OZONE NAAQS PROPOSED RULE – EVALUATION OF THE SCIENCE
FOR
TEXAS PIPELINE ASSOCIATION
AUSTIN, TEXAS

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1.0 INTRODUCTION

On December 17, 2014, EPA proposed to lower both the primary and secondary ozone NAAQS to within a range of 65 - 70 parts per billion (ppb) to increase public health protection and protection of vegetative effects and public welfare. EPA's request for comments on the level of 60 ppb is in recognition of the Clean Air Scientific Advisory Committee's (CASAC's) recommendation that EPA should consider a range of 60 – 70 ppb, although EPA states its position (Pg. 75236 of proposed rule; 79 FR 75234) that setting a standard below 65 ppb would inappropriately place very little weight on the uncertainties in the health effects evidence and exposure/risk information. EPA's request for comment on the option of retaining the current standard of 75 ppb no doubt reflects the many comments received on EPA's *Policy Assessment for the Review of the Ozone National Ambient Air Quality Standards* (EPA, 2014a), *Health Risk and Exposure Assessment for Ozone* (HREA) (EPA, 2014b), and *Welfare Risk and Exposure Assessment for Ozone* (WREA) (EPA, 2014c) arguing that the current standard is already requisite to protect human health and welfare. EPA is also taking comment on the alternative approach of revising the secondary standard to a biologically-based cumulative seasonal form known as W126.

Given the significance of the proposed rule, Zephyr Environmental Corporation (Zephyr) has been retained by the Texas Pipeline Association (TPA) to evaluate the scientific evidence on which the EPA is relying to support its proposal to lower the ozone NAAQS.

EPA's consideration of the scientific evidence for lowering the primary ozone NAAQS is based primarily on information from controlled human exposure and epidemiologic studies, and the use of information from a subset of those studies as input to the HREA and WREA (Pg. 75243 of proposed rule). Consideration of the evidence for lowering the secondary ozone NAAQS is primarily based on information from studies on the effect of ozone on vegetation. Therefore, our evaluation is based on a thorough examination of the controlled human studies and epidemiology studies, and limited evaluation of vegetative effect studies.

Zephyr staff has substantial expertise in evaluating human health and welfare data in connection with health risk assessments, air quality impact assessments, biological assessments and assisting others in interpreting the health benefits and detriments of proposed regulatory standards and screening levels. This evaluation is based on a careful evaluation of the science underlying EPA's proposed ozone NAAQS revisions and consists of opinions developed independently by Zephyr scientists, many of which have been previously expressed in public forums.

This report is organized as follows:

- Section 2 – Controlled Human Studies
- Section 3 – Epidemiology Studies
- Section 4 – Health Risk and Exposure Assessment
- Section 5 – Vegetative Effect Studies
- Section 6 – Conclusions
- Section 7 – References

2.0 CONTROLLED HUMAN STUDIES

As acknowledged in the proposed rule (Pg. 75244 of the proposed rule), controlled human exposure studies provide data with the highest level of confidence since they provide human effects data under closely monitored conditions (hence the term "controlled") and can provide exposure-response relationships (i.e., change in effect caused by differing levels of exposure [or doses] after a certain amount of time).

There are a multitude of controlled human exposure studies on the effect of short-term ozone exposure on respiratory health, but in EPA's HREA it relies exclusively on studies of ozone-induced lung function decrements, meaning a diminution or reduction in lung capacity, as measured by decreases in forced expiratory volume in one second (FEV_1).

There are 23 human exposure studies conducted under controlled laboratory conditions that evaluate the effect of ozone on lung function as measured by FEV_1 and that collected all the necessary information for determining ozone exposure-response relationships. These studies are important to EPA's current review of the adequacy of the ozone NAAQS because they help EPA make conclusions about biological plausibility and about the consistency and coherence of ozone-related health effects at specific concentrations, but most importantly, they were fit to a model used to predict lung function decrements in EPA's HREA (EPA, 2014b).

Of the 23 controlled human exposure studies, however, only a few (five to be exact) of the studies looked at ozone concentrations below 75 ppb. For that reason, only those five studies have been reviewed in this report.

In the sections that follow, we discuss the controlled human studies relied upon by EPA. In short, we conclude that:

- The available controlled human exposure studies consistently demonstrate that statistically significant lung function decrements that meet the American Thoracic Society (ATS) definition of adversity (decrease in FEV_1 accompanied by respiratory symptoms) and the threshold used by EPA for judging clinical relevance (i.e., $\geq$ 10% decrease in FEV_1) do not occur until concentrations of 88 ppb or higher are reached. The current NAAQS of 75 ppb is well below the level at which these effects occur. Therefore, evidence from these controlled human exposure studies suggest that the current NAAQS is protective of public health **with an adequate margin of safety**.

- Lung function decrements observed at concentrations below 75 ppb are not consistently statistically significant, are not usually accompanied by respiratory symptoms and do not reach the $\geq$ 10% threshold that EPA has identified as being clinically meaningful. Therefore, those lung function decrements should not be used in appraising the adequacy of the current NAAQS.

- The evidence from controlled human exposure studies suggesting the potential for lung function decrements at ozone concentrations below 75 ppb is no better today than it was during the last ozone NAAQS review, when EPA decided not to establish a NAAQS lower than 75 ppb because of the uncertainty about the extent to which lung function decrements occur at concentrations below 80 ppb. Therefore, these studies do not support a lowering of the ozone NAAQS.

2.1 KEY CONSIDERATIONS IN EVALUATING CONTROLLED HUMAN EXPOSURE STUDIES

In reviewing controlled human exposure studies, there are several key considerations to keep in mind. First, because changes in FEV_1 can occur for a variety of reasons (e.g., physical activity, breathing cold air) and, in fact, FEV_1 normally varies throughout the day, a basis for distinguishing between "adverse" and "normal" non-adverse changes in lung function is necessary for the interpretation of research findings, particularly if consistency is desired. Two other criteria that are also important to keep in mind when evaluating the results of controlled human exposure studies on lung function are: 1) whether the effects can be definitively tied to ozone exposure as opposed to experimental variables or variability; and 2) whether the effects are of clear scientific and/or medical relevance, not simply of theoretical interest (many precursors to adverse effects of ozone exposure have been looked at but cannot truly be considered injurious).

As discussed below, only FEV_1 decrements definitively determined to be injurious or "adverse", that are due to ozone exposure (not a chance occurrence), and large enough to be considered scientifically and medically important should be considered as evidence of an ozone-attributable lung function decrement.

2.1.1 Distinguishing "Adverse" from Non-Adverse Changes in Lung Function

The ATS (American Thoracic Society) recommends that a small, transient (i.e., reversible) loss of lung function, by itself, should not automatically be designated as "adverse", but instead should be accompanied by respiratory symptoms to be considered "adverse" (ATS, 2000). EPA generally adopts this definition of adversity (footnote no. 42, pgs. 75251, 75287, 75288, and 75304 of proposed rule; pg. 6-5 of HREA), although is not always consistent in applying it (pg. lxxi of the preamble to the *Integrated Science Assessment for Ozone and Related Photochemical Oxidants*; EPA, 2013), particularly in the HREA where a decrease in FEV_1 by itself is considered an adverse endpoint in terms of modeling risk (pg. 3-5, pgs. 5-1, 5-2, 6-1, 6-5, of HREA).

2.1.2 Distinguishing Effects of Exposure from Effects that are "Chance" Occurrences

For ethical reasons, volunteers in controlled human exposure studies can only be exposed to relatively harmless levels of ozone in the laboratory, and since lung function may change for a

variety of reasons and is known to vary throughout the day, what we are looking for as we evaluate the data from such studies are changes in lung function that are small but caused by ozone, not simply the result of random variability or chance. Statistical significance simply means statistically rare. For example, when a result is said to be statistically significant (at the 0.05 level), the probability is at least 19 to 1 (or 100 to 5) that the result did not occur by chance alone. In addition, there is a close relationship between confidence intervals and statistical significance tests. All values in the confidence interval are plausible values for the estimated parameter, whereas values outside the confidence interval are rejected as plausible values for the parameter. Therefore, if a statistic is significantly different from zero at the 0.05 level, then the 95% confidence interval will not contain zero (0). Therefore, any confidence interval that does contain zero should be considered statistically insignificant.

While there may be legitimate reasons why a real change might not reach statistical significance (e.g., sample size is too small), a change that is statistically significant is much less likely to be a chance occurrence. Therefore, statistical significance is a key consideration in determining causality (i.e., whether an effect can be tied to ozone exposure) and to consider results that are not statistically significant as evidence for an effect is to set oneself up for making erroneous inferences because there is always the possibility that a positive result is simply a chance occurrence.

2.1.3 Distinguishing Effects that are Clinically Relevant from those that are Not Medically Important

Clinical relevance typically hinges on the seriousness of the effect, which is usually related to its size. EPA currently defines a decrease in $FEV_1 \geq 10\%$ as clinically meaningful for evaluating ozone effects. In some situations, it is obvious that a certain response has clinical relevance, such as when it is used as the basis for hospital admission (i.e., fever $\geq 104°$ F) or surgical intervention (i.e., severe cardiac chest pain not relieved by drug therapy). However, a completely reversible decrease in FEV_1 that is within the range of normal variability is not an obvious choice as a yardstick by which to judge clinical relevance. We discuss later in this report EPA's rationale for setting a lower threshold ($\geq 10\%$) for ozone than has been used in previous rulemakings on other constituents (EPA used decrease in FEV_1 of $\geq 15\%$ in establishing the 1-hour NAAQS for SO2 (EPA, 2009) and NO2 (EPA, 2008)) and whether it represents an appropriate threshold for distinguishing a clinically meaningful FEV_1 decrement from one that is medically unimportant. While EPA has used the FEV_1 decrement $\geq 10\%$ threshold in previous ozone NAAQS reviews, it was only applied in estimating lung function risk for asthmatics in previous HREAs, contrary to its application to all populations (i.e., healthy children and adults) in the current HREA. FEV_1 decrements need to at least meet the EPA's $\geq 10\%$ threshold to have a noticeable effect.

2.2 CONTROLLED HUMAN EXPOSURE STUDIES DO NOT SUPPORT THE NEED TO LOWER THE CURRENT NAAQS

2.2.1 Health Effects Information in Range of Proposed Alternative NAAQS is Insufficient for Regulatory Decision-Making

Currently, there are 23 published controlled human ozone exposure studies that measure all of the necessary parameters McDonnell et al. (McDonnell, Stewart, Smith, Kim, & and Schelegle, 2012) for use in evaluating the impact of ozone exposure on lung function, and only five of those evaluated ozone concentrations in the range of the proposed alternatives to the ozone NAAQS. Those five studies are:

- Adams, 1998
- Adams, 2002
- Adams, 2006
- Schelegle et al., 2009
- Kim, et al., 2011

In addition, Brown et al. (Brown, Bateson, & McDonnell, 2008) is a re-analysis by EPA of the lung function data for volunteers exposed to 60 ppb ozone in the Adams 2006 study (Adams, 2006), that uses different statistical procedures. The use of this limited number of studies is simply insufficient to support a regulatory decision-making process that will have such broad implications.

2.2.2 There is a Lack of Evidence for Clinically Meaningful "Adverse" Effects that are Clearly Attributed to Ozone Concentrations below the Current NAAQS

2.2.2.1 EPA Adopts American Thoracic Society Definition of "Adverse" Lung Function Decrement but Inconsistently Applies it

EPA relies primarily on guidance provided by the ATS in making judgments about which of the various ozone-related effects should be regarded as "adverse" to the health of individuals (ATS, 2000). Briefly, ATS guidance indicates that healthy people may sustain transient reductions in pulmonary function with exposure to air pollutants but **recommends that reversible loss of lung function only be considered "adverse" when it is accompanied by respiratory symptoms**. EPA appears to have adopted this ATS definition of what constitutes an "adverse" effect in terms of FEV_1 decrements (footnote no. 42, pgs. 75251, 75287, 75288, and 75304 of proposed rule; pg. 6-5 of HREA, but is not always consistent in applying it, particularly in the HREA where a decrease in FEV_1 by itself is considered an adverse endpoint in terms of modeling risk (pg. 3-5, pgs. 5-1, 5-2, 6-1, 6-5, of HREA). Models relied upon by EPA in the HREA are not capable of predicting whether estimated FEV_1 decrements will also be accompanied by respiratory symptoms. Therefore, EPA's predicted FEV_1 decreases are not a sufficient basis for concluding that "adverse" effects occur at levels below the current NAAQS.

2.2.2.2 *EPA's Definition of a Clinically Relevant FEV_1 Decrement is Flawed and Smaller Decrements are Often Cited as Positive Evidence*

EPA considers decrements in $FEV_1 \geq 10\%$ to represent clinically meaningful responses. EPA has defined gradations of individual decrements in FEV_1 and airway responsiveness and symptomatic responses (e.g., cough, chest pain, and wheeze), together with judgments as to the "potential" impact on individuals experiencing varying degrees of these responses and these gradations have been used since the 1997 ozone NAAQS review.

2.2.2.2.1 EPA's Definition of a Clinically Relevant FEV_1 Decrement is Not Well Supported

Gradations of FEV1 Decrements and their Implications

The information discussed in EPA (EPA, 1996, Pg. 59-72) regarding the development of EPA's Gradation of Individual Responses to Short-Term Ozone Exposure does not contain a single reference to articles in the scientific literature, medical textbooks/journals, or any source other than expert opinion (CASAC members and medical doctors that were interviewed).

Numerous studies reporting poor correlation between spirometric measurements (e.g. FEV_1), asthma symptoms, and medication use have become available since the 1997 review when the gradation scheme was developed (Cowie, Underwood, & Feld, 2007; Teeter & Bleecker, 1998; Shingo, Zhang, & Reiss, 2001; Johannes, et al., 2007; Wildhaber et al., 2007). Other studies that report low correlations between pulmonary function tests and quality of life indicators, such as self-reported activity restriction are also available (Cowie et al., 2007; Juniper, et al., 1992; Santanello, et al., 1997). In addition, results from epidemiology studies on the effect of increased ambient ozone concentrations on respiratory symptoms, medication use, and self-limitation of activity in asthmatics is inconsistent at best. Given the availability of new data and the apparent lack of objective documented criteria for the gradation scheme at the time of its development, the gradation of individual responses and their implications in terms of interference with activity and asthma medication use deserves a critical re-examination by EPA.

Pellegrino, et al. (2005)

Despite being cited as a reference for the $\geq 10\%$ FEV_1 decrement threshold that EPA has adopted, Pellegrino et al. (2005) states that "Two-point, short-term changes of > 12% and > 0.2 L in the FEV_1 are usually statistically significant and *may be clinically important.* Changes slightly less than these may, perhaps, be equally significant, depending on the reproducibility..." However, none of the controlled human studies on which EPA has relied provided any information on the reproducibility of their FEV_1 measurements, although as discussed by Lefohn et al. (2010), individual FEV_1 response patterns were inconsistent. Therefore, it is unclear whether the observed FEV_1 decrements $\geq 10\%$ were truly due to the ozone exposures or simply represent outliers due to measurement error or normal variability.

ATS, (1991)

ATS (1991) is also cited as a reference for the ≥ 10% FEV_1 decrement threshold, but ATS (1991) states that "Lower limits of normal are variable and, therefore, should not be considered as **arbitrary limits that correctly classify all patients into normal and abnormal groups**.", which is exactly what EPA has done in identifying a ≥ 10% FEV_1 decrement as an abnormal response.

Asthmatics are Not More Sensitive than Healthy Individuals

The HREA (Pg. 6-43) and the *Integrated Science Assessment for Ozone and Related Photochemical Oxidants* (ISA, Pg. 8-10) (EPA, 2013) justify the ≥ 10% decrease in FEV_1 as the point of departure in the current ozone NAAQS review by stating that asthmatic children may have less reserve lung capacity to draw upon when faced with decrements. Hence, a ≥10% decrement in lung function may be a more adverse event in an asthmatic child than a healthy child. However, the results of the HREA itself suggest, as have many other studies have (Basha, Gross, Gwizdala, Haidar, & Popovich; Scannell, et al., 1996; Mudway, et al., 2001; Alexis, et al., 2000; Goodman, Prueitt, Chandaliaa, & Sax, 2013; Balmes, et al., 1997) that asthmatics do not appear to be more sensitive to the adverse health impacts of ozone than healthy individuals, at least not as measured by decrease in FEV_1. In fact, many asthmatics have normal FEV_1 (Bates, 1987).

