Comments by the Texas Commission on Environmental Quality (TCEQ) Regarding Draft Integrated Science Assessment for Ozone and Related Photochemical Oxidants
EPA Docket ID No. EPA-HQ-ORD-2011-0050

General Comments

The time allowed for comment on the Second ISA is unreasonably short.

In the ISA, EPA indicates that many of the overall conclusions remain generally the same as the last National Ambient Air Quality Standard (NAAQS) review which was completed in 2008. However, contrary to the EPA's statement, the ISA includes conclusions regarding a wide-range of health effects including stronger causal associations for both short-term and long-term exposures to ozone and newer end points such as the effects to the central nervous system, cardiovascular system, and reproductive and developmental effects. In addition, despite lack of compelling evidence, EPA concludes causal associations with long-term exposure to ambient ozone and mortality.

This report has several implications in regulatory context. However, a comment period of only 60 days is insufficient for regulating agencies and other interested parties to provide the most thorough and meaningful comments possible based on an in-depth review and analysis of the ISA. The assessment of the health effects associated with low-level ozone exposure has significant implications in a regulatory context. There is great complexity associated with multiple issues relevant to the assessment of health effects of ozone, especially at low exposure levels close to background ozone levels. Given the complexity and volume of relevant materials, it is not practical for EPA to expect detailed specific comments from external experts in the short period allowed for a critical review of the ISA. Given the limited timeframe, the TCEQ is only able to provide comments based on a cursory review and would prefer to have additional time in order to: (1) perform a more detailed review of the volumes of relevant information; (2) more fully examine statistical procedures and the rationale and scientific support for key EPA decisions and analyses; and (3) provide more detailed specific comments on all problematic issues associated with the ISA.

The EPA should be transparent in its process of choosing key studies and provide clear documentation of how it arrived at its conclusions.

While the EPA should be commended on summarizing a large amount of important information for a wide-range of end points, the conclusions that EPA has derived nonetheless deserve careful scrutiny, especially when they are used for regulatory decisions such as the setting of the NAAQS for ozone. To indicate a health effect having "sufficient evidence of an association," there must be an observed relationship between the exposure and health outcome in studies in which chance, bias, and confounding variables could be ruled out with reasonable confidence. However, some key studies used by EPA in the ISA are inadequate to demonstrate sufficient evidence of an association between short-term and long-term exposures to ozone and cardiovascular and central nervous system effects and mortality.

The roles of uncertainty and bias in EPA's assessments have been severely downplayed and should be reexamined. This is particularly true in EPA's analysis of personal exposure. For ozone, EPA relies on studies that estimate personal exposure (the amount of ozone a person *actually* breathes) by using ambient monitoring data as a surrogate for personal exposure. However, it is very unlikely that people would ever be exposed to those pollutants at concentrations measured at outdoor monitors for very long periods of time. This lack of

exposure occurs partly because the average American spends a large amount of time indoors, especially during the heat of the summer when ozone concentrations tend to be at their highest. In fact, Koutrakis et al. (2005) conducted a study to characterize particulate and gas exposures of sensitive subpopulations living in Baltimore and Boston and reported that subjects from all cohorts in both cities spent the majority of their time indoors, from 65% to 82% of the 24-hour sampling periods. This assumption that the personal exposure of an average American is similar to ambient ozone concentrations oversimplifies personal exposure by assuming that ambient monitoring data accurately reflects personal exposure. Further, EPA doesn't acknowledge or account for this potential overestimate in their standard calculations. Also, it is essential that EPA clearly discuss the uncertainties associated with adverse health effects reported in both ecological epidemiology and clinical studies. These uncertainties should also be clearly communicated in publicly accessible documents in consideration of new standards.

Because of the significant consequences and cost of lowering the standard, it is imperative that EPA distinguish true risk from just causal association because associations are not causations. Statistically, one can find associations by making many comparisons. This does not necessarily demonstrate causation. Application of the modified Hill criteria is necessary to start to prove causality. The recognition of possible overestimation of risk when epidemiology studies are used as a basis of development of regulatory standards requires a great deal of caution.
Below are some of the main issues which, if addressed properly, would result in more accurate estimates to base the ozone NAAQS.

1) The tenuous connection between the air pollution data and the mortality data.

2) The difference between imprecise population-wise exposures and more precise individual exposure estimates.

3) The concerns of the Committee of the National Academy of Sciences (NAS) with EPA's methodology. For example, one key concern of the NAS is EPA's consistent failure to document how studies are selected for review.

4) EPA's bias in study selection. For example, the exclusion by EPA of well-conducted studies if their results showed no adverse health effects and the EPA's policy of discounting or ignoring studies showing no association between ozone exposure and asthma exacerbation.

Many studies have indicated an association between acetaminophen use and asthma. Recently, McBride, a pediatrician, also reported an association of acetaminophen and asthma prevalence and severity in children even with relatively modest doses of acetaminophen (McBride 2011). According to McBride (2011), the clinical relevance of this association is large as many children throughout the world are exposed to such doses. EPA has not yet accounted for the confounding effects from these studies and should do so before arriving at conclusions of ozone exposures and asthma.

