the National Ambient Air Quality Standards (NAAQS) must protect these sensitive populations with an adequate margin of safety.

Given the serious lack of federal funding for ozone health research over the last eight years, the large number of new scientific studies available for review in the draft Criteria Document (CD) is impressive. Compilation of this CD was a massive undertaking and we congratulate the authors. We find this draft to be remarkably thorough and inclusive of almost all major new studies of interest, including relatively recent publications. We agree with the fundamental conclusion that short-term exposures to ozone are causally related to respiratory mortality and morbidity. 8-46. We note some specific omissions which should be covered, and cite some important recent studies that should be included in the next draft.

We have some concerns with the cautious *interpretation* of the recent literature. We find that evidence of serious adverse effects is sometimes downplayed. Some major new studies including those with policy significance are excluded. Emerging evidence of potential effects of ozone on new health endpoints such birth defects and genotoxicity are minimized. A series of new toxicological studies demonstrating remodeling of the airways is relevant to consideration of chronic effects. Major advances have been made in assessing the long-term effects of ozone since the last review, but this body of work is characterized as a “very limited database” 8-46. While the American Lung Association strongly supports additional research on the health effects of ozone air pollution, we find the final conclusion of the CD suggesting that additional research is needed to be somewhat tepid. 8-48.

It is worth noting that countries around the world have adopted or are considering more stringent air quality standards for ozone than the 1997 U.S. standards.^a The Canada wide air quality standard for ozone is 0.065 ppm averaged over 8 hours.¹ The World Health Organization has an ozone guideline of 0.06 ppm for an 8 hour exposure.² The 8-hour ozone standard in New Zealand is 0.05 ppm, and the 1-hour standard is 0.075 ppm.³ Australia has a 1-hour standard of 0.10 ppm and a 4-hour standard of 0.08 ppm to be

^a All units have been standardized for ease of comparison.

exceeded no more than once per year.⁴ The United Kingdom is considering an 8-hour average standard of 0.05 ppm.⁵

In 2005, the staff of the California Air Resources Board completed a review of the state air quality standards for ozone and concluded that their 1-hour standard of 0.09 ppm needed to be supplemented with an 8-hour standard, at the 0.070 ppm level not to be exceeded, in order to protect public health, including the health of children, with an adequate margin of safety.⁶ That report was reviewed by the ten-member Air Quality Advisory Committee, which was unanimous in finding the recommended standards to be well supported by the scientific evidence.⁷ On April 28, 2005 the Air Resources Board unanimously approved the new standards. The results of the California review, which was based on essentially the same scientific studies considered in this draft CD together with the studies reviewed in the 1996 CD, suggest that revisions to the NAAQS may be in order.

II. Omitted Studies

The draft CD appears to have captured most major studies of interest published since 1996 and is remarkably complete, with a few important exceptions. Several papers with policy significance that were omitted are noted below. It is possible that these papers were excluded because they are reviews or otherwise did not fit into the outline for the Criteria Document. We suggest that they are relevant to the review of the science and to the policy issues related to standard setting, and recommend that they be reviewed and included in the next draft of the CD.

A. Effect of Rounding

The Criteria Document appears to have missed a very important technical paper that has bearing on the form of the ozone standard. This paper published in the *Journal of the Air and Waste Management Association* examined the rounding convention used in the 1997 ozone standard that requires rounding of ozone design values to the nearest 10 ppb. The rationale for the rounding convention has been that the design value for the ozone standard is biased upward, and that rounding compensates for this overshoot bias. The analysis found that while there can be substantial overshoot bias in the design value of the older 1-hour standard, this is much less true for the new 8-hour standard. The new ozone standard may have little overshoot bias and may be within 3 percent of the true value most of the time. Thus rounding may tend to misclassify nonattainment areas as attainment, and serves, in effect to weaken the standard by 5 ppb.⁸ EPA should include this pertinent analysis in the next draft of the CD.