2.2.2.2.2 EPA Often Cites FEV_1 Decrements Smaller than 10% as Positive Evidence for Lung Function Decrements

EPA concludes that (Pg. 6-9 of ISA), "exposure to 40 ppb ozone for 6.6 hours produces small, statistically non-significant changes in FEV_1 that are relatively similar to responses from fresh air (FA) exposure (Adams, 2002). Volunteers exposed to 60 ppb ozone experience group mean ozone-induced FEV_1 decrements of about 3% (Kim et al., 2011; Brown et al., 2008; Adams, 2006); those exposed to 80 ppb have group mean decrements that range from 6 to 8% (Adams, 2006, (Adams, 2003; McDonnell, et al., 1991; Horstman, Folinsbee, Ives, Abdul-Salaam, & McDonnell, 1990) at 100 ppb, group mean decrements range from 8 to 14% (McDonnell et al., 1991; Horstman et al., 1990); and at 120 ppb, group mean decrements of 13 to 16% are observed (Adams, 2002; Horstman et al., 1990; Folinsbee et al., 1988)." EPA (Pg. 6-9 of ISA) further states that, "Taken together, these data indicate that mean FEV_1 is clearly decreased by 6.6-hour exposures to 60 ppb ozone and higher concentrations in subjects performing moderate exercise."

As acknowledged by EPA above, exposures to ozone do not cause decreases in FEV_1 large enough to be considered clinically relevant, even using EPA's questionable benchmark, until concentrations above 80 ppb are reached. However, as is often done in the ISA and HREA, EPA confuses the issue by concluding that "FEV_1 is clearly decreased by 6.6-hour exposures to 60 ppb ozone and higher concentrations in subjects performing moderate exercise."

2.2.2.3 *EPA Often Presents Statistically Insignificant Results as Positive Evidence for Health Effects*

Although statistical significance does not guarantee a "cause and effect" relationship or that the treatment caused the effect measured, it does make it more likely that the effect is the result of the treatment as opposed to a chance occurrence.

EPA acknowledges that of the studies conducted at 60 ppb, only Kim et al. (2011) reported FEV_1 decrements at 60 ppb to be statistically significant, but further rationalizes that Brown et al. (2008) found those from Adams (2006) to be highly statistically significant. EPA further states that although group mean decrements following exposures to 60 ppb ozone are biologically small and do not generally attain statistical significance, "a considerable fraction of exposed individuals experience clinically meaningful decrements in lung function" at 60 ppb (Pg. 6-20 of ISA). However, these conclusions are unfounded because the available controlled human exposure studies were designed to evaluate differences in group mean responses, not to evaluate individual susceptibility. To evaluate the fraction of the population that is most responsive to ozone, a study that is specifically designed for that purpose (a "responder analysis") that performs repeat measurements of individual responses at each exposure concentration and time interval would be required. Such studies generally require much larger sample populations than the controlled human exposure studies that have been conducted on ozone to date (studies have only had 30-59 subjects). EPA has experience conducting these types of studies, so it is perplexing that the Agency does not design and carry out a study that is *at least capable* of detecting what it is determined to conclude, instead of over-interpreting existing data to support its preconceived notions of what the findings should show.

2.2.2.4 *Clinically Relevant Statistically Significant FEV_1 Decrements $\geq$ 10% Do Not Occur at Concentrations below 88 ppb*

Given EPA's reliance on the definitions of "adverse" and "clinically meaningful FEV_1 decrements" in the ISA (EPA, 2013) and the need for certainty that observed health effects are indeed the result of ozone exposure, decisions about the adequacy of the current ozone NAAQS and alternative levels for consideration should only be informed by FEV_1 decrements that are: 1) accompanied by respiratory symptoms; 2) $\geq$ 10%; and 3) statistically significant.

Figure 2-1 below shows a graph of the results from studies that evaluate ozone concentrations below 80 ppb (results for the 60 ppb ozone exposures from Adams (1998) are not tabulated and, therefore, could not be included). **Figure 2-2**, which immediately follows, shows the results that meet the three criteria for use in making decisions about the adequacy of the current ozone NAAQS and alternative levels for consideration, FEV_1 decrements that are: 1) accompanied by respiratory symptoms; 2) $\geq$ 10%; and 3) statistically significant.

2.2.2.4.1 Summary of Results

- Blue Bars - A statistically significant decrease in FEV_1 accompanied by respiratory symptoms was achieved at 80 ppb in Adams (2002), but did not reach a level considered clinically relevant by EPA (i.e., 10% decrease in FEV_1) until concentrations reached 120 ppb.
- Green Bars - A statistically significant decrease in FEV_1 accompanied by respiratory symptoms was also observed in Adams (2006) at 80 ppb, but did not reach the 10% level considered clinically relevant by EPA at any of the concentrations tested (i.e., 40, 60, or 80 ppb).
- Red Bars - Schelegle et al. (2009) showed a statistically significant decrease in FEV_1 accompanied by respiratory symptoms (i.e., meets definition of "adverse") at 72 and 81 ppb, but the decrease in FEV_1 did not reach the 10% level considered clinically relevant by EPA until a concentration of 88 ppb was reached.
- Purple Bars - Kim et al. (2011) observed a statistically significant decrease in FEV_1 and an increase in inflammation of the airways at 60 ppb, but the decrease in FEV_1 was small (i.e., not clinically meaningful) and not accompanied by respiratory symptoms (i.e., not "adverse").

These results clearly show that statistically significant, clinically relevant decreases in FEV_1 (i.e., > 10%) that are clearly "adverse" (i.e., accompanied by respiratory symptoms) do not occur until ozone concentrations of 88 ppb or more are reached.

FIGURE 2-1
GROUP MEAN FEV_1 DECREASES IN YOUNG HEALTHY ADULTS EXPOSED TO OZONE

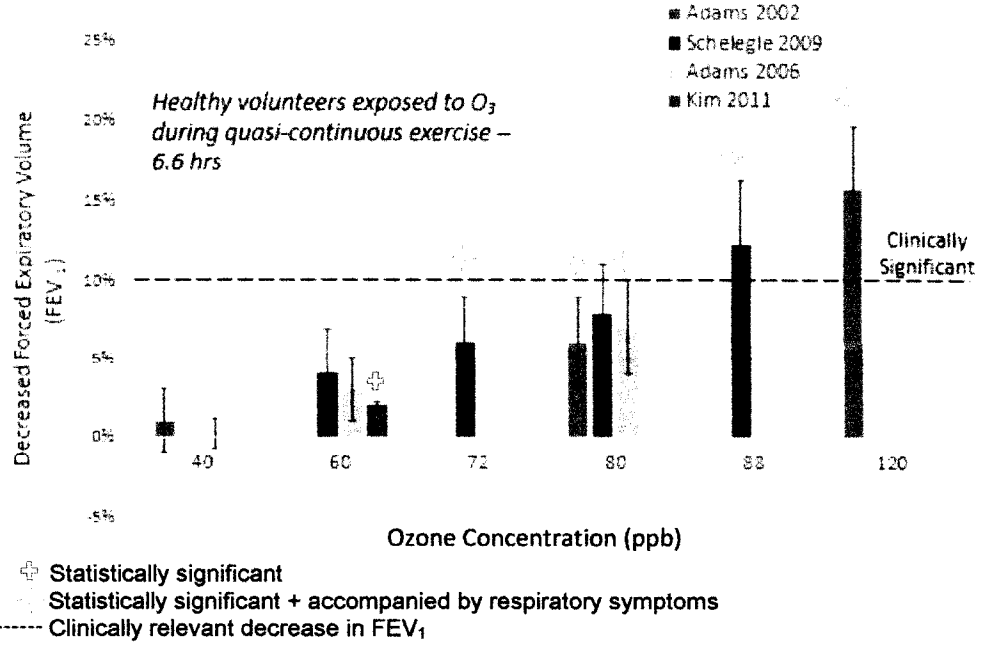
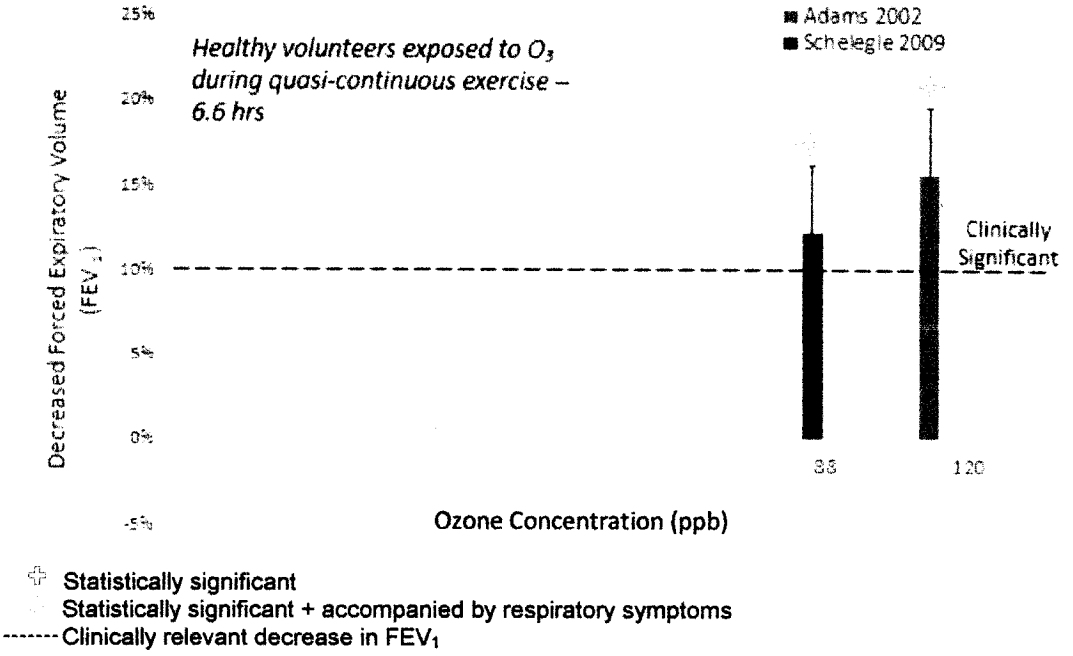


FIGURE 2-2
STATISTICALLY SIGNIFICANT, CLINICALLY MEANINGFUL, CLEARLY ADVERSE GROUP MEAN FEV_1 DECREASES



2.2.3 Controlled Human Exposure Studies were not Adequately Controlled for Confounding and Bias

2.2.3.1 Confounding by Exercise and Diurnal Variations were Not Adequately Accounted for in Identifying the Proportion of Test Subjects Across Studies with ≥ 10% FEV_1

Individuals can experience small changes in respiratory health endpoints, such as decrements in FEV_1, from exercise alone. In addition, diurnal variation (normal fluctuations that occur during each day) in lung function in general, and FEV_1 in particular, is also well documented (Enarson & Yeung, 1985; Spengler & Shea, 2000; McDonnell, Stewart & Smith, 2007; Sridevi & Sembulingam, 2013). Use of responses in individuals exposed to fresh/filtered air (FA) under identical exercise regimens as a control in randomized exposure studies serves to eliminate alternative explanations (i.e., other than ozone exposure) for the measured responses.

The ISA (Pg. 6-19) reports that 6.6-hour exposures to 60 ppb ozone yields a "weighted average proportion" of subjects with ≥ 10% FEV_1 decrements of 10% when responses are averaged across Kim et al. (2011), Schelegle et al. (2009), and Adams (2006 and 1998). However, EPA clearly acknowledges that these results are uncorrected for FA responses. Responses that are

not FA corrected do not represent the impacts from ozone exposure alone; they also include the effect of exercise and diurnal variation on FEV_1.

EPA indicates that they were unable to correct for the FA responses (test subjects are exposed to FA under identical exercise protocols used for ozone exposures) due to limited data provided in the study reports, but justifies the use of these uncorrected results anyway, stating that FEV_1 typically improves upon exposure to FA (Pg. 6-18 of the ISA; Pg. 75240 of proposed rule). However, this is frequently not the case.

Some individuals experience small improvements (increases) in FEV_1, while in others, FEV_1 is decreased upon exposure to FA. For example, Figure 3-1 from Schelegle et al. (2009) illustrates that 15 FA exposures in that study resulted in a decrease in FEV_1, while 16 FA exposures resulted in an increase in FEV_1. Detailed responses for the FA control scenario are listed below.

- 10 FA controls had a 0 to -5% decrease;
- 5 FA controls had a -5 to -10% decrease;
- 9 FA controls had a 0 to +5% increase;
- 6 FA controls had a +5 to +10% increase; and
- 1 FA control had a +10 to +15% increase.

Similarly, as shown in Table 3 of the Horstman (1990) study, more than half of the FA controls responded with a decrease in FEV_1. Finally, as shown in Table 1 of Brown et al. (2008), 25% of the FA controls in Adams (2006) responded with a decrement in FEV_1.

The importance of this issue revolves around the fact that subtraction of an improved (increased) FA-induced FEV_1 increases the size of the change between pre- and post-exposure FEV_1, while subtraction of a FA-induced decrease in FEV_1 decreases the size of the change between pre- and post-exposure FEV_1. Therefore, it is essential to correct each individual test subject's response to ozone exposure with that same individual's response to FA. In this way, each test subject serves as his/her own control, which was an important consideration by the authors in the design of these controlled human studies. Absent correction for FA responses, exercise-induced changes or diurnal variation in FEV_1 may be mistaken for responses due to ozone. This failure by EPA to ensure that study results it has relied upon in making recommendations to revise the ozone NAAQS are adequately controlled for confounding variables is a continuing theme and one that deserves considerably more attention than it is currently receiving.

2.2.3.2 There is Evidence of Investigator Bias in EPA Studies

In 2008, EPA (Brown et al., 2008) re-evaluated the Adams (2006) data. To avoid the need to make multiple comparisons, which is known to reduce the power of statistical tests to detect differences between treatment groups, Brown et al. (2008) ignored all FEV_1 measurements reported by Adams (2006), except the baseline FEV_1 (i.e., pre-exposure) and the 6.6-hour post-

exposure measurements for the FA and 60 ppb ozone scenario (Goodman et al., 2013). Using this approach, Brown et al. (2008) got a different result from Adams (2006). They were able to obtain statistically significant differences in FEV_1 decrements between the FA and 60 ppb exposure protocols. Notably, Nicolich (2007, as cited by Goodman et al. 2013) analyzed the entire Adams (2006) FEV_1 data set using a third set of statistical tests and reported results that were consistent with the original findings of Adams (2006); FEV_1 decrements at 60 ppb were not statistically significant. Omitting the majority of the Adams (2006) data (from different exposure concentrations and time points) from their analysis likely biased the Brown et al. results toward finding a statistically significant difference between the 60 ppb and FA control group (Goodman et al., 2013).

In another EPA study, Kim et al. (2011) reported a statistically significant group mean FEV_1 decrement at 60 ppb, but the decrement was small (< 2%) and was not accompanied by respiratory symptoms. Although FEV_1 decrements were measured at multiple time points, only the pre-exposure baseline and 6.6-hour post-exposure FA and 60 ppb ozone FEV_1 decrements were included in the statistical analysis. Similar to Brown et al. (2008), omitting data on other concentrations and from other time intervals likely biased the analysis toward detecting a difference between the FA and 60 ppb exposure (Goodman et al., 2013).

In an evaluation of the Adams (2006) and four other controlled exposure studies, Lefohn et al. (Lefohn, Hazucha, Shadwick, & WC., 2010) stated that, "Additional common findings, based on our reanalysis, among healthy exercising young adults included (i) high intra-individual variability in subject response within exposure profiles; (ii) inconsistent individual FEV_1 response patterns across exposure profiles; [and] (iii) FA exposure FEV_1 changes up to ± 5% in some subjects..." This indicates that any FEV_1 decrement (or increment) should have an error bar of at least 5% and that a large proportion of most measured FEV_1 responses must be attributable to factors other than ozone in these studies (Goodman & Pruitt, 2011). In other words, measurements of FEV_1 are highly variable, which makes the detection of small changes (e.g., 10%) challenging and reliance on results that are not statistically significant inappropriate.

The over-interpretation of the individual results from these studies is illustrated by a review of the data from the Kim et al. (2011) and Adams (2006) studies. Kim et al. (2011) reported three people with FEV_1 decrements $\geq$10% at 60 ppb. However, two of these people were also exposed to 80 ppb exposures, but had a lesser FEV_1 decrement at 80 ppb than at 60 ppb. Similarly, in the study by Adams (2006), two individuals also had lower FEV_1 decrements after exposure to 80 ppb than to 60 ppb. Because it is not biologically plausible that 80 ppb would have less of an effect on lung function than 60 ppb, the anomalous data from these individuals suggests that the individual data from these studies are not a reliable indicator of the fraction of the general population that are "responders" (those that respond with a $\geq$ 10% FEV_1 decrement).