5) The exclusion of recent reports showing no association between ozone and cardiovascular morbidity (Szyskowica 2009, Symons et al. 2006, Villeneouve et al. 2006, Wellenius et al. 2005, Tolbert et al. 2007, Zanobettei and Schwartz 2006).

6) EPA's acceptance of a positive result for one pollutant from the very same study that was rejected as "notoriously unreliable" for showing a negative result for a second pollutant (EPA (2007) and Mortimer et al. (2002))

7) The discounting of multiple no-effect studies (Schildcrout et al. (2006) and O'Connor et al.(2008)) in favor of a solitary study showing an adverse health effect.

8) EPA calculating the "benefits" from reductions in particulate matter and ozone concentrations that are far below those said to be safe by the Clean Air Scientific Advisory Committee (CASAC).

9) A lack of comprehensive analysis of uncertainty and variability (in some cases, an error in one assumption can virtually eliminate all claimed benefits for PM and ozone reduction).

10) Lack of sensitivity analysis of results to assumptions. Given the highly dependent nature of EPA's overall benefit analysis on this one assumption, TCEQ questions whether EPA is conducting an objective analysis of the data.

Comments on Short-Term Health Effects of Ozone

The TCEQ disagrees with the EPA's conclusions that short-term exposure to ozone is "Suggestive of a Causal Relationship" to cardiovascular and central nervous system effects, and "Likely to be a Causal Relationship" to mortality.

Respiratory Effects

The TCEQ would like to reiterate that while the available scientific evidence supports a casual relationship between acute ambient ozone exposures and respiratory effects, these effects are dose dependant, and that the weight of evidence does not suggest a causal relationship at concentrations below the current National Ambient Air Quality Standard of 75 parts per billion (ppb).

1.   EPA should rely on biological, not just statistical, significance in identifying an adverse health effect in clinical studies.

The definition of "adverse effect" with regard to exposure to air pollution remains ambiguous. Clinical studies evaluating health effects due to ozone exposure have mainly focused on decreases in lung function as measured by forced expiratory volume in one second (FEV_1) and other similar measures. Daily normal activities, exercise, and diurnal variations can themselves cause changes in the FEV_1. Within a single day, FEV_1 in normal subjects can vary by over 5% (Pellegrino et al. 2005) and as much as 17.6% (Medarov et al. 2008). Therefore, controlled exposure studies must properly account for normal changes by including filtered air (FA) exposures and a range of concentrations and exposure durations. The American Thoracic Society (ATS) recommends a comprehensive description of "adverse" effects by combining the loss of lung function in conjunction with respiratory symptoms, such as cough and discomfort while breathing (ATS 2000). Further, OEHHA, the TCEQ, and jointly the ATS and the European Respiratory Society (ERS) consider decrements in FEV_1 of $\leq 20\%$ as "mild," not "adverse." However, in its reevaluation of the Adams (2006) study, EPA identified FEV_1 decrements of only 2.8% to be adverse effects. According to the sources listed previously and Adams himself in his comments to the CASAC indicated that the decrements in the Adams (2006) study at 0.06 ppm are not of biological significance, even though they may be of statistical significance (Adams 2007). Therefore, it is also prudent that the EPA justify the importance of key study results to indicate not just statistical significance, but also biological significance before labeling the result as an "adverse effect."

2.   EPA's reanalysis of Adams (2006) data is not scientifically appropriate and should not be included as part of the final ozone policy decision.

In addition to the issue of whether or not the decrease in FEV_1 was adverse, the EPA also conducted a highly questionable statistical reanalysis of the Adams (2006) data to show

statistical significance in the absence of the effect (Brown et al. 2007, Brown et al. 2008). Dr. Adams himself disagreed with the EPA's reanalysis and statistical reinterpretation of his study during a teleconference on March 5, 2007, and in written comments to the EPA during the 2007 comment period (Adams 2007). EPA's reanalysis was also criticized by other statisticians and scientists, as stated in comments submitted to EPA by Drs. R.L. Smith and J.E. Goodman. The TCEQ concurs with Dr. Adams's peer-reviewed results.

3.   EPA should consider more recent studies as part of the ozone weight of evidence.

Recent clinical studies (Kim et al. 2011, Schelegle et al. 2009) of ozone exposure at 0.06 ppm have further confirmed the Adams's results (2006), showing subtle statistically significant effects at 0.06 ppm. When compared to filtered air, Schelegle et al. (2009) reported statistically significant mean percent change in FEV_1 at 0.07 ppm (5.34%) and Kim et al. (2001) reported statistically significant mean percent change in FEV_1 at 0.06 ppm (1.71%), these are not only within in the range of intra-individual variability but are also substantially less than the 20% decrease identified as adverse by multiple agencies including OEHHA, the TCEQ, the ATS, and the ERS.