B. Children's Health

In late 2004, the American Academy of Pediatrics (AAP) published a major review of ambient air pollution and health hazards to children. The review concludes that the 1997 NAAQS for ozone may not adequately protect the health of infants and children. The paper cites studies showing declines in lung function, hospitalizations for

respiratory tract illness in young children, emergency department visits for asthma, and asthma exacerbations at levels at or below the current standards. In addition, cumulative childhood exposure to ozone may affect lung function when exposed children reach young adulthood. The AAP review suggests that ozone may be toxic to children at concentrations lower than 0.08 ppm.⁹ This important paper from the authorities on children's health should be included in the Criteria Document.

C. Diabetes

Hathout et al studied the role of ambient air pollutants in type 1 diabetes in children. Prediagnosis exposure to five air pollutants was studied in two subgroups with onset of type 1 diabetes before and after five years of age, and two matched subgroups of healthy children. The study concluded that increased ozone exposure may be a contributory factor to the increased incidence of type 1 diabetes.¹⁰

D. Genotoxicity/Carcinogenicity

Cheng et al, citing animal studies showing that ozone exposure can induce lung tumors, performed a study using single-cell gel electrophoresis and flow cytometry to investigate DNA damage to cells exposed to various levels of ozone. The study concluded that ozone levels below the current ambient standards may induce DNA breaks and oxidative DNA damage.¹¹ This study is relevant to the evaluation of the possible genotoxicity/carcinogenicity of ozone.

E. Sensitive Populations

Large differences in the sensitivity of individuals to ozone have been well documented. Those that are particularly sensitive are known as "responders." This study sought to establish the prevalence of "responders" in four different population subgroups: children, asthmatics, the elderly, and athletes, by assessing symptoms and measuring respiratory function. The study found higher rates of ozone responders in asthmatics (21%) and children (18%), as compared to the elderly and athletes (both 5%). This means that children and asthmatics have a higher risk of being ozone sensitive and experiencing more acute lung function decrements than these other population groups.¹² This study has relevance to EPA's determination of sensitive subpopulations. *It raises the larger point that the Criteria Document should include quantitative estimates of various subpopulations at risk from ozone exposure.*

F. Benefits Analyses

A new analysis published in *Environmental Health Perspectives* estimates the health benefits of attaining the 1997 ozone standard, using EPA's Environmental Benefits Modeling and Analysis Program (BenMAP). The analysis estimated that reduction of 2000-2002 ozone levels to the level of the standard would result in reductions of 800 premature deaths, 4,500 hospital and emergency room admissions, 900,000 school absences, and over a million minor restricted activity days each year. Minor restricted

activity days occur when people substitute less strenuous activities or rest for their usual routines. The study estimates the monetary value of these benefits at between \$4.9 billion and \$5.7 billion per year. The analysis notes that benefits would increase two to three times if the form of the standard did not allow any exceedances. (The current standard is based on the 4th highest 8-hour concentration averaged over 3 years.) The authors note that the study understates likely benefits. The study assumes that ozone concentrations will only be reduced at the specific monitors currently recording exceedances, while in reality, a larger geographic region would benefit from controls. In addition, the study notes that mortality estimates may increase by a factor of 2 when new meta-analyses of the ozone mortality literature are available. Key modeling assumptions are examined in a sensitivity analysis.¹³

An earlier publication presented a case study of the public health benefits or reduced ozone concentrations in Houston, and presented benefits estimates for premature mortality, chronic asthma, hospital admissions, and minor restricted activity days based on a probabilistic weighting of the strength of the evidence.¹⁴

These papers are notable because they both included estimates of mortality risks associated with ozone, and are relevant to the risk analysis.

G. Epidemiological Studies

In addition, we question the decision to exclude all epidemiology studies using GAM with default convergence criteria from the draft CD. The significance of the GAM issue was greatly politicized and overblown. The net conclusion was that there is no one “correct” model to use in analyzing time-series data. Analysts choose analytical models and assumptions based on their best judgments at the time of publication. Only a select set of studies have been re-analyzed. Studies should not be automatically excluded from inclusion because of their use of the default GAM model.