2.3 OVERALL CONCLUSION DRAWN FROM CONTROLLED HUMAN EXPOSURE STUDIES

Only two additional controlled human exposure studies that evaluate ozone concentrations below 75 ppb have become available since the last ozone NAAQS review (Schelegle et al., 2009 and Kim et al., 2011). In addition to these two new studies, EPA also conducted a secondary analysis of existing data from Adams (2006) since the last review (Brown et al., 2008). Although the two new studies expand the database regarding the effect of low-level ozone concentrations on lung function, neither of them observed statistically significant lung function changes that meet EPA's definitions of clinical relevance or "adverse" FEV_1 decrements at concentrations below the current NAAQS of 75 ppb. EPA's reanalysis of the Adams (2006) lung function data in Brown et al. (2008) provides nothing new to the knowledge base, other than evidence of the lengths to which EPA is willing to go to support their own position.

The main thing that is new in this current review with respect to the controlled human exposure studies is that, instead of simply considering the variability in responses to ozone levels across test subjects, EPA is placing the greatest weight on responses observed among the most sensitive test subjects in identifying proposed alternative levels for the ozone NAAQS. However, the fraction of the test populations that responded with a $\geq$ 10% FEV_1 decrement varied tremendously across the different studies (i.e., 3% to 20%) and, therefore, these estimates are highly uncertain and unreliable. They certainly are not of a quality that should be relied upon in regulatory decision-making.

In the last ozone NAAQS review, EPA did not propose an ozone NAAQS below 75 ppb because of uncertainty about the extent to which exposures below 80 ppb result in lung function decrements, despite the fact that two controlled human studies were available that reported FEV_1 decrements following exposures to lower concentrations. The paucity of studies, their uniformly small sample sizes, small effect sizes, large measurement errors, and high variation, combine to give less reliable results. In addition, there appears to be evidence of data fishing in two cases (Brown et al., 2008; Kim et al., 2011). In light of these factors, the extremely weak evidence from controlled human exposure studies for lung function decrements at concentrations below 75 ppb is no better today than it was in 2008. Therefore, the studies do not support a lowering of the ozone NAAQS.

3.0 EPIDEMIOLOGY STUDIES

Epidemiology studies the patterns, causes, and effects of health and disease conditions in defined populations in the "real world" as opposed to under controlled laboratory conditions. As a result, sometimes epidemiology studies are called population studies. They attempt to identify factors that are associated with diseases (risk factors). As such, they provide evidence for more serious ozone-associated public health outcomes (e.g., mortality, hospital admissions, emergency department visits) in the general population, which often includes at-risk groups.

Because they are not conducted in controlled environments, epidemiology studies can only show that risk factors are associated (correlated) with a higher incidence of disease or mortality in the populations exposed to the risk factors. In reality, there is always some kind of association detected, and the question of interest is whether the association is positive (i.e., health effects increase as pollution increases), the confidence in the association, and how strong the association is. The higher the correlation the more certain the association, but epidemiology studies cannot prove causation.

There are thousands of epidemiology studies on the effect of ozone on a variety of health endpoints including effects on the respiratory, cardiovascular, endocrine, central nervous and reproductive system, hospital admissions and Emergency Department visits, and mortality. However, EPA focuses on hospital admissions/Emergency Department visits, respiratory symptoms in asthmatics, and mortality in the HREA. The studies that EPA used to estimate risk in the HREA are summarized in **Table 1** (separate document, Attachment 1 to TPA's comments). Those studies are reviewed in this report.

Review of the epidemiology studies that EPA has relied upon in making recommendations to reduce the ozone NAAQS clearly indicate that the associations between ozone and respiratory health effects and mortality are inconsistent and uniformly weak and the confidence in the associations is generally low:

- Lung function decrements do not consistently occur in any population (outdoor workers, adults or children exercising outdoors, or asthmatics) in response to increased ozone levels and neither asthmatic children nor adults consistently respond to ambient ozone levels with an increase in symptoms, medication use, or activity limitation. Multi-city hospital studies report both positive (increases in ozone are associated with increases in hospital admissions) and negative associations for ozone, depending on latency periods (or lag times) and model used, and whether the results are adjusted for other co-pollutants. The uniformly small effect sizes reported in epidemiology studies for all ozone-related health effects suggest that the associations between ozone and short-term respiratory effects, hospital admissions/ Emergency Department visits, respiratory symptoms and medication use in asthmatics, and both short- and long-term mortality, are weak.

- There is enormous uncertainty regarding EPA's "likely causal" and "suggestive of a likely causal" relationship classifications for short-term and long-term mortality, respectively, and neither classification is supported by the available evidence. Notably, the mortality relationships vary across studies and cities and appear to be confounded by particulate matter (PM10/PM2.5). In addition, although a questionable practice, national average mortality coefficients from multi-city epidemiology studies, reporting both positive and negative associations, have been published in several studies relied upon by EPA. This averaging of individual city mortality coefficients dilutes the high and low values and produces overall averaged mortality coefficients that do not accurately characterize the true relationship for any of the cities. Moreover, it conceals the variability and the uncertainty in the estimates. However, it is these "average" mortality coefficients that EPA has chosen from the studies to use in predicting mortality risks in its HREA.

- There was uncertainty about the associations reported in epidemiology studies at levels below 75 ppb in the last ozone NAAQS review that precluded EPA from establishing the NAAQS at a lower level. Despite many new studies, that uncertainty remains today because of the inconsistent and weak association reported, not to mention the prevalent methodological problems that continue to plague the epidemiology studies.

The studies listed in **Table 1** (separate document, Attachment 1 to TPA's comments) are important because EPA develops concentration-response functions from epidemiology studies using linear regression models to estimate the relationship between various health endpoints and ozone concentrations, generally including other secondary explanatory variables, such as other pollutants, temperature and other meteorological parameters, etc. in the model as well. EPA uses linear regression to fit an observed data set (e.g., monitored ozone concentrations in New York City and hospital admissions in New York City) and the result is an equation that can then be used to predict the dependent variable (e.g., hospital admissions) based on a known explanatory variable (e.g., monitored ozone concentration in another location).

3.1 KEY CONSIDERATIONS IN EVALUATING EPIDEMIOLOGY STUDIES

In reviewing epidemiology studies, there are several key considerations for evaluating the weight-of-evidence for a particular health effect, and those are:

- Reported Effects are Positive – An increase in ozone concentration should cause an increase in the observed effect if ozone is responsible for it (this is a positive association). A negative association would be when an increase in ozone is associated with a decrease in effect. Although unlikely to be biologically plausible, the interpretation of such a negative association could be that ozone is protective against the effect.
- Associations are Strong – Epidemiologists usually consider relative risks or odds ratios of 3 or 4 as strong evidence for "causation" and some courts require that epidemiologic studies used to support an argument that an alleged exposure caused a particular health effect in a plaintiff must show a relative risk of two or more (i.e., there is a doubling of risk). A relative risk of 3 means that the incidence in the exposed group is three times the incidence in the unexposed group.

- Confidence Intervals are Large/Small – Wide confidence intervals indicate that the estimate is uncertain. In addition, there is a close relationship between confidence intervals and statistical significance tests; any confidence interval for a percent increase in effect that contains zero should be considered statistically insignificant, likewise, a confidence interval for a relative risk or odds ratio that contains 1 is not statistically significant.
- Reported Effects are Statistically Significant – Determining whether risk statistics used in epidemiology studies are statistically significant is similar, but not identical, to determining whether percent increases in risk are statistically significant. Relative risks are used to compare the difference in results between two groups and odds ratios compare the odds that an outcome will occur given a particular exposure to the odds of the outcome occurring in the absence of that exposure. Confidence intervals for odds ratios or relative risks provide both the risk measure and a range (interval) within which the risk likely would fall if the study were repeated numerous times. A relative risk = 1 means there is no difference in risk between the two groups (i.e., no association or no increased risk). Therefore, a relative risk of 1.8 indicates an 80% increased relative risk of disease and a relative risk of 0.8 indicates a decreased risk of 20%. The odds ratio is essentially equivalent to the relative risk, so an odds ratio = 1 means that exposure does not affect the odds of the outcome. Therefore, if the confidence interval for a relative risk or odds ratio contains "1", it is not statistically significant. This differs from percent increases in risk for which a confidence interval containing "0" is not statistically significant.
- Reported Effects are Consistent – Consistency of effects (type and magnitude) across studies strengthens the evidence for causation.
- Confounding Factors and Biases are Controlled – Confounders are hidden variables in the population being studied that can easily generate an association that may be real, but is not what the epidemiologist thinks it is (e.g., lifestyle factors, such as smoking, that increase the risk of respiratory-related hospitalization or death) and biases are problems within study design (e.g., cities evaluated are not randomly chosen but are then used to estimate national response) and implementation.
- Lag Times are Consistent – Exposure information in epidemiology studies is lagged to account for latency periods between exposure and its observed effect; Lag-0 represents an association between same day responses and ambient concentrations (i.e., today), lag-1 is an association between a response and the concentration measured yesterday, while lag-2 is the response associated with concentrations measured 2 days ago.

3.2 EPIDEMIOLOGY STUDIES ARE PLAGUED BY EXPOSURE MEASUREMENT ERROR AND CONFOUNDING

There are a variety of issues that are inherent to epidemiological studies of air pollutants that require some upfront discussion.

Epidemiology studies are plagued with concerns about exposure misclassification and the potential for factors other than air pollution to influence the results, also known as "confounding". If confounding factors are not adequately controlled, health effects that are caused by another variable may be erroneously attributed to the pollutant of interest.

3.2.1 Epidemiology Studies Do Not Measure Actual Exposure

Exposure estimates in virtually all of the epidemiology studies relied upon by EPA are based on central site ambient air monitors, which are generally known to be poor surrogates for personal exposures. Concerns about exposure misclassification stem from the fact that no exposure information is collected for the deceased or individuals admitted to the hospital. Instead, epidemiology studies assume that concentrations monitored at a single (or a few) centrally-monitored location(s) represent the concentration to which these individuals were exposed. Depending on where the deceased or hospital/Emergency Department patients lived or worked relative to the monitored locations, the monitored concentrations may not be a good representation of outdoor ozone levels to which those patients were exposed.

3.2.1.1 People Spend the Majority of Time Indoors Where Ozone Concentrations are Much Lower than Outdoors

In addition, ozone concentrations indoors are about 10% of those found outdoors, so an ambient ozone concentration of 80 ppb would correspond to an indoor concentration of about 8 ppb. Adults spend approximately 7.6% of time outdoors, while children spend about 10% of time outdoors. Therefore, in general, personal exposure of an individual that is well described by these general statistics at an ambient concentration of 80 ppb ozone can be calculated as follows:

$$90\% \times 8 \text{ ppb} + 10\% \times 80 \text{ ppb} = 15.2 \text{ ppb ozone}$$

Where:

% time indoors	=	90%
% time outdoors	=	10%
Concentration outdoors	=	80 ppb
Concentration indoors	=	8 ppb

3.2.2 Lifestyle Factors are Rarely Adequately Addressed in Epidemiology Studies

Lifestyle factors such as smoking, diet, body mass index (BMI), and employment status can have a large impact on illness and mortality and are rarely, if ever, fully accounted for in epidemiological studies. In addition, there are many reasons for regional differences in disease patterns that have nothing to do with air pollution. For example, ischemic heart disease tends to be higher in the northeastern states, strokes are more common across a wide region of the South, respiratory disease mortality seems to be more common in certain mountain states, and people generally tend to live longer in Sunbelt cities and in the West. Levels of medical care are higher on both coasts of the US than in Appalachia, where studies also show that people tend to be less physically active.

Unless these non-pollution related regional disease patterns are considered, some of the regional differences in disease based on epidemiological studies will be erroneously associated with air pollution. Thus, health-effects models that relate spatial differences in air pollution to mortality rates may find a statistical association between some measure of air pollution and health if they fail to account for intervening variables (Lipfert, 1997) (Darrow, et al., 2011). This is a concern for all of the epidemiology studies that EPA relies upon in this current NAAQS review.

3.2.3 Co-Pollutants are Rarely Adequately Addressed in Epidemiology Studies

In addition, co-pollutant exposure is often not sufficiently addressed in epidemiology studies and EPA has a tendency to focus on results from one-pollutant models (those not corrected for the possibility of other co-pollutants, such as particulate matter or PM, to influence the results). It is often not clear as to what extent each pollutant's risk estimate represents its own effects or whether the pollutant in question acts as a surrogate for some other pollutant. There are many studies suggesting that the effects of ozone on health are confounded by PM.

3.2.4 Epidemiology Studies Depend on Controversial Statistical Models to Quantify Relationships between Risk Factors and Health Effects

Finally, epidemiology studies rely on statistics for establishing and quantifying the relationships between risk factors and disease. The statistical models used to describe the relationship between ambient ozone concentrations and risk continue to be questioned and refined both with regard to the selection of particular models and the specification of the variables in the models. When results from epidemiological studies using the same monitoring data and health statistics are compared, it becomes clear that the results are sensitive to the models and inputs chosen (see discussion of studies by Tolbert et al. (Tolbert, Klein, Peel, Sarnat, & Sarnat, 2007), Strickland et al. (Strickland, et al., 2010) and Darrow et al. (Darrow, et al., 2011) in **Table 1** (separate document, Attachment 1 to TPA's comments) and later in this section).

3.3 EPIDEMIOLOGY STUDIES ON SHORT-TERM RESPIRATORY EFFECTS DO NOT SUPPORT THE NEED TO LOWER THE CURRENT NAAQS

3.3.1 EPA Relies on 10 Studies in Estimating Risk of Respiratory Effects and Hospital Admissions/Emergency Department Visits

3.3.1.1 Short-Term Respiratory Effects

The best evidence from epidemiology studies for association with short-term ambient ozone concentrations is for the following respiratory effects:

- Decreased lung function in populations with increased outdoor exposures;
- Increases in respiratory symptoms and asthma medication use in asthmatic children; and
- Increased respiratory-related hospital admissions.

3.3.1.1.1 Lung Function

Epidemiological studies evaluating the association between short-term ozone exposure and lung function decrements are too numerous to list but are summarized in Tables 6-3 through 6-14 of the ISA (EPA, 2013). However, EPA relies on a model developed by McDonnell et al. (2012) that uses data from 23 controlled human exposure studies to estimate lung function decrements in the HREA (see previous section for discussion). Therefore, the epidemiology studies on lung function decrements are not used by EPA in quantifying risk. Rather they are used as evidence in the "causality" determination and as supportive evidence for biological plausibility.

3.3.1.1.2 Respiratory Symptoms in Asthmatics

There are two primary panel studies (Gent, et al., 2003; Mortimer, Neas, Dockery, Redline, & Tager, 2002) on the association between short-term increases in ambient ozone concentrations and increases in respiratory symptoms and medication use in asthmatic children. EPA relies on the Gent et al. (2003) study to estimate respiratory symptoms in asthmatics from Boston in the HREA.

3.3.1.2 Hospital Admissions/Emergency Department Visits

Studies that evaluate the association between short-term ambient ozone concentrations and hospital admissions are also too numerous to list, but are listed in Table 6-26 of the ISA (Pg. 6-132-134). However, the studies that have been published since the last ozone NAAQS review that EPA relies upon for estimating hospital admission/ Emergency Department visit risks in the HREA include:

- Darrow, et al., 2011;
- Ito, Thurston, & Silverman, 2007;
- Katsouyanni & Samet, 2009;
- Lin, Liu, Le, & Hwang, 2008;
- Medina-Ramon, Zanobetti, & Schwartz, 2006
- Strickland, et al., 2010;
- Silverman & Ito, 2010;
- Tolbert, Klein, Peel, Sarnat, & Sarnat, 2007; and
- Zanobetti & Schwartz, 2008.

These studies are summarized in **Table 1** (separate document, Attachment 1 to TPA's comments).

Multi-city studies (Katsouyanni et al., 2009, Medina-Ramon et al., 2006) generally provide more robust results than single-city studies, which typically exhibit too much statistical variation from city to city for clear conclusions to be drawn (Smith, Xu, & Switzer, 2009). One of the major benefits of looking at results from multi-city studies is that they are usually analyzed using uniform statistical methods, which removes one area of variability across regions.

3.3.2 EPA Makes Misleading Claims that Inconsistent Evidence is "Consistent"

3.3.2.1 Short-Term Respiratory Effects

According to the ISA (Pg. 6-2), epidemiologic studies have provided clear evidence for decrements in lung function related to short-term ambient ozone concentrations and these effects have been demonstrated in healthy children attending camps, adults exercising or working outdoors, and children with and without asthma.