4.   EPA needs to emphasize the importance of having realistic controls for clinical studies.

Many of the clinical studies use filtered air (no ozone) for the control groups (Schelegle et al. 2009, Kim et al. 2011), which creates an unrealistic scenario as the natural background ozone concentration in the atmosphere is around 0.04 ppm (Last et al. 2010). In its analysis of the clinical studies, EPA has not adjusted for this background factor and has not provided any justification for not doing so. Using an unrealistic background exposure, can greatly distort the estimated slope of the exposure-response relationship, and overestimate any risks associated with exposures above the true background. This can translate to overestimating the severity of the observed effects as "adverse effects," when in fact the effects were not adverse. Based on the clinical studies, it can be inferred that the weight of evidence at the lower range of exposure levels (i.e., 0.06 – 0.07 ppm) is weak and inconclusive. Thus, TCEQ concludes that the clinical studies used to justify the lower end of the proposed range do not support lowering the ozone standard below the present NAAQS of 0.075 ppm (Adams 2002 and 2006, Schelegle et al. 2009, Kim et al. 2011). Further, these studies are conservative since they do not consider personal exposure and assume that people are exposed to the ambient concentrations, when in fact the average person spends a majority of their time indoors.

Cardiovascular Effects

In the 2006 Air Quality Criteria Document (AQCD), EPA concluded that the limited evidence is highly suggestive that ozone directly and/or indirectly contributes to cardiovascular-related morbidity, but much remains to be done to more fully substantiate the association. In the 2011 ISA, the EPA concluded the evidence is "Suggestive of a Causal Relationship."

The TCEQ disagrees with EPA's conclusion in regards to the suggestive causal relationship of short-term exposure to ozone and adverse cardiovascular effects.

The 2006 EPA assessment determined that there was limited evidence that ozone directly and/or indirectly contributes to cardiovascular-related morbidity, but much remained to be done to more fully substantiate the association. In the 2011 ISA, EPA cited a recent controlled exposure study conducted by Fakhri et al. 2009 as providing evidence that ozone causes adverse cardiovascular effects in humans (increased high frequency heart rate variability, p=0.051). In fact, Fakhri et al. 2009 actually concluded that ozone did not significantly increase high frequency heart rate variability after adjusting for respiratory parameters known to influence this effect. EPA cited a controlled exposure study conducted by Gong et al. 1998 in which

exercising humans exposed to 300 ppb ozone for three hours experienced a small increase in the alveolar-to-arterial PO2 gradient. The biological relevance of this effect is questionable since subjects in the Gong et al. 1998 study did not experience significant ECG changes or myocardial ischemia and/or injury. EPA provided detailed information on numerous epidemiological studies investigating the association between short-term ozone exposure and adverse cardiovascular morbidity and mortality. EPA concluded "…there is weak coherence between associations for cardiovascular morbidity and mortality. Further, there is no apparent biological mechanism to explain the association observed for short-term ozone exposure with cardiovascular mortality."

While animal toxicological studies can be helpful and supportive in providing the weight of evidence to human clinical studies and epidemiology studies, they are often conducted at very high concentrations that are not representative of actual ambient conditions and personal exposures of humans. Recent animal toxicological studies discussed in the 2011 ISA are summarized in Table 6-39 of the report. Animals were exposed to ozone concentrations of 500 ppb to 1,000 ppb, concentrations that are much higher than typical ambient concentrations relevant to humans. These high concentration effects are also not relevant to humans who are exposed to much lower levels. Cardiovascular effects observed in short-term animal studies presented in the 2011 ISA included alterations in heart rate and heart rate variability, induction of vascular oxidative stress and proinflammatory mediators, and alteration in the regulation of the pulmonary endothelial system. It is not clear in the discussion whether EPA considers these observed effects to be biologically significant or adverse. As mentioned above, EPA should rely on biological, not just statistical, significance in identifying an adverse health effect. These short-term animal studies require careful extrapolation to relevant human exposure levels and endpoints and the interpretation of the observed effects has to be done cautiously.

Mortality

In the 2006 AQCD, EPA concluded that the evidence was highly suggestive that ozone directly or indirectly contributes to non-accidental and cardiopulmonary-related mortality. In the 2011 ISA, the EPA concluded that there is "Likely to be a Causal Relationship" from short-term ozone exposure and mortality.

The TCEQ disagrees with EPA regarding its conclusions that there is "likely to be a causal relationship of short-term exposure to ozone and mortality" because the TCEQ believes that the weight-of-evidence for mortality estimates due to short-term exposure to ozone is not conclusive.

Similar to the 2006 Air Quality Criteria Document (AQCD), the present ISA has relied strongly on ecological epidemiology studies as the basis for conclusions by the EPA. Many of the key studies in the 2006 AQCD were based on observations made when the levels of ozone and other pollutants were much higher than they are today. Further, EPA relies on studies that take mortality data from ecological epidemiology studies to calculate the number of theoretical deaths that would be avoided with a lower ozone standard. While there is some understanding of the mode of action for higher short-term exposures and mortality, the complete physiopathological mechanism leading to death is not understood.

Not only do ecological epidemiology studies suffer from severe limitations, but estimates of theoretical lives saved are also meaningless from a scientific and practical standpoint especially since such estimates depend on unrealistic assumptions about future exposures and the future state of the environment with regard to other pollutants. It is not possible to verify either the current number of deaths due to exposure or the future change in deaths if the standard is lowered. All estimates of lives saved are theoretical, not factual. There is no guarantee of

increased life expectancy or degree of confidence in such an estimation, since some degree of risk is present in all aspects of daily life. It is impossible to tease out the miniscule risks from low levels of air pollution from the overwhelming risks of diet, genetics, smoking, etc.