III. Interpretation of Major New Research Since Last Review

A. Toxicological Studies in Rhesus Monkeys

One of the most important developments in recent years has been the series of studies evaluating the long-term morphological effects of ozone exposure in infant rhesus monkeys. The CD reports that these studies in primates have demonstrated that long-term exposures can lead to “remodeling” of the distal airways, abnormalities in tracheal basement membrane, eosinophil accumulation in conducting airways, and decrements in airway innervation. 5-34.

The CD acknowledges that these are disturbing findings. But when discussing them in the integrated synthesis, the CD states:

“Most of the research results alluded to [in] the ensuing discussion come from toxicology studies using various laboratory animal species that were usually exposed to higher, non-ambient concentrations of O₃....Again, caution should be exercised in extrapolating these observations to humans, due to species-specific differences, as outlined earlier (see Section 8.2.7.3)” 8-32.

The section referred to appears to be missing from the document. The CD goes on to state “Again, one must be cautious in extrapolating these observations in animals to humans, given the exposure regimens and doses used.” 8-33.

These studies suggest that ozone may be cause serious long-lasting effects in infants and young children whose airways are undergoing rapid growth and development. Toxicological studies must employ high doses because of the small number of animal subjects tested. Since humans cannot be studied experimentally, these studies were designed to use a non-human primate model to provide information about health effects and mechanisms in humans. EPA’s interpretation of these studies should give them meaning in the context of setting standards to protect against acute and chronic effects in humans.

B. Controlled Human Exposure Studies

The clinical chamber studies conducted in the late 1980’s and early 1990’s conclusively demonstrated that a host of adverse health effects -- decrements in pulmonary function; increased respiratory symptoms such as cough and shortness of breath; heightened airway responsiveness; and inflammation of the airways -- were caused by 6.6 to 8-hour exposures to ozone at concentrations below both the 1-hour standard.

The chamber studies have reported clinically significant declines in lung function, respiratory symptoms, and biochemical evidence of inflammatory damage in healthy young adults at ozone concentrations of 0.08 ppm. For ethical reasons, children and those with serious lung disease are not tested. This implies that standards must be set below this level to protect sensitive populations with a margin of safety.

The findings of the earlier human exposure studies are reinforced by a meta-analysis published recently in the *American Journal of Respiratory and Critical Care Medicine*. The meta-analysis looked at 21 human chamber studies where airway responses were assessed using bronchoscopy-based lavage. Linear relationships were observed between ozone dose, airway inflammation, and protein leak into the airways over the early- and late-acute response time periods. Researchers found that exposure to ozone concentrations at 8-hour concentrations of 0.08 ppm at moderate ventilation rates would be sufficient to trigger acute airway inflammation. The researchers noted that since chamber studies use only healthy subjects, individuals with lung disease or other risk factors will experience responses at even lower levels.¹⁵

With effects observed in relatively healthy subjects down to the level of the standards, the results of the chamber studies call into question the adequacy of the current 8-hour standards to protect public health with an adequate margin of safety.

C. Ozone and Hospital Admissions

Petroeschovsky et al investigated the effects of ambient air pollution on 13,000 hospital admissions in Brisbane, Australia. The authors used the Air Pollution on Health: European Approach protocol to examine the effects of particles, ozone, sulfur dioxide, and nitrogen dioxide on daily hospital admissions for asthma and respiratory, cardiovascular, and digestive disorders (control diagnosis) that occurred during the period 1987-1994. Ozone was consistently associated with admissions for asthma and respiratory disease-with little evidence of a threshold. In two-pollutant models, the ozone effect was relatively unaffected by the control for high levels of other pollutants. The CD should make the point that ozone levels in Brisbane are relatively constant year round, and that aerosol sulfates were not present so the effect was due to ambient ozone alone.¹⁶

D. Asthma Exacerbations

Yale University researchers studied a group of 271 asthmatic children under age 12, living in Connecticut and Springfield, Massachusetts involved in a prospective study of asthma severity. The children's mothers tracked their asthma symptoms such as wheeze, persistent cough, chest tightness, and shortness of breath, and their medication use, on a daily basis. The study published in the *Journal of the American Medical Association*, reported that a 50 ppb increase in 1-hour ozone concentrations dramatically increased the likelihood of wheeze (by 35%) and chest tightness (by 47%).