EPA also claims that short-term increases in ambient ozone concentration are associated with increases in respiratory symptoms (e.g., cough, wheeze, shortness of breath) in children with asthma (Gent, et al., 2003; Mortimer, Neas, Dockery, Redline, & Tager, 2002) and with increased asthma medication use and self-limitation of activity in asthmatics.

As discussed in the sections that follow, studies of lung function decrements in response to ambient ozone concentrations are far from consistent and asthmatics do not consistently respond to increases in ozone concentrations with increased symptoms and medication use or by limiting their activity.

3.3.2.1.1 Ozone Does Not Consistently Cause Lung Function Decrements

As discussed below, most epidemiology studies report small lung function decrements in association with ozone that are frequently not statistically significant. In fact, some even show improvement in lung function in response to ozone concentrations. Furthermore, asthmatic children did not consistently respond to increasing ozone concentrations with a decrements in lung function.

Adults and Children Exercising Outdoors Do Not Consistently Experience Lung Function Decrements

Epidemiological studies of populations with increased outdoor exposure generally tend to report small ozone-associated lung function decrements, but with one or two studies showing an improvement in lung function. This argues against EPA's statement that there is clear evidence of lung function decrements in adults and children exercising outdoors. The results shown in Figure 6-5 and Table 6-4 of the ISA (Pg. 6-36 and 6-37) of lung function decrements in exercising adults and children show primarily small decreases in lung function, with one study showing an increase. In addition, the magnitude of the decrease in lung function in exercising

adults was generally not found to depend strongly on duration of outdoor time or ambient ozone concentration.

Adults Working Outdoors Do Not Consistently Experience Lung Function Decrements

Results shown in Figure 6-6 and Table 6-5 of the ISA (Pg. 6-4- and 6-41) showed slightly larger lung function decrements in adults working outdoors, but wider CIs, most of which crossed zero (i.e., not consistently decreased and not statistically significant). This argues against EPA's statement that there is clear evidence of lung function decrements in adults working outdoors.

Asthmatic Children Do Not Consistently Experience Lung Function Decrements

Studies of lung function decrements in children with asthma rely primarily on self-reported lung function measured by subjects. Self-reported lung function measurements are known to have a higher rate of error (Goodman, Prueitt, S.N., Bailey, & Rhomberg, 2013b). Figure 6-7 from the ISA (Pg. 6-45), which is reproduced below in **Figure 3-1**, shows percent change in FEV_1 in children with asthma associated with increases in ambient ozone concentrations. As can be seen, the CIs are wide and almost all of them include zero, indicating that some asthmatics in each of the studies experienced a decrease in FEV_1, while others experienced an increase in FEV_1 in response to increasing ozone concentrations and that the results are mostly statistically insignificant.

Similar results are shown in Figure 6-8 of the ISA (Pg. 6-48), which shows percent change in PEF (peak expiratory flow) or $FEF_{25-75\%}$ (forced expiratory flow between the times at which 25% and 75% of the vital capacity is reached) associated with increases in ambient ozone concentrations among children with asthma. The confidence intervals are not as wide as those in Figure 6-7, but most cross zero, indicating that some asthmatics experienced a decrease in PEF or $FEF_{25-75\%}$ and others experienced an increase in response to increasing ozone concentrations and that the most of the results are not statistically significant.

3.3.2.1.2 Ozone Does Not Consistently Cause Respiratory Symptoms and Self-Limitation of Activity in Asthmatics

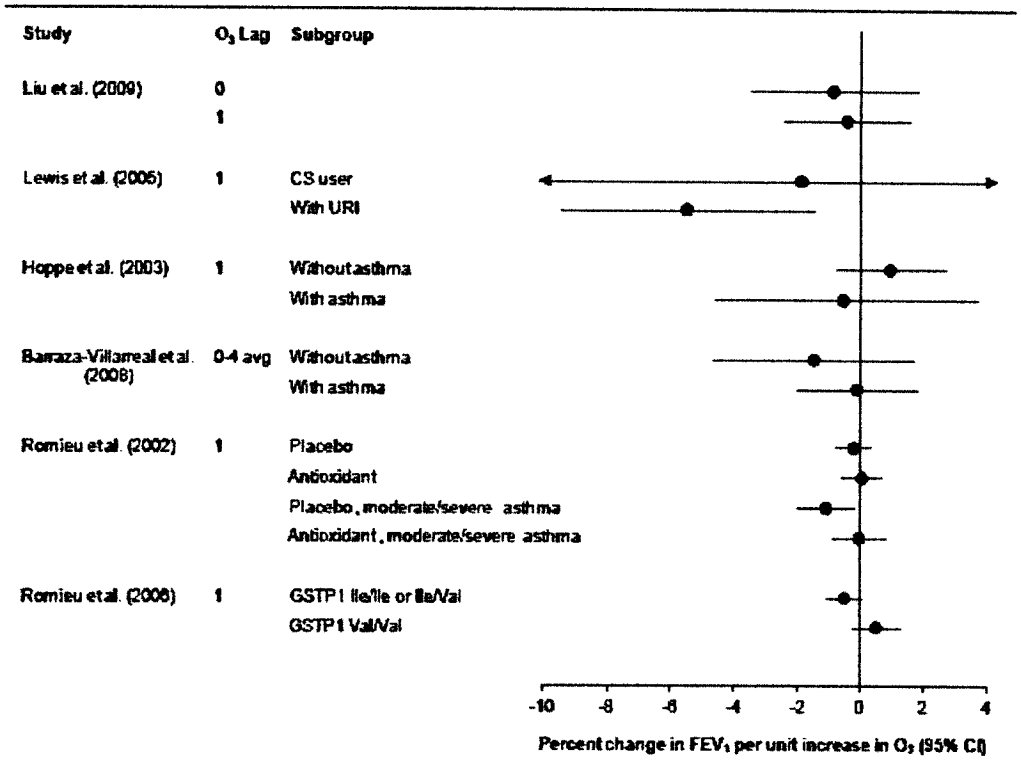
The ozone ISA acknowledges that evidence does not consistently demonstrate ozone-associated diminished activity in children with asthma (O'Connor, et al., 2008; Delfino, Gone, Linn, Pellizzari, & Hu, 2003). As discussed below, the effect of ozone on symptoms, medication use, and self-limitation of activities in asthmatics was far from consistent.

Asthmatic Children Do Not Consistently Experience Increased Symptoms

Out of 17 studies listed in Table 6-20 of the ISA (Pg. 6-106) on the effect of ambient short-term ozone concentrations on respiratory symptoms in children with asthma, *only half reported*

statistically significant increases in symptoms. Therefore, increases in ozone concentrations do not consistently increase symptoms in asthmatic children.

FIGURE 3-1
OZONE-RELATED FEV_1 DECREASES IN ASTHMATIC CHILDREN



Note: Results generally are presented in order of increasing mean ambient O_3 concentration. CS = Corticosteroid, URI = Upper respiratory infection. Effect estimates are from single-pollutant models and are standardized to a 40-ppb increase for 30-min or 1-h max O_3 concentrations, a 30-ppb increase for 8-h max or 8-h avg O_3 concentrations, and a 20-ppb increase for 24-h avg O_3 concentrations.

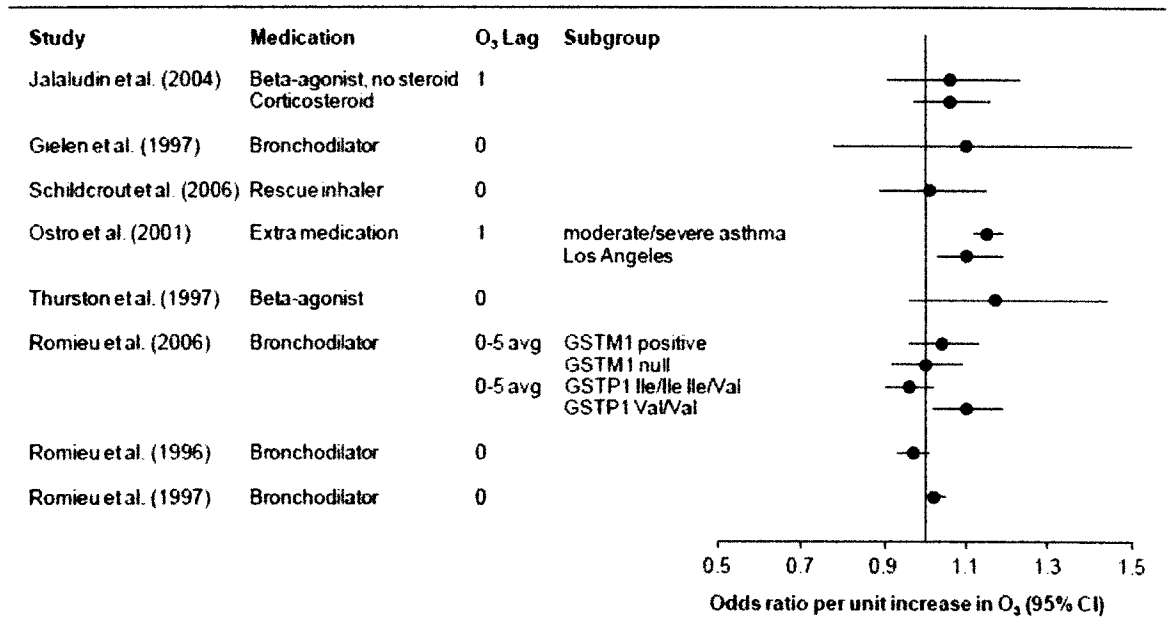
Figure 6-7 Percent change in FEV_1 in association with ambient O_3 concentrations among children with asthma.

Source: EPA, 2013

Asthmatic Children Do Not Consistently Experience Increased Medication Use

Similarly, Figure 6-13 of the ISA for ozone (Pg. 6-110), which is reproduced in **Figure 3-2** below, shows that out of eight studies cited, the odds ratio for increases in medication use per unit increase in ozone was statistically significant in only two of the studies (Ostro, Lipsett, Mann, Braxton-Owens, & White, 2001; Romieu, et al., 2006). Additional studies on associations between short-term ambient ozone concentrations and medication use are presented in Table 6-21 of the ISA (Pg. 6-111), but the additional studies did not produce statistically significant ORs. In addition, with the exception of one study (Just, et al., 2002, odds ratio = 3.95 [1.22, 12.9]), the odds ratios were all uniformly small (< 1.2). Epidemiologists typically consider ORs and RRs of > 1.5 as moderate to strong indicators of causation and odds ratios or relative risks of 3 or 4 as providing strong evidence.

FIGURE 3-2
ODDS RATIOS FOR MEDICATION USE PER UNIT INCREASE IN OZONE



Note: Results generally are presented in order of increasing mean ambient O_3 concentration. Odds ratios are from single-pollutant models and are standardized to a 40-ppb increase for 1-h max O_3 and a 30-ppb increase for 8-h max or 15-h avg O_3.

Figure 6-13 Associations between ambient O_3 concentrations and asthma medication use.

Source: EPA, 2013.

Asthmatic Children Do Not Consistently Limit Their Activity

According to the ISA (Pg. 6-112), O'Connor et al. (2008) found that a 20 ppb increase in the average concentration over the preceding 19 days was associated with a 10% lower odds (-26, 10) of slow play (days child slowed down or stopped play). This represents a negative relationship (i.e., increased ozone seemed to increase activity) and the relationship was not statistically significant (confidence interval contains 0).

In addition, clinical studies demonstrate that the respiratory effects of ozone occur soon after exposure (Goodman et al., 2013b). Responses that occur on the day of the measured ozone concentration (0-day lag), 1 day after the measured pollutant concentration (1-day lag), or a few days after, are biologically plausible. However, findings for longer lag times are inconsistent with plausible biological mechanisms for short-term ozone effects and, therefore, it is unlikely that the O'Conner et al. (2008) finding was due to ozone exposure. The O'Connor et al. (2008) study also reports that after adjustment for community and month, there was a substantial correlation among other daily pollutant levels and lung function, **but not ozone**. In single

pollutant models, FEV_1 was significantly related to 5-day average concentrations of PM2.5, NO2, SO2, **but not ozone** and effect estimates for 1-day and 5-day averages for ozone did not differ. Finally, ozone concentrations were not significantly associated with symptoms or school absences. Therefore, the O'Connor et al. (2008) study does not support EPA's contention that ozone exposure cause asthmatics to limit their activities.

According to the ISA, Delfino et al. (2003) found that a 40 ppb increase in the 1-hour maximum ozone concentration (lag-0) was associated with an increase in symptoms that interfered with daily activity with an odds ratio of 7.14 (1.18, 43.2). While the odds ratio reported in the paper for the 1-hour maximum ozone concentration was statistically significant (odds ratio = 1.99 (1.06–3.72), the confidence interval was wide and the results were only based on seven test subjects. Therefore, the Delfino et al. (2003) study also fails to provide strong evidence that ozone exposure causes asthmatics to limit their activity.

Several studies reported increases in school absenteeism in children with asthma in association with increases in ambient ozone concentrations with long lag times (14-day and 30-day distributed lags, 19-day average) (O'Connor et al., 2008; Gilliland, et al. 2001; Chen, Jennison, Yang, & Omaye, 2000). As discussed above, findings for longer lags are inconsistent with plausible biological mechanisms for short-term ozone effects and, therefore, it is unlikely that these absenteeism findings are related to ozone exposure.

Asthmatic Adults Do Not Consistently Experience Increased Symptoms

The ozone ISA (Pg. 6-112) indicates that Ross, et al., (2002) found that an increase in the average 8-hour maximum concentration of ozone over the preceding three days was associated with an increase in symptom score and asthma medication use in adult asthmatics. However, although a positive association was noted, it was not statistically significant.

Asthmatic Adults Do Not Consistently Experience Increased Medication Use

Park, et al. (2005) found inconsistent associations between average ozone concentrations (24-hour) measured at 10 monitoring sites and medication use in adults with asthma in Korea during a period of dust storms. A panel study of individuals with asthma (ages 13-78 years) in Thailand found that a 20 ppb increase in 24-hour average ozone concentrations (lag-4) was associated with a 26% (4, 43) lower odds of symptoms that interfered with activities (Wiwatanadate & Liwsrisakun, 2011), which suggests that ozone decreases symptoms that interfere with activities (the opposite of what is expected).

Asthmatic Adults Do Not Consistently Limit their Activity

The ISA also cites Khatri, et al. (2009) as support for a positive association between increases in ozone concentrations and self-limitation of activity in adult asthmatics. However, the study indicates that individual perception of air pollutant exposures were related to lung function and

appeared to play a role. Therefore, these results do not likely represent independent effects of ozone (i.e., there were other factors that appear to have influenced the results).

3.3.2.1 Hospital Admissions and Emergency Department Visits

EPA claims that epidemiologic studies have also demonstrated consistent associations between short-term increases in ambient ozone concentration and increases in respiratory hospital admissions and Emergency Department visits, specifically during the summer or warm months (Pg. 6-3 of ISA). However, there is still substantial debate over the extent to which exposure to ozone is directly responsible for hospital admissions and Emergency Department visits relative to other environmental factors (e.g., exposure to other air pollutants, heat, humidity, allergens), which could confound the association with ozone.

The hospital admission and Emergency Department visit studies are summarized in **Table 1** (separate document, Attachment 1 to TPA's comments). As discussed below, ozone does not consistently cause increases in Hospital Admissions or Emergency Department visits.

3.3.2.1.1 Ozone Does Not Consistently Increase Hospital Admissions

Katsouyanni et al. (2009) – Association Not Statistically Significant When Corrected for PM10 (Detroit Only)

One of the larger studies on the association of short-term ozone and hospital admissions is the Air Pollution and Health: A European and North American Approach (APHENA) study (Katsouyanni et al., 2009), which included datasets from the US (90 cities), European (32 cities), and Canadian (12 cities) multi-city studies. However, hospital admission data were only available for 14 US cities.

Study results from the APHENA study natural spline models (a spline function is a method of fitting a smooth curve to a set of noisy observations) with 8 df/yr (degrees of freedom indicates the number of values in the final calculation of a statistic that are free to vary), uncorrected for PM10, for a 40 ppb increase in 1-hour maximum ozone concentrations are summarized in Figure 6-15 of the ISA (Pg. 6-137), which is reproduced in **Figure 3-3**, below.