Ecological Epidemiology Studies

Ecological epidemiology studies are observational studies designed to look for correlations. To accomplish this they examine the relationships between exposure and disease at a population-level rather than on an individual-level. These types of studies are intended to be followed up by more rigorous epidemiology studies to determine if the correlations are real. While ecological epidemiology studies are useful in evaluating *potential* associations between health effects and ambient exposures to environmental pollutants, they are severely limited due to their study design. Another drawback of these studies is that they often make inferences from data in years when the air pollution levels were higher. Air pollution levels have been declining throughout the country, and therefore, conclusions from these studies should be cautiously interpreted as those air pollution levels may not be directly applicable to the present scenario where ozone levels are close to background ozone levels. Further limitations of ecological epidemiology studies are outlined below:

1.   Ecological epidemiology studies are not designed to determine if ozone caused the health effects observed.

The assumption that ozone caused all evaluated health effects, including aggravation of asthma and premature mortality, in ecological epidemiology studies is not well-grounded in science. Ecological epidemiology studies do not collect data on when, how long, and how much exposure occurred; if exposure occurred before the health effects; or if it makes biological sense that the chemical could cause the effect. In other words, the study designs are incomplete. In general, scientists agree that the incomplete study design does not provide enough information to determine the actual cause of studied effects. Ecological epidemiology studies are not supposed to be used quantitatively and they certainly are not rigorous enough to set environmental policy.

2.   Lack of personal exposure data severely limits the utility of ecological epidemiology studies.

The issue of limited or entirely absent personal exposure data is significant. Personal exposure is a measurement of the amount of an air pollutant that a person actually breathes. In the case of air pollutants like ozone, ecological epidemiology studies rely on ambient monitoring data as a surrogate for personal exposure. However, it is very unlikely that people would ever be exposed to those pollutants at concentrations measured at outdoor monitors for very long. This is partly because the average American spends a large amount of time indoors, especially during the heat of the summer when ozone concentrations tend to be at their highest (Koutrakis et al. 2005). Ozone concentrations in most buildings are characteristically low, due to the reactive nature of ozone, the tendency of ozone to deposit on surfaces, and the ventilation systems inside buildings (McClellan et al. 2009). Other additional factors such as time spent outdoors, outdoor activity level, and weather (especially temperature and relative humidity) can dramatically change the potential for ozone exposure and the resultant estimate of risk. Therefore, ambient ozone concentrations alone do not adequately characterize, and easily overestimate, personal exposures (Sarnat et al. 2006). This position is shared by the National Academies of Science (NAS 2008) and the Clean Air Science Advisory Committee (Henderson 2006). That ecological epidemiology studies continue to derive inconsistent and vastly differing conclusions about the adverse effects of ozone is perhaps evidence of this fact.

3.   Ecological epidemiology studies frequently do not take into account the heterogeneity of regional air pollution and oversimplify their exposure analysis by relating health effects to only ozone.

In most ecological epidemiology studies, exposure is estimated to be either some statistical representation (e.g., average or weighted average) of several air monitors or concentrations at the monitor with the highest readings. This assumption oversimplifies outdoor exposure because concentrations vary across a given area. Moreover, few studies fully account for simultaneous exposure to multiple other pollutants, such as particulate matter, nitrogen dioxide, and sulfur dioxide. The ratios of these pollutants can vary tremendously from region to region, making it difficult to determine which effects are related to which pollutants. This complication blurs the association between health effects and ozone exposure, as documented in recent studies. Furthermore, it has been repeatedly demonstrated that the association between ozone and health effects is confounded by temperature and relative humidity (which alone can cause physical stress), and population characteristics, such as age, health status, socioeconomic status, and exercise.

4.   Ecological epidemiology studies have considerable uncertainty in their identification of health effects.

To determine prevalence of a health issue, epidemiologists frequently use readily-available information, including hospital admissions records and death certificates or participant surveys. In some of the ecological epidemiology studies EPA used for the proposed ozone standard, death certificates for thousands of people who died at a hospital from any non-accidental cause were compared to outdoor ozone levels from up to three days before the person died. Because of the broad selection criteria, it is highly likely that many of these people died due to non-respiratory health issues unrelated to ozone exposure. This problem is compounded when paired with the lack of personal exposure data, making it impossible to know if decedents were actually well enough to be outdoors in the days preceding their deaths. The data is further confounded by the frequent use of a single monitor to represent exposures throughout the city – as if a single monitor can accurately reflect personal exposure with measurements sometimes miles away. In this case, patient history records from physicians would be more reliable than hospital admission records or death certificates for determining the presence and severity of any health effects potentially caused or aggravated by ozone exposure. EPA would better serve the public trust by recognizing the limitations on the information and data used and to fully consider these limitations when making policy decisions.

5.   Additional statistical analysis (time-series and multi-city time-series studies) further complicate the interpretation of ecological epidemiology studies.

The shortcomings of ecological epidemiology studies are compounded when researchers perform time-series studies, which try to correlate health effects collected from epidemiology studies and ambient ozone concentrations measured during the hours and days leading up to their hospital visit or death. Some studies are called meta-analysis because they compare even broader sets of data from multiple cities averaged over multiple years (Bell et al. 2004). In addition to the issues regarding uncertainty in the original ecological epidemiology studies discussed previously, this additional analysis fails to take into account the high degree of variability between and within cities, seasons, and years. It is therefore, imperative that the epidemiology studies adequately incorporate all sources of variability and characterize uncertainty to the extent possible before arriving at conclusions of causality.