The study found that asthmatic children using maintenance medication were particularly vulnerable to ozone even after controlling for co-exposure to fine particles, and even at pollution levels below EPA's current air quality standards for ozone. The highest levels of ozone on a 1-hour and 8-hour average basis were associated with increased shortness of breath and rescue medication use. PM_{2.5} was not significantly associated with a worsening of asthma when both ozone and fine particles were co-analyzed.¹⁷

This study has important implications for policy in light of the low levels of ozone found to exacerbate asthma symptoms in children with moderate to severe asthma.

Another important new finding that should be highlighted in the CD is that asthmatic children born prematurely or with low birth weight have the greatest response to ozone. Mortimer et al sought to ascertain which subgroups in a cohort of 846 inner-city asthmatic children aged 4-9 years old were most susceptible to the effects of summertime ozone. Children were recruited from emergency departments and primary care clinics in the Bronx and East Harlem in New York City, Baltimore, Washington, DC, Detroit, Cleveland, Chicago, and St. Louis, MO. The study reported that "children of low birth weight or of premature birth are at greater risk for respiratory problems, and appear to be

substantially more susceptible to the effects of summer air pollution than children of normal birth weight or full-term gestation."¹⁸

This study is important because it identifies premature or low-birth weight babies at increased risk of ozone exposure.

E. Epidemiologic Studies of Effects of Chronic Exposure

The most important new information available since the completion of EPA's review of the literature in 1996 has been in the area of long-term exposures. In addition to the toxicology studies of chronic effects discussed above, the draft report reviews epidemiologic studies that have found that:

--respiratory inflammation is increased in high vs. low ozone exposure groups or time periods;

--seasonal average ozone exposures affect lung function and respiratory symptoms;

--multi-year exposures diminish lung function growth; and

--long-term exposures may be associated with asthma prevalence particularly among children active in several sports.

Yet EPA devotes less than seven pages of the multi-volume Criteria Document to discussion of these important studies. Most of the major studies are included in the tables that form the Annex to Chapter 7, but this format does not allow for an integrated assessment of the epidemiological and field studies with the critical toxicological studies reporting effects of long-term exposures.

The conclusion that "a very limited database" is available on the long-term effects of ozone on respiratory morbidity (8-46) diminishes the substantial progress that has been made in quantifying the effects of chronic exposures. The conclusion should be restated in positive terms about what has been learned about the chronic effects of ozone exposure in studies of humans and laboratory animals. The availability of a considerable number of new long-term epidemiological studies, coupled with laboratory toxicology studies, autopsy studies, and field studies of children and animals in Mexico City, demands that EPA must give serious consideration to the question of whether the existing short-term standards are adequately protective of chronic exposures.

1. Lung Function

A number of long term-studies published since the last review have reported diminished lung function is associated with long-term exposure to ozone.

Galizia et al examined data from health status questionnaires and lung function measurements in relation to residence histories to examine the effect of long-term ozone

exposures on over 500 non-smoking Yale college students. Investigators found that "living for four or more years in regions of the country with high levels of ozone and related copollutants is associated with diminished lung function and more frequent reports of respiratory symptoms."¹⁹

Künzli et al developed a protocol to relate lifetime cumulative ozone exposure to small airway pulmonary function. In this study, 130 nonsmoking, non-asthmatic freshmen from the University of California at Berkeley who were lifelong residents of the Los Angeles Basin or the San Francisco Bay Area volunteered to participate in lung function testing. Researchers observed declines in mid- and end-expiratory flow measures of the small airways that are considered early indicators for pathologic changes that might ultimately progress to chronic obstructive lung disease. These declines were associated with estimated long-term ozone exposures.²⁰