As shown in **Figure 3-3**, US estimated percentage increases in respiratory admissions were positive (i.e., hospital admissions increased with ozone concentrations), but adjusting for PM10 (open circles in **Figure 3-3**), the ozone effects were decreased and became statistically insignificant (CIs touch or cross 0) in all models (also see Table 39 of Katsouyanni et al., 2009).

Despite including results for 14 US cities, the APHENA study (Katsouyanni et al., 2009) was used in EPA's HREA to estimate the risk of respiratory-related hospital admissions for Detroit only.

Medina-Ramon et al. (2006) – Negative Association for Same-Day Chronic Obstructive Pulmonary Disease Hospital Admissions but Positive 2-Day Cumulative Association

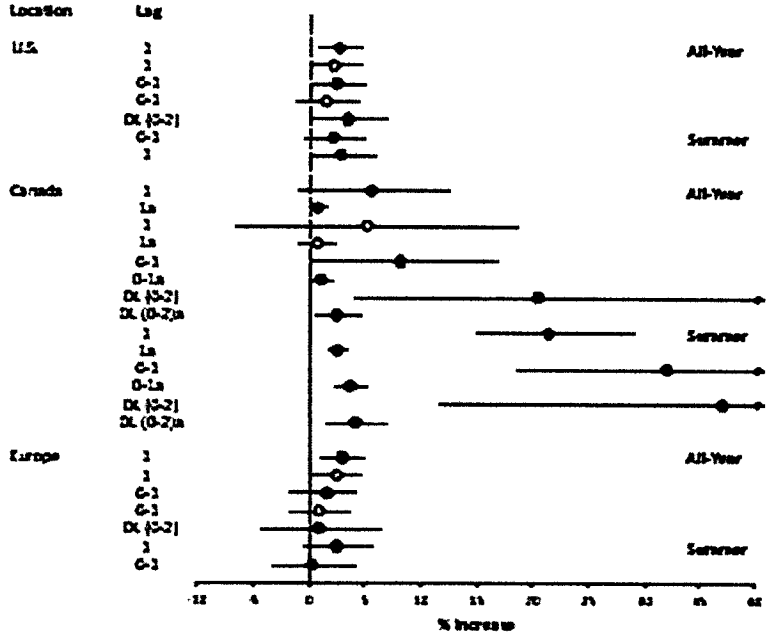
The Medina-Ramon et al. (2006) study is a case-crossover study that was conducted in 36 US cities to evaluate the effect of ambient ozone concentrations (1986-1999) on respiratory hospital admissions. This study is the most influential of the hospital admission studies because it is used to estimate chronic obstructive pulmonary disease hospital admissions for all 12 Urban Areas evaluated in the HREA.

The Medina-Ramon et al. (2006) study reported that the 2-day cumulative effect (ozone concentrations averaged over 2 days prior to hospital admission) of a 5-ppb increase in 8-hour average ozone concentrations (during the warm season) was a 0.27% (0.08, 0.47) increase in chronic obstructive pulmonary disease admissions (1.6% increase per 30 ppb increase in ozone) and a 0.41% (0.26, 0.57) increase in pneumonia (2.5% increase per 30 ppb ozone) admissions during the warm season, but not the cold season. However, the associations for chronic obstructive pulmonary disease and pneumonia were negative on the day of admittance (i.e., at lag-0). If interpreted literally, this would indicate that an increase in ambient ozone concentration would result in a decrease in same-day hospital admissions for chronic obstructive pulmonary disease and pneumonia (i.e., ozone is protective). This result seems inconsistent with what we know about the timing of acute ozone effects (i.e., they occur soon after exposure). More importantly, it serves to highlight the extreme variability of results in many of the epidemiology studies, the sensitivity of results to choice of lag time, and the folly of focusing on single risk estimates from a study rather than the full distribution of risks.

The cumulative effect referenced above was calculated by summing the estimates from lag-0 (decrease in hospital admissions) and lag-1 (increase in admissions), to get a small overall increase in hospital admissions, despite the fact that a negative association (i.e., no association or protective effect of ozone) was observed for same-day hospital admissions for chronic obstructive pulmonary disease. In addition, as shown in Figure 1 of Medina-Ramon (2006), the individual-city associations for chronic obstructive pulmonary disease hospital admissions in the summer were highly variable, ranging from approximately –30% to +40% for a 30 ppb increase in 8-hour ozone, while the individual-city associations for pneumonia hospital admissions ranged from –20% to + 30% for a 30 ppb increase in 8-hour ozone. Despite this variability, it was this combined hospital admission coefficient from the study that EPA used in estimating hospital admission risk in the HREA.

This regional heterogeneity is consistently shown in multi-city studies. It is not appropriate to use response functions from averages taken across highly variable city-specific risk coefficients because that methodology masks the regional variability and, therefore, the estimated risks do not properly reflect the uncertainty in the estimates.

FIGURE 3-3
PERCENT INCREASE IN RESPIRATORY-RELATED HOSPITAL ADMISSIONS: APHENA STUDY



Note: Black circles = all-year results, open circles = all-year results in copollutant models with PM_{10}, and red circles = summer only results. For Canada, lag days with an "a" next to them represent the risk estimates standardized to an approximate IQR of 5.1 ppb for a 1-h max increase in O_3 concentrations.

Figure 6-15 Percent increase in respiratory hospital admissions from natural spline models with 8 df/yr for a 40 ppb increase in 1-h max O_3 concentrations for each location of the APHENA study.

Zanobetti and Schwartz (2006) – Negative Association for Same-Day Pneumonia Hospital Admissions (Boston Only)

Zanobetti and Schwartz (2006) examined the association between ozone and hospital admissions for pneumonia in Medicare patients in Boston and reported a 3.8% decrease (-7.9, -0.1%) in pneumonia admissions (the opposite of what is expected) for a 20 ppb increase in 24-hour average ozone concentrations at lag-0 and a 6% decrease (-11.1, -1.4%) for the average of lag-0 and 1.

Silverman and Ito (2010) – Statistically Significant Association for ICU Asthma Admissions but Not for Non-ICU Admissions (New York City Only)

Silverman and Ito (2010) examined the association of 8-hour maximum ozone concentrations and severe acute asthma admissions (i.e., those admitted to the Intensive Care Unit [ICU]) in New York during the warm season in the years 1999 through 2006. They reported positive and

statistically significant associations with non-ICU asthma admissions for the 6- to 18-year age group (26.8% [1.4, 58.2%] for a 30 ppb increase in 8-hour maximum ozone concentrations at lag-0-1), but mostly statistically insignificant results for ICU admissions.

Linn et al. (2000) – Negative or Non-Statistically Significant Associations for Cardiopulmonary Hospital Admissions (Los Angeles Only)

Linn et al. (Linn, Szlachcic, Gong, Kinney, & Berhane, 2000) evaluated the association between ozone and daily hospital admissions for cardiopulmonary illnesses in Los Angeles. The authors concluded that only a few equivocally positive relationships were found with ozone and only when other pollutants and heat stress confounded results. Positive associations with ozone only occurred when weather variables, which are always included in regression models for air pollutants, were not included. Summer ozone did not present higher risk of hospital admissions, which is inconsistent with other studies. Only negative or non-statistically significant positive relationships were observed with cardiovascular, pulmonary, cerebrovascular, and abdominal disease (control) admissions in year-round and single season analyses. The model was not PM-corrected.

Linn et al. (2000) was relied upon in the HREA to predict cardiovascular hospital admissions/Emergency Department visits in Los Angeles. Appendix 7 of ISA, Table 7B-1 shows that, when the Linn et al. (2000) study was used as the basis for estimates in Los Angeles, there was an increase in pulmonary-related hospital admissions associated with modeled concentrations of 75 ppb (the current NAAQS) and each of the proposed alternative NAAQS levels (i.e., 70 – 60 ppb) relative to hospital admissions associated with recent monitored ozone concentrations in Los Angeles. This suggests that public health in Los Angeles will suffer if the current NAAQS is met or is reduced to a lower level. This result is counter-intuitive and suggests that the concentration-response function from this study is unreliable and should not have been used in the HREA. It is unclear why this study was chosen by EPA for use in the HREA.

Lin et al. (2008) – Statistically Significant Associations for Pediatric Respiratory Hospital Admissions in 5 of 11 New York Regions (New York City Only)

Lin et al. (2008) evaluated pediatric respiratory hospital admissions in the state of New York and found mixed results for the association between ambient ozone level and respiratory hospital admissions in different regions. Associations were statistically significant in only 5 of 11 regions evaluated. However, this study was only used to estimate respiratory-related hospital admissions in New York City in the HREA (no other cities in New York were evaluated) and the study did observe a small increase in respiratory-related hospital admissions for New York City. The association for New York City was the smallest of those that were statistically significant (1.75% [1.01-2.48]) and the confidence interval was wide, so the estimate is uncertain.

This study produced much lower risk estimates than Silverman and Ito for New York City, but looked at a different health endpoint (pediatric respiratory hospital admissions vs ICU and non-ICU asthma admissions), used different lag times, and controlled for more confounding effects (e.g., demographic characteristics, PM10, meteorological conditions, day of the week, seasonality, various lag times, and long-term trends).

Conclusions Drawn from Hospital Admissions and Emergency Department Visit Studies

The results of these studies are summarized in Figure 6-19 of the ISA (Pg. 6-153), which is reproduced as **Figure 3-4**. As can be seen in the figure, the associations between short-term ozone concentrations and hospital admissions in the US are consistently small in the two multi-city studies (Katsouyanni et al. [2009] and Medina-Ramon et al. [2006]) with correspondingly narrower CIs, indicating less variability. The two multi-city studies reported negative or small, but inconsistent increases in hospitalization (depending on lag times) in association with increased short-term ozone concentrations. The effect estimates reported in the single city studies are generally somewhat larger, but also much more variable. Results from the two multi-city studies likely provide more robust estimates of the effect of short-term ambient ozone concentrations on hospital admissions, although they have limitations since they represent averages across variable city-specific estimates.

3.3.2.1.2 Ozone Consistently Increased Emergency Department Visits in Atlanta and New York City

Emergency Department Visits – Atlanta

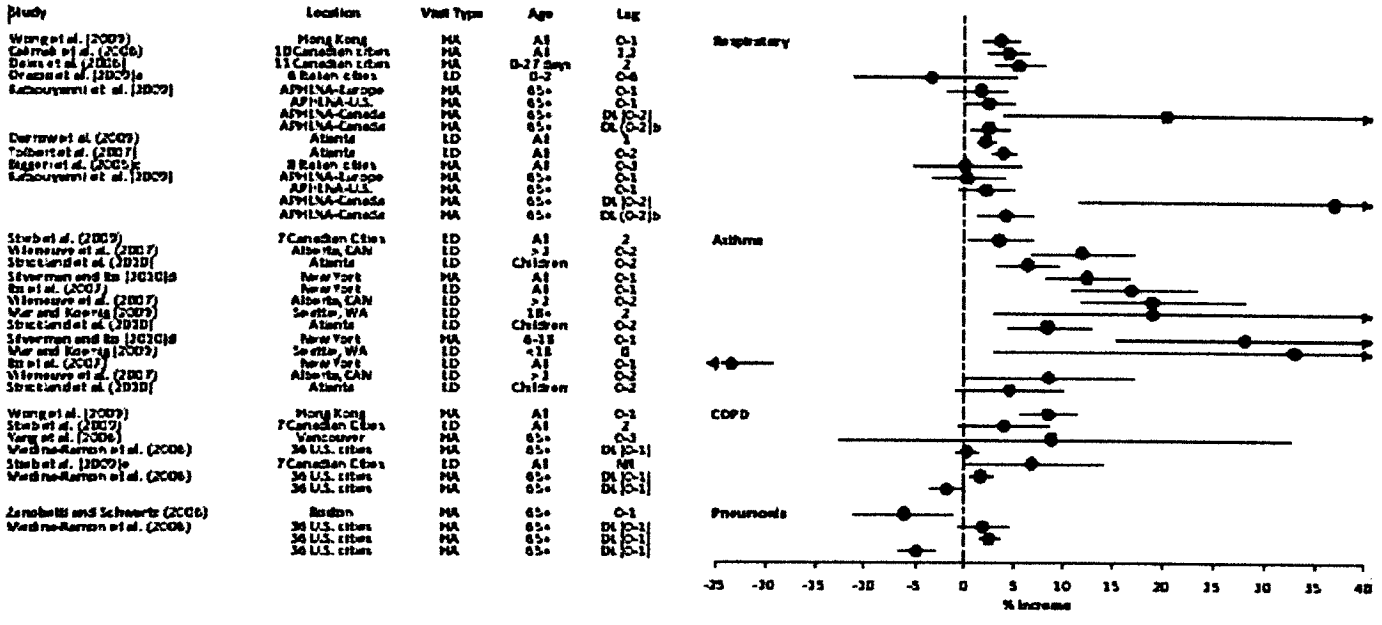
Tolbert et al. (2007), Strickland et al. (2010), and Darrow et al. (2011) used the same Emergency Department visit data and Atlanta air quality data from 1993-2004, but different air quality averaging techniques. These three studies illustrate the sensitivity of Emergency Department visit risk estimates to model specification, inclusion of covariates, air monitoring data averaging techniques, and populations evaluated. These same sensitivities also apply to estimates of hospital admissions, as well as mortality estimates, which are discussed later.

Tolbert et al. (2007) – Smaller Risk Estimate than Strickland – Pollutant Concentrations Averaged Over Multiple Monitors (Atlanta)

A large single-city study conducted in Atlanta by Tolbert et al. (2007) evaluated evidence for an association between short-term ambient ozone concentrations in Atlanta (1993 – 2004) and respiratory and cardiovascular Emergency Department visits in all age groups. Air quality data were averaged across multiple monitors. Tolbert et al. (2007) reported a statistically significant 3.9% increase (2.7, 5.2) in respiratory Emergency Department visits for a 30 ppb increase in 8-hour maximum ozone concentrations during the warm season. Ozone-related respiratory Emergency Department visit associations when corrected for carbon monoxide (CO), NO2, and

PM10, were attenuated, but remained positive. Results were not statistically significant for cardiovascular Emergency Department visits.

FIGURE 3-4
PERCENT INCREASE IN RESPIRATORY-RELATED HOSPITAL ADMISSIONS AND EMERGENCY DEPARTMENT VISITS



Note: Effect estimates are for a 20 ppb increase in 24-h, 30 ppb increase in 8-h max, and 40 ppb increase in 1-h max O_3 concentrations. HA=hospital admission; ED=emergency department. Black=All-year analysis; Red=Summer only analysis; Blue=Winter only analysis.

[a] Wheeze used as indicator of lower respiratory disease.

[b] APHENA-Canada results standardized to approximate IQR of 5.1 ppb for 1-h max O_3 concentrations.

[c] Study included 8 cities; but of those 8 only 4 had O_3 data.

[d] non-ICU effect estimates.

[e] The study did not specify the lag day of the summer season estimate.

Figure 6-19 Percent increase in respiratory-related hospital admission and ED visits in studies that presented all-year and/or seasonal results.

Strickland et al. (2010) – Population Weighted Air Pollutant Concentrations (Atlanta)

Strickland et al. (2010) examined the association between ozone exposure and pediatric asthma Emergency Department visits (ages 5-17 years) in Atlanta between 1993 and 2004, using population-weighting to combine daily pollutant concentrations across monitors (as opposed to simple averaging of monitor concentrations in Tolbert et al. [2007]). They observed a statistically significant 6.4% (3.2, 9.6) increase in Emergency Department visits for a 30 ppb increase in 8-hour maximum ozone concentrations at lag 0-2 in an all-year analysis and stronger associations during the warm season (i.e., May-October) (8.4% [4.4, 12.7%]; lag 0-2)

than the cold season (4.5% [-0.82, 10.0%]; lag 0-2). Authors reported that ozone risk estimates were not substantially changed when controlling for other pollutants.

Darrow et al. (2011) – Smallest Risk Estimate of 3 Studies – Air Pollutant Concentrations from Single Centrally-Located (Atlanta)

Darrow et al. (2011) was a reanalysis of the Tolbert et al. (2007) data, using different air quality data (one centrally-located monitor instead of the average across multiple monitors in Tolbert et al. [2007] or population weighted average in Strickland et al. [2010]) and 1-day lag. Respiratory-related Emergency Department visits were lower than reported by Tolbert (2007) and Strickland et al. (2010) for Atlanta. This illustrates sensitivity of results to inclusion of covariates, averaging of ambient pollutant concentrations, and lag times chosen. It is unclear whether models controlling for NO2, CO, PM10 and NO2/NOx were used by EPA in the HREA.