In addition, time-series studies are limited in that they are confounded by the effect of other pollutants that contribute or cause the same effects, the inconsistent ambient air sample collection period between cities, socioeconomic factors such as age, access to healthcare, etc., and mortality differences among cities. Further, analysis of time-series data indicates the studies are highly influenced by the type of statistical models used (often, the model showing most health effects) and publication bias (studies showing effects are more likely to get published than those showing no effects). Due to the substantial uncertainty in these studies, policy decisions should not be based on these studies and EPA should revise its study selection criteria to use studies of higher scientific quality.

6.   Modifiers of short-term effects of ozone on mortality.

Results of ecological epidemiology studies are inconsistent and it remains unclear if ozone is truly correlated to increased health effects. While it is important to realize that some subgroups of the population are more sensitive than the others, only a few studies (Medina-Ramon and Schwartz 2008) have identified sensitive subgroups and susceptibility factors related to ozone related mortality (Stafoggia et al. 2010). Medina-Ramon and Schwartz (2008) was unable to correlate the death of persons due to stroke or diabetes to susceptibility to ozone when compared to those who died from other causes. However, Ren et al. (2010) reported the opposite and their results indicated that people with diabetes or stroke were at a higher risk to ozone related mortality than others.

The issue of personal exposure and the contribution of ambient ozone to personal exposure have also been investigated to a great extent. Central air conditioning is often not available to people with low socioeconomic status (SES). The windows are usually kept open during warm weather, resulting in a greater contribution of ambient ozone into their living spaces. Very few studies have examined effect modification by SES at the city level. Ren et al. (2010) examined whether SES can modify ozone and daily mortality at the census tract level or at the individual level using a study population consisting of 162,146 deceased subjects aged 35 years or older from three counties in eastern Massachusetts, USA. They concluded that there was no evidence that the effects of ozone on mortality were significantly modified by SES and individual characteristics. On the other hand, Stafoggia et al. (2010) investigated the susceptibility factors for ozone-related mortality and identified elderly people, women, and those with diabetes as being more vulnerable to ozone effects. Stafoggia et al. (2010) indicate that many of the elderly in the study did not have access to air conditioning and therefore had a greater contribution of outdoor ambient ozone. This study, like other ecological studies, was limited by the potential for exposure misclassification, as discussed by the authors. Further, because the study was limited to a certain subgroup, it had a smaller sample size, that resulted in the less confidence in the study results. The authors also reported that the ozone respiratory mortality association decreased and became insignificant after adjustment of exposure to PM_{10}.

Comments on Long-Term Health Effects of Ozone

The TCEQ disagrees with the EPA's conclusions that long-term ozone exposure is "Suggestive of a Causal Relationship" with regards to respiratory, cardiovascular, and central nervous system effects and mortality. Furthermore, TCEQ strongly believes that some key studies used by EPA in the ISA are inadequate to demonstrate sufficient evidence of an association.

Respiratory Effects

In the 2006 AQCD, EPA concluded that the current evidence, while being suggestive, was inconclusive for respiratory health effects from long-term ozone exposure. However, in the 2011 ISA, EPA concluded that there is "Likely to be a Causal Relationship" between long-term exposure to ozone and respiratory effects.

The TCEQ disagrees with the EPA's conclusions that long-term ozone exposure is "Likely to be a Causal Relationship" with regards to respiratory effects.

Ecological Epidemiology Studies

Results of ecological epidemiology studies are inconsistent and it remains unclear if ozone is truly related to increased health effects on long-term exposure to ambient ozone. The ecological studies that EPA relied on for reporting associations between long-term exposure to ambient ozone and respiratory effects have the same limitations as the ecological epidemiology studies used as a basis for reporting an association between short-term exposure and respiratory effects. Forbes et al. (2009) studied the association between chronic exposure to outdoor air pollutants and adult lung function. They examined whether average exposure to outdoor air pollutant levels of ozone, PM_{10}, nitrogen dioxide, and sulfur dioxide caused decrements in lung function in several cross-sectional studies of adults in England. They reported deficits in adult FEV_1 not to be associated with ozone but reported associations with PM_{10}, nitrogen dioxide, and sulfur dioxide.

Further limitations of ecological epidemiology studies are outlined below:

1.   Ecological epidemiology studies are not designed to determine if ozone caused the health effects observed

The assumption that ozone caused all observed health effects, including aggravation of asthma and premature mortality, in ecological epidemiology studies is not well-grounded in science. Ecological epidemiology studies do not collect data on when, how long, and how much exposure occurred; if exposure occurred before the health effects; or if it makes biological sense that the chemical could cause the effect. In other words, the study designs are incomplete. In general, scientists agree that the incomplete study design does not provide enough information to determine the actual cause of studied effects. Ecological epidemiology studies are by their nature designed to provide qualitative information and are not supposed to be used quantitatively. Furthermore, they certainly are not rigorous enough to set environmental policy.