Frischer et al followed a group of 1,150 first and second grade children in two counties in Austria from 1994-1996, to investigate the long-term effects of ambient ozone. The highest and lowest exposure to ozone differed by a factor of two. Researchers found small but consistent decrements in lung function associated with ambient ozone. They conclude: "This is the first study that suggests chronic effects of ozone on lung function growth in children. Thus, ozone would constitute a risk factor for premature respiratory morbidity during later life."²¹ This effect of ozone was confirmed in a follow-up study.²²

Swiss researchers followed a group of 3,900 nonsmoking adults from eight areas of Switzerland that represent a range of urbanization, air pollution, altitude, and weather conditions. In this study, researchers obtained three different measures of lung function and compared the results with prior days' measurements of ozone, total suspended particulates, and nitrogen dioxide. Daily average concentrations of ozone were significantly associated with mean respiratory function measures during the summer months. Associations remained stable after controlling for other pollutants and for pollen. Though the effects were small, researchers conclude that current levels of air pollution have public health significance.²³

The California Children's Health Study annually measured the lung function of 1,700 fourth-graders enrolled in 1996, monitored the communities' air pollution for four years until 2000, and analyzed the relationships between their lung function growth and the levels of six pollutants. Exposure to ozone was correlated with reduced growth in peak flow rate. Larger deficits in lung function growth rate were observed in children who reported spending more time outdoors. Slower lung growth over a period of several years is evidence of a chronic effect of air pollution on children's respiratory health. Children whose lungs have grown more slowly may have lower maximum lung function as adults, making them more susceptible to respiratory diseases and chronic problems as they age.²⁴

These studies should be evaluated in the context of the negative findings that have also been reported.

2. Field Studies of Children in Mexico City

Children in Mexico City are chronically exposed to a complex mixture of air pollutants, including hydrocarbons, ozone concentrations well above the NAAQS, and significant concentrations of metal-containing PM. Researchers followed 174 children aged 5-17, and compared them to 27 control children living in low-polluted areas. Researchers assessed several measures of respiratory damage in the children, including nasal abnormalities, hyperinflation and interstitial markings in the lungs observed by chest X-ray, lung function changes, and blood concentrations of proteins that are indicative of the health of the immune system.

Researchers found that the air pollution exposure produces significant chest X-ray abnormalities in the exposed children, depressed lung function, and an imbalance of blood proteins important to immune response. Twenty-two percent of the exposed children had grossly abnormal nasal mucosa, which can impair nasal defense mechanisms against inhaled gases and particles. The lung damage observed is similar to the chronic inflammatory damage observed in an earlier study of dogs in Mexico City. Researchers report that the x-ray and lung function changes they found in the exposed children could be due to pollution-associated chronic bronchiolitis, which could put the children at greater risk of developing chronic obstructive airway disease later in life. They conclude that lifelong exposure to urban air pollution causes respiratory damage in children and may predispose them to development of chronic lung disease and other problems due to suppression of the immune system.²⁵

Another study by some of the same researchers reported that biopsies taken from these children exhibit a wide range of pathologic changes to the cells of the nasal passages. “The severe structural alteration of the nasal epithelium together with the prominent acquired ciliary defects are likely the result of chronic airway injury in which ozone, particulate matter, and aldehydes are thought to play a crucial role,” concluded the researchers. “The nasal epithelium in SWMMC [Southwest Metropolitan Mexico City] children is fundamentally disordered, and their mucocilliary defense mechanisms are no longer intact. A compromised nasal epithelium has less ability to protect the lower respiratory tract and may potentially leave the distal acinar airways more vulnerable to reactive gases.”²⁶ These findings are extremely significant to EPA’s evaluation of long-term effects.