Emergency Department Visits – New York City

Ito et al. (2007) – Consistently Positive Associations (New York City Only)

Ito et al. (2007) examined the association between short-term exposure to air pollution and asthma Emergency Department visits for all ages in New York City from 1999 to 2002 and reported a positive association with asthma Emergency Department visits, during the warm season across the models (ranging from 8.6 to 16.9%). Ozone risk estimates were not substantially changed in co-pollutant models that used every-day data for PM2.5, NO2, SO2, and CO during the warm season.

3.3.3 EPA Selectively Reports Positive Results, Often Ignoring, or Worse, Obscuring Negative Results

EPA only reported positive results from the APHENA study (Katsouyanni et al., 2009) that occurred when natural smoothing splines were used (results using penalized splines were often negative). In addition, EPA mostly only reported results that were not corrected for PM10, despite the fact that correction for PM10 occasionally caused the results to become negative and almost always caused them to become statistically insignificant.

The most influential study on hospital admissions was the Medina-Ramon et al. (2006) study, which includes all 12 Urban Areas evaluated in the HREA and was used to estimate hospital admissions for all 12. EPA focused on the small increase in hospital admissions for chronic obstructive pulmonary disease reported for a 2-day cumulative lag period in the study. However, that small increase in hospital admissions was derived by combining the lag-0 change in hospital admissions, which was negative (admissions decreased), and the lag-1 change, which was positive, leading to an overall small increase in hospital admissions in association with increasing ozone concentrations. However, using this distributed lag result conceals the fact that the study showed an inverse relationship between same day ozone concentrations and

chronic obstructive pulmonary disease hospital admissions, a seemingly biologically implausible result.

3.3.4 Uniformly Small Effect Estimates Suggest the Association with Ozone is Weak

3.3.4.1 Short-Term Respiratory Effects

Epidemiological studies of populations with increased outdoor exposure (see Table 6-3 of ISA, Pg. 6-34) produced primarily small ozone-associated lung function decrements (i.e., <1% to 3.4% per unit increase in ozone), small enough that they are within the range of measurement variability (i.e., < 150 ml; Pellegrino et al., 2005). In addition, the magnitude of decrease was generally not found to depend strongly on duration of outdoor work or ambient ozone concentration.

3.3.4.2 Respiratory Symptoms

Out of 16 studies listed in Table 6-20 of the ISA (Pg. 6-106) on the effect of ambient short-term ozone concentrations on respiratory symptoms in children with asthma, with the exception of one study, the ORs were uniformly small (i.e., odds ratio = < 1.2). Although the magnitude of an odds ratio (or relative risk) has no bearing on whether the association is real, the smaller the odds ratio (or relative risk), the more likely the association is spurious or due to confounding or bias. Small odds ratios (or relative risks) indicate weak associations that could easily be affected by uncontrolled confounding. An odds ratio of 1.2 is very small and indicates that the association between short-term ambient ozone concentrations and medication use in asthmatics is a weak one.

3.4 EPIDEMIOLOGY STUDIES ON MORTALITY DO NOT SUPPORT THE NEED TO LOWER THE CURRENT NAAQS

3.4.1 EPA Only Relies on Two Epidemiology Studies in Estimating Short-Term Mortality Risk and a Single Study in Estimating Long-Term Mortality Risk

EPA acknowledged that multiple uncertainties remained in the assessment of the ozone-mortality relationship in the previous review. There are several studies that have evaluated the relationship between short-term ambient ozone concentrations and premature mortality that were published since the last ozone NAAQS review.

However, the following two studies evaluate the relationship between short-term ambient ozone concentrations and non-accidental, cardiovascular, and respiratory mortality and are exclusively relied upon by EPA to estimate short-term mortality risks in the HREA:

- Smith et al., 2009; and
- Zanobetti and Schwartz, 2008.

The core short-term mortality risk assessment relied on the Smith et al. (2009) study, while Zanobetti and Schwartz (2008) was used in conducting a sensitivity analysis on short-term mortality to explore the potential impact that variation in specific model design elements can have on the core risk estimates.

3.4.2 EPA Makes Misleading Claims that Inconsistent Evidence is "Consistent"

Previous epidemiologic evidence has not clearly supported a relationship between short-term ambient ozone concentrations and mortality. However, according to EPA, recent multi-city studies and a multi-continent study have reported consistent positive associations between short-term ozone exposure and total (non-accidental) mortality.

The multi-continent study referenced by EPA is the APHENA study (Katsouyanni et al., 2009), which reports that small generally positive associations between short-term ozone concentrations and all-cause mortality were observed for the US, Canada, and Europe. However, the US results were quite inconsistent, reporting both positive and negative effects (for all-cause and cause-specific mortality), depending on splines and degrees of freedom (Tables 21 – 24 of Katsouyanni et al., 2009). The effect estimates on all-cause mortality became negative when corrected for PM10 in some cases and statistically insignificant in all cases (Tables 21 of Katsouyanni et al., 2009). Therefore, the APHENA study did not consistently report positive associations between short-term ozone concentrations and mortality.

3.4.3 Uniformly Small Mortality Risks Suggests Weak Association with Ozone

3.4.3.1 All-Cause Mortality Estimates are Uniformly Small

Although the all-cause (non-accidental) percent increase in mortality estimates for US cities (only) in Table 6-42 are positive and statistically significant, they are all < 2%, except for the summer APHENA study results (see discussion on selectively reporting positive results for APHENA results). Therefore, although the associations between short-term ozone exposure and total (non-accidental) mortality reported in Table 6-42 of the ISA are consistently positive, the associations are also consistently weak.

3.4.3.2 Cause-Specific Mortality Estimates are Uniformly Small and Frequently Not Statistically Significant

Although mostly positive, 26 of the 44 percent increases in cause-specific mortality presented in Table 6-53 of the ISA (Pg. 6-260 and 6-261) are statistically insignificant. Six out of 10 year-round results on short-term cardiovascular mortality were not statistically significant, six out of 12 summer-only results on short-term cardiovascular mortality were not statistically significant, all 10 year-round studies of short-term respiratory mortality were not statistically significant, and four of 12 summer-only results of short-term respiratory mortality were not statistically significant. Therefore, while the cause-specific mortality associations are consistently positive,

they are uniformly small (with the exception of the APHENA study US results; see discussion on selective reporting of positive results) and mostly statistically insignificant.

3.4.4 EPA Selectively Reports Positive Results, Often Ignoring, or Worse, Obscuring Negative Results

Several studies that reported no association between ozone and short-term mortality were not included in EPA's review (Dominici et al., 2005; Goldberg et al., 2006). EPA also omitted a study by Lipsett et al. (2011), which only reported statistically insignificant mortality ratios for long-term ozone mortality (the only statistically significant result for ozone was for ischemic heart disease, and it was only marginally significant and became null upon adjustment for PM2.5).

EPA also selectively reported only the positive associations between short-term ozone concentrations and mortality from the APHENA study. EPA provided an explanation in the ISA as to why only results from models with certain specifications were reported, but with other model specifications, the associations between short-term ozone concentrations and all mortality categories were negative. Furthermore, in reporting mortality results, EPA consistently focuses only on the direction of the effect (i.e., whether it is positive), not whether a statistically significant effect was observed.

The National Morbidity, Mortality, and Air Pollution Study Part II: Morbidity and Mortality from Air Pollution in the US (NMMAPS) data, which are the data from which the concentration-response function for ozone and short-term mortality was derived, are highly variable across (95) cities, showing both positive and negative associations between short-term ozone and mortality, and mostly statistically insignificant associations. However, EPA used the national average concentration-response function from those data (Smith et al., 2009) to estimate the risk of short-term mortality in the HREA, which conceals the fact that negative association were shown for numerous cities, as well as obscures the variability in the estimates. EPA similarly calculates a national average concentration-response function from Jerrett et al. (2009) for long-term ozone concentrations and mortality, despite the fact that city-specific mortality estimates in that study also consisted of both positive and negative associations with mortality.

3.4.5 EPA Does Not Adequately Control for Confounders in Estimating Mortality Risk

3.4.5.1 Short-Term Mortality Estimates are Not Controlled for PM10

Smith et al. (2009) examined the sensitivity of the individual-city short-term mortality estimates from the NMMAPS data to the inclusion of co-pollutants. They concluded that the overall ozone-mortality coefficient is reduced between 22% and 33% when PM10 is included in the model, despite the fact that in many cities, PM10 is only sampled once every 6 days (this has been EPA's excuse for not using PM-corrected mortality coefficients). Some other authors (Huang, Dominici, & Bell, 2005) have also reported a decrement in the ozone-mortality effect

when PM10 is included, while others (Schwartz, 2005)have concluded that there was no effect. The concentration-response function from Smith et al. (2009) that is used to estimate short-term mortality in the core risk assessment is not corrected for PM10 (a model that adjusted for PM10 is used as a sensitivity analysis).

3.4.5.2 Long-Term Mortality is Not Adequately Controlled for Co-Pollutants

Jerrett et al. (2009) reported a weakly positive respiratory mortality estimate in a multi-pollutant model with PM2.5. However, potential effects of PM2.5 were not adequately controlled. Although the study examined ozone air concentrations from 1977 to 2000, only two years of data on PM2.5 (1999-2000) were considered because of limited availability of data prior to 1999. Levels of ozone and PM2.5 decreased considerably between 1977 and 2000. Therefore, the analysis of ozone included higher levels observed in the past, whereas the analysis of potential confounding by PM2.5 considered more recent, lower levels observed in 1999 and 2000. Furthermore, the exposure metric for ozone focused on daily maximum hourly levels in the warm seasons, whereas for PM2.5, the annual average concentration was used. Thus, this approach increased the potential to observe an association between ozone and mortality and decreased the potential to observe PM2.5 as a confounder of this association (Pruitt and Goodman, 2011). The authors noted this limitation in their paper, stating, "Since particulate air pollution has probably decreased in most metropolitan areas during the follow-up interval of our study, it is likely that we have underestimated the effect of PM2.5 in our analysis." (Jerrett et al., 2009).

Another limitation of the Jerrett et al. (2009) study was the failure to evaluate the possibility of confounding by other pollutants, such as SO2. In an earlier study of the ACS cohort, SO2 demonstrated a stronger association with mortality than PM2.5 (Krewski et al., 2000 as cited in Pruitt and Goodman, 2011). Because of this, as well as the likely underestimation of confounding by PM2.5, the study by Jerrett et al. (2009) does not demonstrate an association between ozone and respiratory mortality that is independent of other co-pollutants (Pruitt and Goodman, 2011).

3.4.6 EPA's "Causal" Classifications of the Associations between Ozone and Short-Term and Long-Term Mortality are Not Supported

3.4.6.1 The Evidence Does Not Support a "Likely Causal Relationship" Classification for Short-Term Mortality

In 2006, EPA stated that the evidence for total mortality from short-term exposure to ozone was "suggestive of a causal relationship" (EPA, 2006), while in the 2013 ISA, EPA concluded that evidence supported a "likely causal relationship", and included the short-term mortality endpoint in the HREA.

EPA states (Pg. 6-224 of ISA) that the associations between short-term ozone exposure and mortality are robust across studies (Table 6-42 and Table 6-53). However, one need not

examine the results in Tables 6-42 and 6-53 very critically to notice that most of the mortality estimates are quite small. Only 11 of the mortality increases listed (out of 30) in Table 6-42 were greater than 2%. Although 29 of 44 of the cause-specific mortality estimates in Table 6-53 were greater than 2%, only eight (of 44) were greater than 5%. Given the general issues associated with epidemiological studies (i.e., ability of measurements from urban monitoring stations to approximate "actual" personal exposure, confounding by other pollutants, differences in estimates at different lag times, uncontrolled confounding due to failure to collect individual level data), increases in mortality estimates of 2-5% could easily be due to measurement error. Therefore, the strength of the association is not compelling.

The results discussed above suggest that short-term ozone mortality risk estimates are highly sensitive to the choice of models, lag times, and correction for co-pollutants and that the consistently small associations are most likely due to confounding, bias, or chance. Therefore, ozone has not been shown to result in health effects in studies in which chance, bias, and confounding could be ruled out with any confidence at all. EPA nevertheless highlights these short-term mortality risk estimates as being supportive of a "likely causal relationship" even though many findings in US cities were not statistically significant. Therefore, these and other factors cast serious doubt on EPA's conclusion that there is a "likely causal relationship" between short-term ozone exposure and premature mortality.

3.4.6.2 The Evidence Does Not Support a "Suggestive of Causal Relationship" Classification for Long-Term Mortality

As an initial matter, EPA incorrectly states in the HREA (pg. 2-13) that "With regard to effects associated with long-term O_3 exposures, the ISA states that the relationship between O_3 and respiratory-related effects, including respiratory symptoms, new-onset asthma, and respiratory mortality is likely causal (U.S. EPA, 2013, Table 2-3)." Table 2-3 of the ISA (pg. 2-49) does not indicate that the relationship between long-term ozone and respiratory mortality is "Likely Causal", nor does Table 7-13 of the ISA (pg. 7-91). As indicated in the ISA (pg. 7-90) the Jerrett et al. (2009) findings of an association between long-term ambient ozone concentrations and respiratory mortality provides supportive evidence that the relationship between long-term ozone and total mortality is "Suggestive of a Causal Relationship" and also (pg. 7-36 of ISA) supports that the relationship between long-term ozone and respiratory effects is "Likely Causal", but EPA appropriately stops short of stating that the relationship between long-term ambient ozone and respiratory mortality itself is "Likely Causal", as one study is not sufficient to warrant such a determination.

Several large studies that have evaluated long-term ozone exposure and respiratory or cardio-pulmonary mortality have not reported positive associations. No associations were reported for cardio-pulmonary mortality in the Harvard Six Cities Study by Dockery et al. (Dockery, et al., 1993), the ACS study by Pope et al. (Pope, et al., 2002), or the Adventist Health Study of Smog (AHSMOG) by Abbey, et al. (1999) also reported no association between long-term ozone exposure and non-malignant respiratory mortality. A recent study by Wang et al. (Wang, Hu, & Tong, 2009) examined cardio-respiratory mortality in Australia and found that long-term exposure to SO2 was associated with this endpoint, but ozone was not. EPA acknowledges

that the available data on long-term ambient ozone exposure and respiratory/cardio-pulmonary mortality show no association, with the exception of one study by Jerrett et al. (2009) (Goodman and Pruitt, 2011).

The threshold for a "Suggestive of a Causal Relationship" classification is that at least one high-quality epidemiologic study shows an association with a given health outcome but the results of other studies can be inconsistent. However, the Jerrett et al. (2009) study had many limitations, most notably the inadequate control for PM2.5 confounding, that keep it from being considered a high quality study. Furthermore, results from other studies are consistently negative, rather than inconsistent.

Reproducibility of findings constitutes one of the strongest arguments for causality. According to EPA, if there are discordant results among investigations, possible reasons such as differences in exposure, confounding factors, and the power of the study are considered (Pg. lxv, preamble to ISA). No other studies of the ACS cohort have produced similar results and there certainly does not appear to have been any investigation into why the Jerrett et al. (2009) are discordant with previous findings in this same cohort. One study that provides weak evidence for respiratory-specific mortality simply is not enough to provide suggestive evidence for a causal relationship. Concluding that there is a "suggestive of likely causal relationship" between long-term ozone concentrations and mortality flies in the face of every aspect of EPA's formal framework for evaluating the weight of scientific evidence.