2.   Lack of personal exposure data severely limits the utility of ecological epidemiology studies.

The issue of limited or entirely absent personal exposure data is significant. Personal exposure is a measurement of the amount of an air pollutant that a person actually breathes. In the case of air pollutants like ozone, ecological epidemiology studies rely on ambient monitoring data as a surrogate for personal exposure for percentages. However, it is very unlikely that people would ever be exposed to those pollutants at concentrations measured at outdoor monitors for very long. This is partly because the average American spends a large amount of time indoors, especially during the heat of the summer when ozone concentrations tend to be at their highest (Koutrakis et al. 2005). Ozone concentrations in most buildings are characteristically low, and

around 60% of the ambient levels (due to the reactive nature of ozone, the tendency of ozone to deposit on surfaces, and the ventilation systems inside buildings (McClellan et al. 2009). Other additional factors such as time spent outdoors, outdoor activity level, and weather (especially temperature and relative humidity) can dramatically change the potential for ozone exposure and the resultant estimate of risk. Therefore, ambient ozone concentrations alone do not adequately characterize, and easily overestimate, personal exposures (Sarnat et al. 2006). This position is shared by the National Academies of Science (NAS 2008) and the Clean Air Science Advisory Committee (Henderson 2006). That ecological epidemiology studies continue to derive inconsistent and vastly differing conclusions about the adverse effects of ozone is perhaps evidence of this fact.

3.   Ecological epidemiology studies frequently do not take into account the heterogeneity of regional air pollution and oversimplify their exposure analysis by relating health effects to only ozone.

In most ecological epidemiology studies, exposure is estimated to be either some statistical representation (e.g., average or weighted average) of several air monitors or concentrations at the monitor with the highest readings. This assumption oversimplifies outdoor exposure because concentrations vary across a given area. Moreover, few studies fully account for simultaneous exposure to multiple other pollutants, such as particulate matter, nitrogen dioxide, and sulfur dioxide. The ratios of these pollutants can vary tremendously from region to region, making it difficult to determine which effects are related to which pollutants. This complication blurs the association between health effects and ozone exposure, as documented in recent studies. Furthermore, it has been documented in studies that the association between ozone and health effects is confounded by temperature and relative humidity (which alone can cause physical stress), and population characteristics, such as age, health status, socioeconomic status, and exercise.

4.   Ecological epidemiology studies have considerable uncertainty in their identification of health effects.

To determine prevalence of a health issue, epidemiologists frequently use readily-available information, including hospital admissions records and death certificates or participant surveys. In some of the ecological epidemiology studies EPA used for the proposed ozone standard, death certificates for thousands of people who died at a hospital from any non-accidental cause were compared to outdoor ozone levels from up to three days before the person died. Because of the broad selection criteria, it is highly likely that many of these people died due to non-respiratory health issues unrelated to ozone exposure. This problem is compounded when paired with the lack of personal exposure data, making it impossible to know if decedents were actually well enough to be outdoors in the days preceding their deaths. In this case, patient history records from physicians would be more reliable than hospital admission records or death certificates for determining the presence and severity of any health effects potentially caused or aggravated by ozone exposure. EPA would better serve the public trust by recognizing the limitations on the information and data used and to fully consider these limitations when making policy decisions.

5.   Additional statistical analysis (time-series and multi-city time-series studies) further complicate the interpretation of ecological epidemiology studies.

The shortcomings of ecological epidemiology studies are compounded when researchers perform time-series studies, which try to correlate health effects collected from epidemiology studies and ambient ozone concentrations measured during the hours and days leading up to

their hospital visit or death. Some studies are called meta-analysis because they compare even broader sets of data from multiple cities averaged over multiple years (Bell et al. 2004). In addition to the issues regarding uncertainty in the original ecological epidemiology studies discussed previously, this additional analysis fails to take into account the high degree of variability between and within cities, seasons, and years. It is therefore, imperative that the epidemiology studies adequately incorporate all sources of variability and characterize uncertainty to the extent possible before arriving at conclusions of causality.

In addition, time-series studies are limited in that they are confounded by the effect of other pollutants that contribute or cause the same effects, the inconsistent ambient air sample collection period between cities, socioeconomic factors such as age, access to healthcare, etc., and mortality differences among cities. Further, analysis of time-series data indicates the studies are highly influenced by the type of statistical models used (often, the model showing the most health effects) and publication bias (studies showing effects are more likely to get published than those showing no effects). Due to the substantial uncertainty in these studies, policy decisions should not be based on these studies and EPA should revise its study selection criteria to use studies of higher scientific quality.

6.   Modifiers of short-term effects of ozone on mortality.

Results of ecological epidemiology studies are inconsistent and it remains unclear if ozone is truly correlated with increased adverse health effects. While it is important to realize that some subgroups of the population are more sensitive than the others, only a few studies (Medina-Ramon and Schwartz 2008) have identified sensitive subgroups and susceptibility factors related to ozone related mortality (Stafoggia et al. 2010). Medina-Ramon and Schwartz (2008) was unable to correlate the death of persons due to stroke or diabetes to susceptibility to ozone when compared to those who died from other causes. However, Ren et al. (2010) reported the opposite and their results indicated that people with diabetes or stroke were at a higher risk to ozone related mortality than others.