3. Asthma development

Two prospective cohort studies have reported an association between ozone exposures and asthma induction.

The ASHMOG prospective cohort study of over 3,000 adults in the nonsmoking Seventh Day Adventist community sought to examine the whether long-term exposure to ozone air pollution can contribute to the prevalence of asthma. The study found that 8-hour average ambient ozone concentration averaged over a 20-year period was associated with doctor diagnoses of adult-onset asthma in nonsmoking males.²⁷

An analysis from the California Children's Health Study points to ozone as a cause in the development of asthma in young people who did not previously have the disease. The study compared new asthma cases in 3,535 children who were followed over five years in 12 Southern California communities to determine the potential health damage caused by growing up in polluted air. Six of the communities had higher than average ozone concentrations while six had lower than average concentrations. The study found that children in the high ozone communities who played three or more sports developed asthma at a rate three times higher than those in the low ozone communities. Because participation in some sports can result in a child drawing up to 17 times the "normal" amount of air into the lungs, the study indicates that young athletes may be more likely to develop asthma.²⁸

F. Short-term Mortality

Since EPA's last review of the ozone standards in 1997, a growing number of epidemiological studies have reported an association between short-term exposures to ozone and premature mortality. Short-term increases in ozone were found to increase total non-accidental mortality and deaths from cardiovascular and respiratory causes in a large 14-year study of residents of 95 U.S. cities. The relationship between mortality and ozone was evident even on days when pollution levels were below the EPA 8-hour standard of 0.08. The ozone and mortality results did not appear to be confounded by temperature or PM₁₀.²⁹ The California Staff Report has noted that the "NMMAPS study may generate an underestimate of the impact of mortality due to the modeling methodology used to control weather factors. Specifically, this effort included four different controls for temperature and dewpoint, where most other times-series analyses used only two or modeled extreme weather events more carefully and used city-specific models to ensure the best fits."³⁰

A large multi-city European study (APHEA2) reported a positive association between one- and eight-hour concentrations of ozone air pollution and daily mortality, especially respiratory mortality, during the warm season.³¹

A recent case-crossover study of 14 U.S. cities was designed to control for the effect of temperature on daily deaths attributable to ozone. The study concluded that the association between ozone and mortality risk reported in the multi-city studies is unlikely to be due to confounding by temperature.³²

A new meta-analysis of time-series studies has been undertaken by the World Health Organization. Using results from only European cities, this study reports an effect estimate of about 0.78% per 10 ppb increase in daily ozone concentrations,³³ providing strong evidence of the effect of ozone on mortality. This is the main conclusion to be drawn from this study, not the "reported evidence of publication bias" emphasized by the CD. 7-65.

Three new meta-analyses of the effects of ozone on mortality commissioned by EPA are in press in the journal *Epidemiology* report a significant association between ozone levels and total mortality.

The Bell et al meta-analysis (in press) reports that a 10 ppb increase in daily ozone is associated with a 0.83 % increase in total mortality, as compared with the NMMAPS estimate of 0.25 %.³⁴ Both the meta-analysis and NMMAPS reported larger effects for cardiovascular and respiratory mortality.

A summary of the results of the studies prepared by Dr. David Bates for an editorial in press in the journal *Epidemiology* was presented at a meeting of the California Air Quality Advisory Committee.³⁵

“One author (Levy) used data from 14 U.S. cities, 13 Canadian cities, and 21 European cities, and excluded data from the NMMAPS (National Morbidity and Mortality Air Pollution Study) and from Mexico City; the second (Bell) used the data from the NMMAPS study of 95 cities, together with European studies for a total input of 144 datasets; ... the third (Ito) was more restricted and used data from 7 U.S. cities plus other worldwide data for different parts of the analysis. Another difference was that one author (Levy) used data on the prevalence of air conditioning in both the U.S. and Canada. Bayesian hierarchical models were used in the analyses. PM interaction with ozone was found generally to be unimportant; all three studies noted that the response function was higher in the summer (when ozone levels are higher) than in the winter, and this means that if the data are not stratified by season, the overall response outcome is likely to be diminished. Other factors noted were that the prevalence of air conditioning affected the outcome (Levy); that the NMMAPS data alone yielded lower response outcomes than most other analyses; and that there was generally satisfactory concordance between US and European data.