3.4.7 EPA's Use of "Average" Mortality Coefficient Derived from Highly Variable City-Specific Estimates Undermines the Mortality Analyses

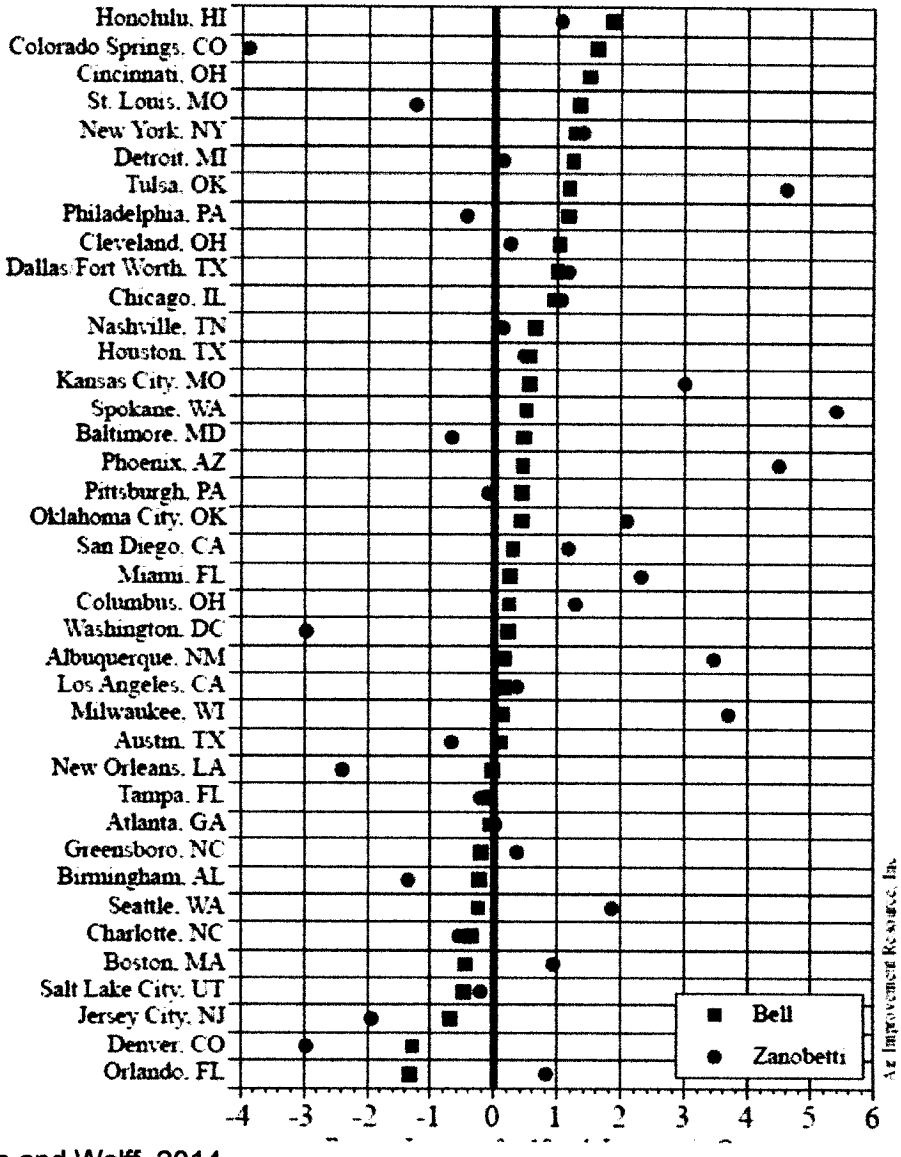
3.4.7.1 Short-Term Mortality

Table 6-42 of the ISA (Pg. 6-222), which shows all-cause (non-accidental) short-term mortality from all-year and summer season analyses, indicates a percent increase in mortality of 1.04 (0.54, 1.55) from the Bell (2004) study, which evaluated the mortality risk associated with 24-hour average ozone concentrations in 95 US communities (0.78 [0.26, 1.30] for summer only) using the NMMAPS data. It also reports a percent increase in mortality of 1.51 (1.14, 1.87) for lag-0 or 1.60 (0.84, 2.33) for lag 0-3 from Zanobetti and Schwartz (2008), summer only. However, **Figure 3-5** below shows the individual city results from Bell et al. (Bell, McDermott, Zeger, Samet, & Dominici, 2004) and Zanobetti and Schwartz (2008) and, as can be seen, the mortality estimates are positive for some cities and negative for others (i.e., increasing ozone decreases *premature* mortality). The figure illustrates the problem with calculating an average mortality coefficient from a group of city-specific mortality coefficients that are highly variable. It does not take a statistician to see why such an average might not be representative for any of the included cities. In addition, for some of the cities included in both studies, the mortality estimates were very different (e.g., Colorado Springs, St. Louis, Washington DC. New Orleans, Orlando). According to EPA, when studies report discordant results, the reason for the discordance needs to be investigated.

3.4.7.1.1 Smith et al. (2009)

Smith et al. (2009) reexamined the evidence of an association between short-term ambient ozone and non-accidental all-cause mortality, based on a series of papers by Bell and co-authors (Bell et al., 2004) that used the publically available NMMAPS database, which was highly influential in the previous ozone NAAQS review. This study (Bell et al., 2004) reported a statistically significant association between ambient 24-hour ozone and short-term mortality when averaged across 98 US cities, but the results were highly variable from city to city, showing both positive and negative associations (as shown in **Figure 3-5** below).

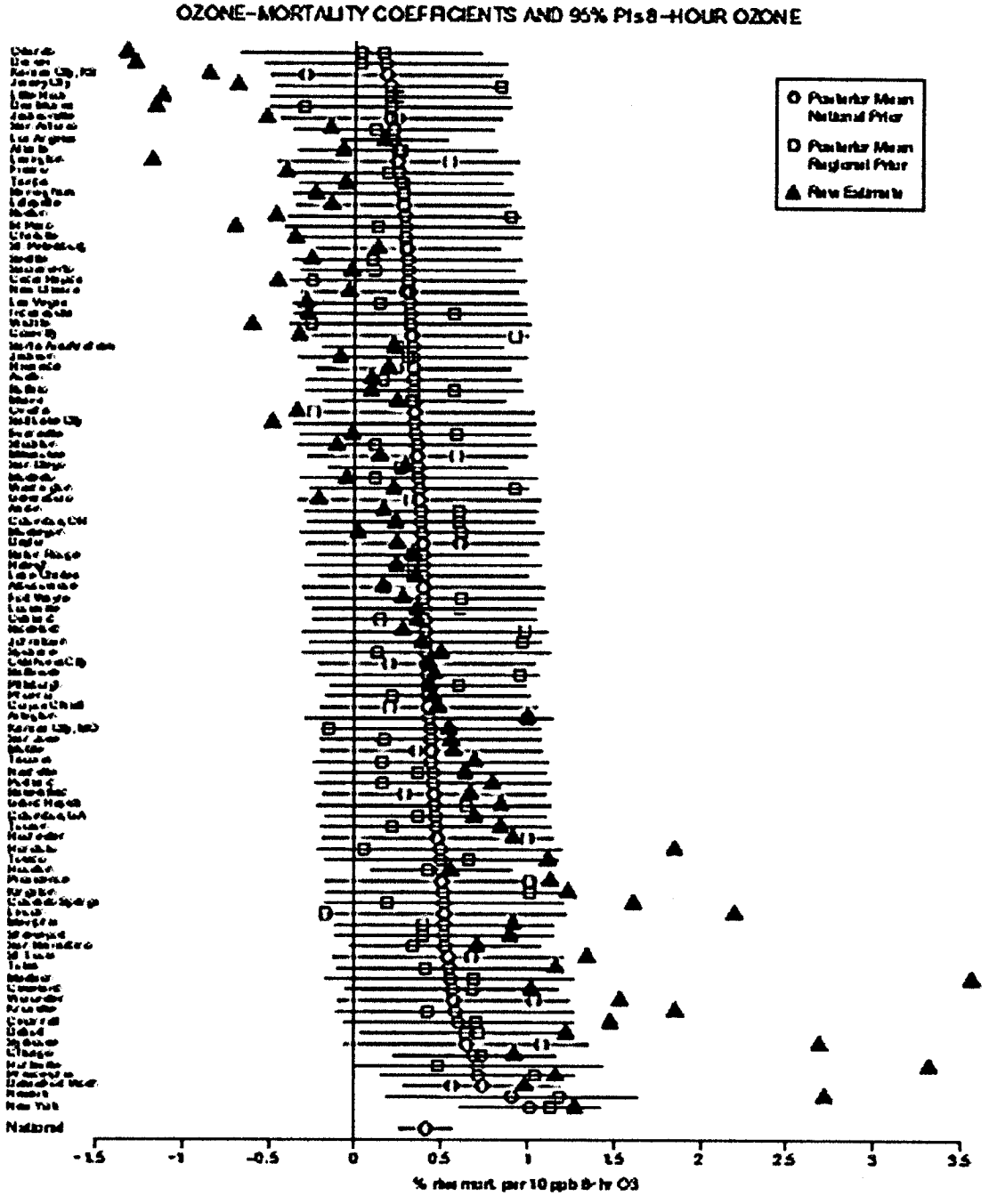
FIGURE 3-5
PERCENT INCREASE IN MORTAILTY PER 10-PPB 24-HOUR OZONE CONCENTRATION BY CITY IN BELL ET AL. (2004) VS ZANOBETTI AND SCHWARTZ (2008)



Source: Heuss and Wolff, 2014

Figure 3-6, which is reproduced from Smith et al. (2009), illustrates the strong regional variability and the wide prediction intervals (lack of certainty of estimates) in the association between short-term ozone concentrations and mortality. In addition, the short-term ozone-mortality effect is not statistically significant for most cities across the US.

FIGURE 3-6
PERCENT INCREASE IN MORTAILTY PER 10-PPB 8-HOUR OZONE CONCENTRATION OVERALL AND BY CITY



Source: Smith et al., 2009

Figure 3-6 also serves to illustrate why using a single value that represents an average across highly variable cities to estimate mortality in the 12 Urban Areas evaluated in the HREA might be construed as misleading. The single resulting value for each Urban Area does not convey the variability in the individual city estimates. EPA could completely avoid the issue of masked regional variability inherent to an average morality coefficient by simply using the city-specific mortality coefficients from Smith et al. (2009) since all 12 Urban Areas are included in the NMMAPS data re-evaluated by Smith et al. (2009). That way, at least the mortality coefficient would be reflective of the local population. However, had this approach been taken, a decrease in mortality would have been estimated for some of the Urban Areas (Atlanta, Los Angeles, Sacramento, St. Louis), which would not support the conclusion that a reduced NAAQS is needed to protect public health.

3.4.7.1.2 Zanobetti and Schwartz, 2008

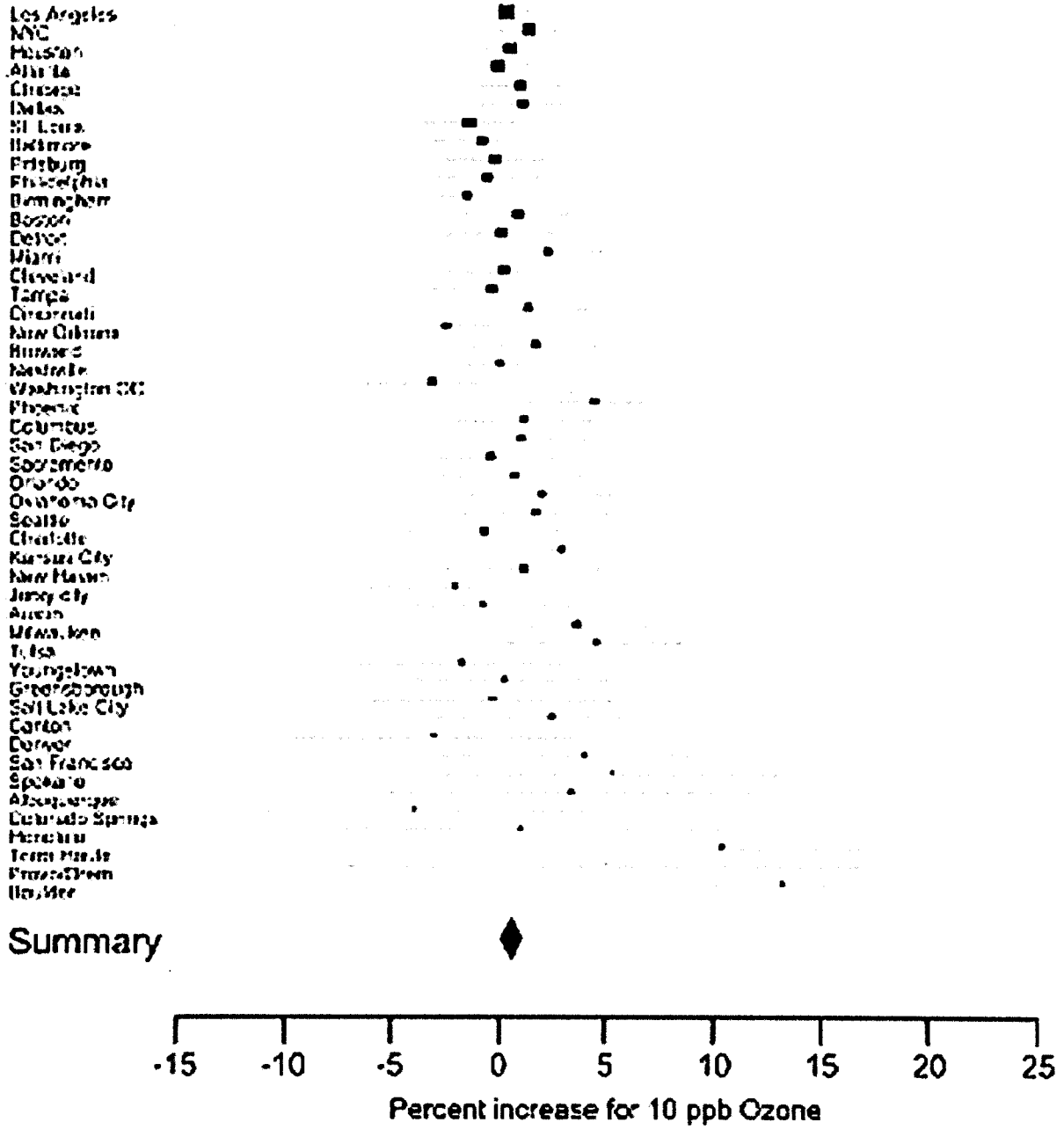
Zanobetti and Schwartz, (2008) analyzed the effect of summer-only short-term ambient ozone concentrations on all-cause mortality in 48 US cities between 1989 and 2000. They found a statistically significant increase of 0.3% (0.2–0.4) in total mortality for a 10-ppb increase in 8-hour ozone concentrations at lag-0 during summer months using a national average obtained by averaging the city-specific effects of ozone on mortality. Figure 1 of the Zanobetti and Schwartz (2008) paper, which is reproduced below, shows the city-specific mean increase in mortality and 95% CIs per 10 ppb increase in 8-hour ozone concentration.

As shown in **Figure 3-7**, similar to **Figure 3-6** from Smith et al. (2009), the effect of short-term ambient ozone concentrations on mortality is highly variable across cities, with most cities not reporting a statistically significant association between ozone and short-term mortality. Therefore, the Zanobetti and Schwartz (2008) study also leads one to the conclusion that calculating a national average value across cities conceals the heterogeneity in the effect estimates across cities and results in a value for the association that is not representative of the relationship for any city.

3.4.7.2 Long-Term Mortality

Similar to the evidence on the association between short-term ozone concentrations and mortality, there is a high degree of regional heterogeneity in risk estimates for long-term mortality (Jerrett et al., 2009). Positive associations were only reported in two of the seven regions examined. Because of this high geographic heterogeneity, it is also inappropriate for data to be combined across cities to develop a US national long-term mortality risk estimate (Goodman and Pruitt, 2011).

FIGURE 3-7
PERCENT INCREASE IN MORTALITY PER 10-PPB 8-HOUR OZONE CONCENTRATION OVERALL AND BY CITY



Source: Zanobetti and Schwartz, 2008

3.4.8 EPA Overestimates Mortality Risks by Ignoring Evidence of a Threshold

3.4.8.1 Short-Term Mortality

Although they did not identify a threshold "per se", Smith et al. (2009) showed that the relationship between ozone and short-term mortality was different for different concentration ranges (i.e., 0-40 ppb, 40-60 ppb, 60-80 ppb.). In fact, they showed that it was only by combining data across the three ranges (e.g., assuming a linear ozone-mortality relationship across 0–80 ppb) that a statistically significant association was established. This suggests that the relationship between ozone concentrations and short-term mortality is not linear and also raises the question of whether the association between short-term ozone and mortality is "causal". Despite this, EPA used a "No Threshold" model based on Smith et al. (2009) in predicting short-term mortality risks in the HREA. By using a "No Threshold" model that predicts risks all ozone concentrations down to zero, short-term mortality risks are likely greatly overstated.

3.4.8.2 Long-Term Mortality

The best fit model for long-term respiratory mortality risk in Jerrett et al. (2009) was a threshold model, with the best fit among alternative thresholds tested being 56 ppb according to Dr. Anne Smith of NERA (Smith, 2014). These findings were summarily ignored by EPA in the HREA.

The long-term mortality risk estimates were extremely sensitive to whether a threshold was included in the risk analysis and that should have been a central consideration in the long-term mortality risk assessment, rather than EPA's singular focus on a non-threshold model, which does not represent the best fit of the data (Smith, 2014).