The issue of personal exposure and the contribution of ambient ozone to personal exposure have also been investigated to a great extent. Central air conditioning is often not available to people with low socioeconomic status (SES). The windows are usually kept open during warm weather, resulting in a greater contribution of ambient ozone into their living spaces. Very few studies have examined effect modification by SES at the city level. Ren et al. (2010) examined whether SES can modify ozone and daily mortality at the census tract level or at the individual level using a study population consisting of 162,146 deceased subjects aged 35 years or older from 3 counties in eastern Massachusetts, USA. They concluded that there was no evidence that the effects of ozone on mortality were significantly modified by SES and individual characteristics. On the other hand, Stafoggia et al. (2010) investigated the susceptibility factors for ozone-related mortality and identified elderly people, women, and those with diabetes as being more vulnerable to ozone effects. Stafoggia et al. (2010) indicate that many of the elderly in the study did not have access to air conditioning and therefore had a greater contribution of outdoor ambient ozone. This study, like other ecological studies, was limited by the potential for exposure misclassification, as discussed by the authors. Further, because the study was limited to a certain subgroup, it had a smaller sample size, that resulted in the less confidence in the study results. The authors also reported that the ozone respiratory mortality association decreased and became insignificant after adjustment of exposure to PM_{10}.

Animal Toxicological Studies

In the ISA, the EPA concludes that the biochemical and morphological changes observed in animal studies are suggestive of irreversible long-term ozone impacts on the lung. While, animal toxicological studies can be helpful and supportive in providing the weight-of-evidence to human clinical studies and epidemiology studies, they are often conducted at very high concentrations that are not representative of actual ambient conditions and personal exposures relevant to humans. These studies require careful extrapolation to relevant human exposure levels and endpoints and the interpretation of the observed biochemical and morphological changes must be done cautiously. The observed effects in animal studies are difficult to replicate in longer-term human epidemiology studies where lung function declines are often the endpoints of interest.

Cardiovascular effects

In the 2006 AQCD, EPA reported that there were no studies to evaluate cardiovascular effects on long-term exposure to ozone. However, in the 2011 ISA, EPA concluded that there is a likely to be "Suggestive of a Causal Relationship" between long-term exposure to ozone and cardiovascular effects.

The TCEQ disagrees with the EPA's conclusions that long-term ozone exposure is "Suggestive of a Causal Relationship" with regards to cardiovascular effects.

While there has been a greater focus on the role of ozone in respiratory function, there exists a paucity of data regarding its role in systemic inflammation and oxidative stress. Some epidemiological studies have shown a positive association between ozone exposure and serum inflammatory markers such as IL-6 (Thompson et al. 2010) while others show no such association (Forbes et al. 2009, Hermans et al. 2005, Rudez et al. 2009). In fact, multiple reports indicate that ozone may be correlated with increased serum concentrations of some markers (IL10, IL6 and IL8 – Calderon-Garciduenas et al. 2003 and Thompson et al. 2010) while other markers show no such pattern (TNFα, IL2, ET-1, fibrinogen - Calderon-Garciduenas et al. 2003 and Thompson et al. 2010). With regard to systemic oxidative stress: a single human study indicates that serum levels of the antioxidant α-tocopherol may be reduced after a 390 minutes exposure to ozone with high concentrations (250-450 ppb escalating dose) that was spread over three days (Foster et al. 1996). However, this data should be interpreted with caution as retinol levels were not affected and a second study by Kadiiska et al. 2011 determined that serum antioxidants are not sensitive biomarkers for in vivo oxidative damage induced by ozone. In summary, the current weight of evidence does not support a causative role for ozone in systemic inflammation and oxidative stress. Furthermore, changes in serum biomarkers by themselves do not constitute adverse effects.

Publications on cardiovascular (CV) health effects of long-term exposure to ozone are few and these ecological epidemiology studies mostly involved analysis of data from a few large cohorts from multiple geographic locations that differ in the average chronic ambient concentrations and mixtures of air pollutants. No association has been found for some markers of CV dysfunction (ST-segment depression – Delfino et al. 2011), while other markers of CV function such as blood pressure and total cholesterol may be affected by increased ozone exposure (Chuang et al. 2011). The Chuang study should be interpreted with caution, however, since the study population was outside the US, and one or more unaccounted-for factors (such as diet or gene-environment interactions) may be important determinants of health risk.

Reproductive and Developmental

In the 2006 AQCD, EPA concluded that there was limited evidence for a relationship between air pollution and birth-related health outcomes, including mortality, premature births, low birth weights, and birth defects, with little evidence being found for ozone effects. However, in the 2011 ISA, the EPA concludes that the evidence is "Suggestive of a Causal Relationship" between long-term exposure to ozone and reproductive and developmental effects.

The TCEQ disagrees with the EPA's conclusions that long-term ozone exposure is "Suggestive of a Causal Relationship" with regards to reproductive and developmental effects.

The weight-of-evidence showing association of ambient ozone levels and reproductive and developmental effects is inconclusive. There are no reports of extra-pulmonary distribution of inhaled ozone at any dose. The EPA themselves report that ozone "reacts rapidly on contact with respiratory system tissue and is not absorbed or transported to extrapulmonary sites to any significant degree as such."