“One study found a change in total mortality of 0.86% per 10 ppb in summer (Levy); the second (Bell) found a change of 0.83% per 10 ppb in total mortality overall, and agreed that U.S. and non-U.S. data were similar; the third study (Ito) provided a detailed seasonal breakdown and showed that the main effect occurred in the warm season. In an analysis for a single pollutant model, data from 8 US regions, 8 European cities, two Australian cities, plus Mexico City, Sao Paulo, Santiago, and two regions of South Korea are plotted in this paper. Below zero data (insignificant) were noted for 5 cities, and all the rest were positive. The highest was for Brisbane in Australia, at about a 3.5% mortality increase per 10 ppb for the 24 hour average ozone. *Reviewing all the data, I would regard the value of 0.86% change in mortality per 10 ppb as a minimal figure since inclusion of data from Brisbane and Mexico City would increase this significantly.* (emphasis added).

“The European data was derived from 23 different regions with mortality data over a three year period. The authors reported no association between ozone and mortality over the winter months, but a significant association in summer with a mean increase of 0.33% in total mortality, 0.45% in cardiovascular deaths, and 1.13% in respiratory deaths for an increase of 10 micrograms/m³ of ozone. As this is equivalent to 5 ppb, the percentage increases should all be doubled for a 10 ppb change. They also found that PM₁₀ values were not a confounder, but reported some possible interaction with NO₂ and CO....

“These three new meta-analyses and the European study, each with unique features, appear to resolve the question of whether ambient ozone levels are associated with increased mortality. It seems unlikely that PM_{2.5} is an important confounder, and the effect appears to be independent of temperature. A final question (biological plausibility) is in some ways, the easiest to answer. Ozone is capable of causing inflammation in the lung at lower concentrations than any other gas. Such an induced effect would be a hazard to anyone with heart failure and pulmonary congestion, and would worsen the functioning condition of anyone with advanced lung disease. The ozone/mortality relationship is therefore supported by strong biological probability.”

In addition, another paper in press in the journal *Environmetrics* provides additional evidence in support of an association between ozone and mortality. Huang et al analyzed data for 19 large U.S. cities and reported that on average, a 10 ppb increase in summer ozone level for every day in the previous week was associated with 1.25 percent increase in cardiovascular and respiratory mortality.³⁶

Collectively, these studies will significantly strengthen the CD’s conclusion that the relationship between ozone and mortality can now be considered causal.

The three meta-analyses were specifically commissioned by the U.S. EPA for use in benefits analyses and risk assessments, and should be included in the Criteria Document, and used as the basis for the risk assessment in the Staff Paper.

IV. New Health Endpoints

A. Adverse Birth Outcomes

A UCLA study provides compelling evidence that contemporary concentrations of ozone air pollution may play a role in causing some birth defects. Pregnant Los Angeles-area women living in regions with higher levels of ozone and carbon monoxide pollution were as much as three times as likely to give birth to children who suffered from serious heart defects. Researchers analyzed information collected by the California Birth Defects Monitoring Program on more than 9,000 babies born from 1987 to 1993 in Los Angeles,

Orange, San Bernardino and Riverside counties. Using measurements made regularly at 30 locations by the South Coast Air Quality Management District, researchers compared air quality near the homes of cases to air quality in the neighborhoods of children born healthy. Pregnant women who were exposed to increased levels of ozone and carbon monoxide faced an elevated risk of having a child with conotruncal heart defects, pulmonary artery/valve defects and aortic artery/valve defects. This group of heart defects occurs 1.76 times per 1,000 births, with about 935 cases in California each year. Many of these babies face open-heart surgery before age one.³⁷