This is a very important and sensitive issue because of the potential implications to childhood morbidity and mortality based on the exposure during pregnancy and *in utero*. Time activity patterns need to be considered to estimate the personal exposure. Many potential confounding factors (particulate matter, sulfur dioxide, maternal smoking, nutrition, and diet) may occur during the critical windows of exposure and influence the reproductive and developmental outcomes.

Many studies have reported exposure measurement error and residual confounding as being associated with estimates of several health effects including reproductive and developmental effects, and these factors can lead to overestimation of risks. Some of these studies were conducted in 2007 and 2008 in Los Angeles metropolitan area (Ritz et al. 2007, Ritz and Wilhelm 2008). In their 2007 study, Ritz et al. highlight the importance of reducing exposure misclassification when evaluating the effect of traffic-related pollutants. They specifically concluded that exposure to traffic-related pollutants (carbon monoxide and fine particles) especially in the first trimester and also prior to delivery to be associated with preterm birth in the Los Angeles metropolitan area. No associations for ozone-related reproductive and developmental outcomes were reported.

Mortality

In the 2006 AQCD, EPA concluded that there was little evidence to suggest a causal relationship between chronic ozone exposure and increased risk for mortality in humans. However, in the 2011 ISA, the EPA concludes that the evidence is "Suggestive of a Causal Relationship" between long-term exposure to ozone and mortality.

The TCEQ disagrees with EPA regarding its conclusions that there is sufficient evidence "Suggestive of a Causal Relationship" of long-term exposure to ozone and mortality because the TCEQ believes that the weight-of-evidence for mortality estimates due to long-term exposure to ozone is not conclusive.

Mortality estimates for ambient ozone are often confounded by $PM_{2.5}$ by itself and/or with specific fractions of the $PM_{2.5}$ such as sulfate and black carbon. In addition, Jerrett et al. (2009) reported that all cause mortality was not statistically significantly increased when the effect of ozone was adjusted for the effects of $PM_{2.5}$. Further, many of the cross-sectional studies and meta-analysis have used data sets from years when the air pollution levels were much higher. Conclusions drawn from these studies have to be interpreted with caution as the air pollution levels are generally lower at the present time.

Studies addressing CV mortality are limited and contradictory. Zanobetti and Schwartz (2011) reported a significant hazard ratio for CV-related mortality. This study was unable to control for $PM_{2.5}$, as multiple studies have found no effect of ozone on risk of death from CV causes when concentration of particulate matter was taken into account (Jerrett et al. 2009, Miller et al. 2007, Abbey et al. 1999 and an updated analysis of the Abbey et al. data by Chen et al. 2005). Jerret et al. (2009) reported estimated relative risk of death attributable to a 10-ppb change in the ambient ozone concentration. Relative risk is also known as the risk ratio and it includes the incidence rates for people with a known (or suspected) risk factor and the incidence for people without the risk factor. For example, for respiratory effects, Jerret et al. (2009) reported relative risks of 1.029 for single pollutant model and 1.040 for two-pollutant model. These are "statistically significantly" different than 1.0; however, that evaluation of statistical significance only reflects a "within study evaluation" and does not address numerous other sources of uncertainty. EPA needs to characterize uncertainty by addressing the following concerns:

1) The tenuous connection between the air pollution data and the mortality data.
2) The difference between imprecise population-wise exposures and more precise individual exposure estimates.
3) The exclusion of well-conducted studies showing no adverse health effects by the EPA in the current ISA.
4) A lack of comprehensive analysis of uncertainty and variability (in some cases, an error in one assumption can virtually eliminate all claimed benefits for particulate matter and ozone reduction).

The American Cancer Society study (ACS) and the Harvard Six City study initially found no significant associations between ozone and mortality on the basis of one-year ozone records (Dockery et al. 1993; Pope et al. 1995). In the most recent analysis of the American Cancer Society cohort, annual average ozone concentrations were not clearly linked with mortality; but a positive and statistically significant association was observed between ozone measured in the April-to-September period and both all and cardiopulmonary disease CPD causes of death; no association was observed between ozone and ischemic heart disease (IHD) deaths (Krewski et al. 2009).

Although the largest meta-analysis to date (Smith et al. 2009) with 352,000 people, 66 US cities, and 18 years of follow up indicates that ozone may be associated with increased risk of death from cardiopulmonary disease, the authors as well as the NAS (2008) are careful to note that "further replication in other cohorts and settings is needed to ensure estimates of benefits are accurate and reliable for policy decisions." Specifically, the authors reported lower cardiopulmonary mortality estimates for ozone (2.83; 0.84- 4.86) for single pollutant models when compared to 5.60 (3.31 – 7.95) for $PM_{2.5}$ and 5.96 (0.89-5.49) for sulfate.

For the extrapolation of short-term effects to long-term impact on CV mortality, two frequently utilized studies are highly relevant (Levy et al. 2005 and Bell et al. 2004, 2005). Ozone mortality effects were greater after same-day than after previous-day exposures (Levy et al. (2005) and Bell et al. 2004, 2005) and after exposures averaged over the week preceding death than after a single day (Bell et al. 2004). These results suggest that the effects of ozone on mortality are largest on the day or day's immediately preceding death but cannot be explained fully by these exposures as they accumulate over the week. This pattern could reasonably be applied to chronic exposure to ozone, making it implausible to estimate long-term mortality due to CV events attributable to ozone based on short-term measurements.

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