Without citing this particular study, the CD finds:

“Recent studies tend to confirm previous conclusions that prenatal exposures to O₃ concentrations < 1.0 ppm do not cause major or widespread somatic or neurobehavioral effects in the offspring of laboratory animals. These studies generally add some weight toward a negative interpretation of the importance of contributions of low, ambient O₃ to lower birth weights and gross development defects reported in neonates born to women exposed to typical ambient pollution (e.g., Renner, 2002; Chen et al., 2002; Ritz and Yu, 1999). Some postnatal O₃ exposure studies continue to find a few, subtle or borderline somatic and behavioral deficits that will require further research to better assess potential risk to developing humans.” 5-52.

The Ritz 2002 study, which is not discussed in detail in the CD, would alter this conclusion.

B. Cardiovascular Effects

New evidence is beginning to emerge about the potential cardiovascular effects of ozone. A population-based study recently published in the journal *Circulation* after the publication of the draft CD reported that short-term exposures to ozone predict alterations in cardiac autonomic function as measured by heart rate variability among older adults.³⁸

A case-crossover study in France has reported that ozone exposure within a period of 1 to 2 days is associated with heart attacks in middle-aged adults without heart disease.³⁹

These studies should be evaluated and included in the next draft of the CD.

IV. New Studies for Inclusion in CD

It is a hard task to keep the CD current in the face of newly published information. A number of important new studies on the health effects of ozone have been published since the draft CD was issued in January 2005. These studies point to health endpoints ranging from asthma to heart attacks and cancer. EPA will want to review these studies for inclusion in the next draft CD.

A. Lung Function Decrements in Outdoor Workers

An important study in press in *Environmental Health Perspectives* reports that acute lung function reduction occurs in mail carriers exposed to ozone concentrations below current ambient air quality standards. This study is especially relevant to the assessment of populations at risk such as outdoor workers.⁴⁰

B. In Vitro Studies

A new study of cultured human blood cells reports a significant relationship between cytokine production and ozone concentrations.⁴¹

C. Toxicological Study of Sensitive Subgroups

A newly published laboratory toxicology study in rats found that immature and aged rates displayed lung oxidative stress after ozone exposure, as compared to adult specimens.⁴²

D. Carcinogenicity

A recently published study in São Paulo, Brazil found that exposure to ozone was correlated with tumors of the larynx and lung.⁴³

E. Asthma

A recent German study has reported that NO_x and ozone air pollution modifies proteins from pollen and other sources in ways likely to make them more allergenic and more likely to trigger an asthma attack.⁴⁴

F. Respiratory Emergency Department and Hospital Admissions in Children and Adults

A time-series study of respiratory emergency department visits in Atlanta has reported an association between ozone and upper respiratory infection visits, specific to infants and children. The association with ozone persisted in multipollutant models. During warm months a 25 ppb increase in ozone was associated with a 2.6% increase in pediatric asthma visits to the emergency room.⁴⁵ An Australian study air pollution and childhood asthma emergency hospital admissions reported a positive association with ozone only in the Western regions of Melbourne.⁴⁶ And a study in Portland, Maine found that ozone increases were correlated with emergency room visits for asthma.⁴⁷

The Criteria Document should be updated to include these and other studies in press documenting the health damage caused by ozone air pollution and the potential benefits of reductions in ambient concentrations.

VI. Conclusion

This first draft criteria document could be substantially strengthened by inclusion of recent and missing studies, and more precautionary interpretation of the evidence of adverse effects of ozone.

¹ http://www.ccme.ca/assets/pdf/pmozone_standard_e.pdf

² <http://w3.whosea.org/techinfo/air.htm>

³ http://www.mfe.govt.nz/publications/air/ambient_-_air-quality-may02/html/table1_-_guideline-values.html

⁴ http://www.ephc.gov.au/nepm_s/air/air_nepm.html

⁵ <http://www.defra.gov.uk/environment/airquality/aqs/ozone/index.htm>

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