The analysis submitted by Dr. Anne Smith (Smith, 2014) in comments filed for the May 28, 2014 CASAC teleconference on the ozone NAAQS using the HREA's ozone data, shows that a 56 ppb threshold in the Jerrett et al. (2009) study is equivalent to a NAAQS level higher than the current standard of 75 ppb in 10 of the 12 of the urban areas studied. In the remaining 2 cities, it appears to be equivalent to a NAAQS level somewhere between 65 and 70 ppb.

By using a "No Threshold" model that predicts risks all the way down to an ozone concentration of zero, EPA also greatly overstates the long-term mortality risks.

3.4.9 EPA's Reliance on a Single Study Reporting an Association between Long-Term Ozone Concentrations and Respiratory Mortality as the Basis for Estimating Long-Term Mortality is Misguided

Despite concluding that the evidence for a causal relationship between chronic ozone exposure and increased mortality risk was insufficient in the last ozone NAAQS review, based on review of several new studies that have become available since the last review, EPA has concluded that there is:

- Limited evidence for an association between long-term exposure to ambient ozone and total mortality that is Suggestive of a Causal Relationship;
- Inconsistent evidence for an association between long-term exposure to ambient ozone and cardiopulmonary mortality that is Suggestive of a Causal Relationship; and
- Strongest evidence for an association between long-term ambient ozone concentrations and mortality is from Jerrett et al. (2009), who reported evidence for an association with respiratory mortality.

The ecologic study conducted in Australia observed no association between cardiopulmonary mortality and ozone (Wang et al., 2009). Two re-analyses of the ACS cohort were conducted, with one providing weak evidence for an association with cardiopulmonary mortality (Smith et al., 2009b) and the other pointing to a relationship between long-term ozone exposure and a marginally statistically significant increased risk of respiratory mortality (Jerrett et al., 2009). EPA relies entirely on the association with long-term respiratory mortality identified in Jerrett et al. (2009) in estimating long-term mortality risks in the HREA.

Jerrett et al. (2009) correlated data from the American Cancer Prevention Study II with air pollutant data from 96 metropolitan statistical areas (MSAs) in the US and data were analyzed from 448,850 subjects, with 118,777 deaths in an 18-year follow-up period. Monitoring data were available on the concentration of ambient ozone from all 96 and on the concentration of PM2.5 from 86 MSAs. Several ecologic and individual covariates were accounted for in the models.

As shown in Table 7-12 of the ISA and reproduced as **Figure 3-8** in this report, Jerrett et al. (2009) reported small increases in mortality risk, particularly respiratory mortality, but the results were inconsistent across mortality endpoints evaluated. In two-pollutant models that controlled for PM2.5, risks between long-term ozone exposure and all-cause and cardiovascular-related mortality were significantly decreased and became statistically insignificant.

As shown in **Figure 3-8**, the relative risk of long-term ozone-attributable mortality remained statistically significantly after correction for PM2.5 only for respiratory mortality (CIs contain 1 for other endpoints).

3.5 OVERALL CONCLUSIONS DRAWN FROM EPIDEMIOLOGY STUDIES

There is always some kind of association detected in epidemiology studies. Therefore, the important question is whether:

- The association is positive (i.e., health effects increase as pollution increases);
- The confidence in the association is high; and
- The association is strong.

FIGURE 3-8
RELATIVE RISK (AND 95% CONFIDENCE INTERVAL) OF DEATH ASSOCIATED WITH LONG-TERM INCREASE IN AMBIENT OZONE CONCENTRATION

Table 7-12 Relative risk (and 95% CI) of death attributable to a 10-ppb change in the ambient O_3 concentration.

Cause of Death	O_3 (96 MSAs)[a]	O_3 (86 MSAs)[a]	O_3 +$PM_{2.5}$ (86 MSAs)[a]
Any Cause	1.001 (0.996, 1.007)	1.001 (0.996, 1.007)	0.989 (0.981, 0.996)
Cardiopulmonary	1.014 (1.007, 1.022)	1.016 (1.008, 1.024)	0.992 (0.982, 1.003)
Respiratory	1.029 (1.010, 1.048)	1.027 (1.007, 1.046)	1.040 (1.013, 1.067)
Cardiovascular	1.011 (1.003, 1.023)	1.014 (1.005, 1.023)	0.983 (0.971, 0.994)
Ischemic Heart Disease	1.015 (1.003, 1.026)	1.017 (1.006, 1.029)	0.973 (0.958, 0.988)

[a]Ozone concentrations were measured from April to September during the years from 1977 to 2000, with follow-up from 1982 to 2000; changes in the concentration of $PM_{2.5}$ of 10 $\mu g/m^3$ were recorded for members of the cohort in 1999 and 2000.

Source: Reprinted with permission of Massachusetts Medical Society (Jerrett et al., 2009).

Source: EPA, 2013

For ozone, the associations are only inconsistently positive, the confidence in the associations is generally low due to uncontrolled confounders and standard issues that always arise in epidemiology studies, and the associations are uniformly weak.

Despite EPA's claims that clear and consistent relationships have been demonstrated between short-term ozone and a variety of respiratory effects, including lung function in healthy people and asthmatics and increased symptoms and medication use in asthmatics, the data are overwhelmingly inconsistent. Lung function decrements do not consistently occur in any population (outdoor workers, adults or children exercising outdoors, asthmatics) in response to increased ozone levels and neither asthmatic children nor adults consistently respond to increases in ambient ozone concentrations with an increase in symptoms, medication use, or activity limitation.

While EPA also reports that consistent associations between short-term ambient ozone concentrations and respiratory hospital admissions and Emergency Department visits have been demonstrated, the multi-city hospital studies report both positive and negative associations for ozone, depending on the lag times used, model specification, and whether the results are adjusted for other co-pollutants. In addition, the uniformly small effect sizes reported in epidemiology studies for all ozone-related health effects suggest that the association between ozone and short-term respiratory effects, hospital admissions/Emergency Department visits, respiratory symptoms and medication use in asthmatics, and mortality are weak and, in fact, they are so small that they could easily be affected by uncontrolled confounding and possibly, not even real.

There is enormous uncertainty regarding EPA's "likely causal" and "suggestive of a likely causal" relationship classifications for short-term and long-term mortality, respectively, and neither classification is supported by the available evidence. The primary study relied on for the short-term mortality concentration-response functions questions whether the short-term ozone relationship is causal because of the variability of the relationship at different ozone concentrations. The study concludes that the relationship is only statistically significant if all concentration intervals are combined (assumed to be linear). Furthermore, EPA relies on a single study for the long-term mortality evidence, despite the fact that this study only reported a marginally statistically significant increase in mortality; had the study adequately controlled for PM10, it likely would not have reached such a finding. Other investigators, using the same study population, did not consistently find associations. Therefore, there is also a question of whether the long-term ozone mortality relationship is causal.

In addition, although a questionable practice, national average mortality coefficients from multi-city epidemiology studies, reporting positive (increased ozone causes increased mortality) associations in some cities and negative (increased ozone causes decreased mortality) associations in others, have been used by EPA in estimating short-term and long-term mortality in the HREA. This averaging of individual city mortality coefficients dilutes the high and low values and generally produces an overall small positive mortality coefficient. However, this average likely does not accurately characterize the true relationship for any of the cities and it conceals the variability and the uncertainty in the estimates.

There was uncertainty about the associations reported in epidemiology studies at levels below 75 ppb in the last ozone NAAQS review. That uncertainty precluded EPA from establishing the NAAQS at a level lower than 75 ppb. Despite the availability of many new epidemiology studies, that uncertainty remains today.

4.0 HEALTH RISK AND EXPOSURE ASSESSMENT

A fundamental step in the review of NAAQS is the evaluation of thousands of scientific studies and incorporation of a subset of that information into evaluations that help EPA determine the adequacy of the existing standard. The HREA (*Health Risk and Exposure Assessment for Ozone* [EPA, 2014b])) developed in connection with the current ozone NAAQS review is one of the reports that is intended to help inform EPA's decision-making process on the ozone NAAQS.

While it is understood that individual scientists reviewing the same scientific studies may reach different judgments in applying the science in the standard-setting process, there are major questions about the conduct of and reporting in the HREA, which are discussed in the following sections.

4.1 INTRODUCTION

The HREA states that it is focused on health effect endpoints for which EPA has judged that the weight of the evidence, as assessed in the ozone ISA (EPA, 2013), supports a "likely causal" or "causal" relationship between a health effect category and ozone. The health effects evaluated in the HREA are based on the following conclusions from the ISA (EPA, 2013).

Short-Term Ozone-Attributable Effects

- Short-term respiratory effects (causal relationship):
  - Emergency Department Visits (asthma, wheeze, all respiratory symptoms);
  - Hospital Admissions (chronic obstructive pulmonary disease, asthma, all respiratory); and
  - Respiratory symptoms.
- Short-term mortality (likely causal relationship):
  - All-cause (non-accidental);
  - Cardiovascular; and
  - Respiratory.

Long-Term Ozone-Attributable Effects

- Long-term mortality (suggestive of a causal relationship):
  - Respiratory.

As noted above, the relationship between long-term ambient ozone and mortality is only "Suggestive of a Causal Relationship", although the HREA erroneously concludes that the relationship between long-term ozone concentrations and respiratory mortality is "Likely Causal". As appropriate, the ISA stops short of stating that this relationship is causal, given that there is a single study reporting the association. Instead, the ISA cites the evidence for long-term respiratory mortality as supportive evidence for the "Likely Causal Relationship" for respiratory effects and for the "Suggestive of a Causal Relationship" for total mortality.

The HREA estimates: 1) incremental changes in monitored ozone concentrations (used as a surrogate for exposure in epidemiology studies); 2) modeled personal exposures (lung function risk assessment); and 3) risks (lung function decrements, respiratory symptoms, and hospital admission/Emergency Department visit and premature mortality) between just meeting the existing standard of 75 ppb and just meeting potential alternative standard levels of 70, 65, and 60 ppb using the form and averaging time of the existing standard.

The HREA discusses air quality and models personal exposure and lung function decrements for 15 urban case study areas. It also estimates increases in hospital admission/Emergency Department visits and premature mortality in a subset of 12 urban case study areas based on forecasted ambient ozone concentrations. The analysis includes estimates of mortality risk associated with short-term 8-hour maximum or 8-hour mean ozone concentrations in all 12 urban case study areas, as well as risk of hospitalization for chronic obstructive pulmonary disease. In addition, the analysis includes estimates of hospitalizations for additional respiratory diseases in Los Angeles, New York City, and Detroit, risk of respiratory-related Emergency Department visits in Atlanta and New York City, and risks of respiratory symptoms in Boston.

In addition, to place the Urban Area analyses in a broader context, the HREA includes estimation of the national burden of mortality associated with recent long-term ozone levels, and evaluated the representativeness of the urban areas in characterizing ozone exposures and risks across the US.

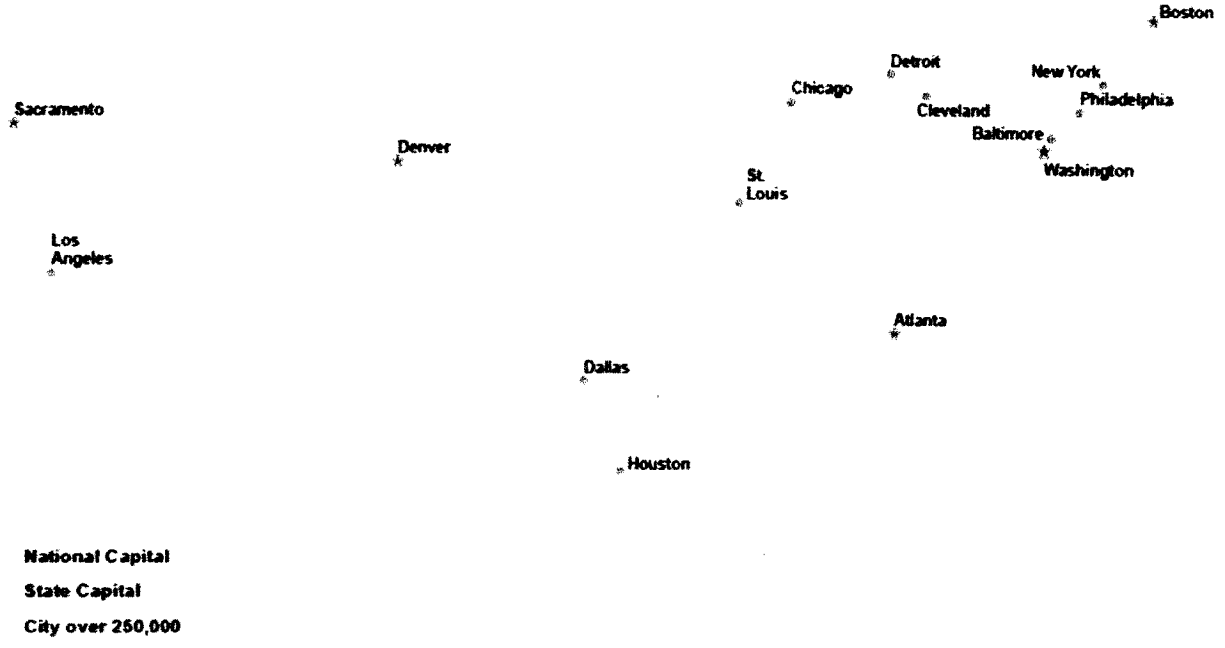
4.1.1 More Objectively Chosen Urban Areas Would Have Produced Even Less Compelling Results

Although the concentration-response functions for the lung function (FEV_1) decrement portion of the HREA come from studies conducted in controlled laboratory studies, those studies played no role in selecting Urban Areas for the risk assessment since they were conducted in a controlled environment that was not specific to any particular geographic area. Instead, according to the HREA (Pg. 5-6 and 5-7), the selection of Urban Areas for inclusion in the HREA considered the location of ozone epidemiological studies (they are specific to a geographic location), the availability of ambient ozone monitoring data, and the desire to represent a range of geographic areas, encompassing variability in climate and population demographics, **starting with the Urban Areas evaluated in the 2007 ozone NAAQS review** (Atlanta, Boston, Chicago, Cleveland, Detroit, Houston, Los Angeles, Philadelphia, New York City, Sacramento, St. Louis, and Washington DC). In addition to the 12 Urban Areas identified in the 2007 Risk and Exposure Assessment, Dallas and Denver were added and Baltimore was separated from Washington DC and evaluated in the current hospital admissions and mortality risk assessments.

Despite being one of EPA's primary criteria for selecting the Urban Areas, as shown in **Figure 4-1**, the 15 Urban Areas are not geographically representative of the US as a whole. There is a high density of cities in the northeastern US, four cities in the upper mid-west, one southeastern city, two cities in Texas, one southwestern city, and two cities in California. Ozone data are

widely available in urban areas, so availability of data is unlikely to have substantially informed the choice of cities. Although not highlighted as a criterion for selection, according to Pg. 2-19 of the HREA, "To make the exposure analysis most useful in addressing the key policy-relevant questions, urban case study areas were also chosen such that most of them exceeded the existing 8-hour ozone NAAQS and potential alternative standards during the time period of interest." In fact, it turns out that the Urban Areas evaluated in the HREA have some of the highest ozone levels in the country.

FIGURE 4-1
GEOGRAPHIC DISTRIBUTION OF 15 URBAN AREAS EVALUATED IN HEALTH RISK AND EXPOSURE ASSESSMENT



Interestingly, an EPA-funded study (Medina-Ramon et al., 2006) that evaluated all 12 of the Urban Areas ended up playing a prominent role in the hospital admission risk assessment for the current review as a result of EPA's decision to keep the same 12 core Urban Areas from the 2008 review in the current review. Use of the APHENA study (Katsouyanni et al., 2009), on the other hand, was limited in the current hospital admission risk assessment because of EPA's decision to keep the same 12 core Urban Areas that were evaluated in 2007, despite the fact that it is a well-respected study. For the most part, the APHENA study (Katsouyanni et al., 2009) failed to produce statistically significant associations between short-term ambient ozone concentrations and respiratory/cardiovascular hospital admissions. It appears that study quality

played no role whatsoever in selecting the Urban Areas for evaluation and, for that reason, the concentration-response functions, which are the backbone of the of the hospital admission/mortality risk assessments, are not necessarily from the best studies available. Had the core Urban Areas considered in this HREA been chosen more objectively, the results would have no doubt been even less compelling than they currently are.

4.1.2 EPA Uses Scientific Studies as Input for Models and to Derive Concentration-Response Functions for Use in the HREA

The goals of the HREA are to provide information relevant to answering questions regarding the adequacy of the existing ozone standard and the potential improvements in public health from meeting alternative standards. To meet the goals, the HREA provides results from several analyses, including estimates of the:

- Number of people in the general population and in so called "at-risk" populations and life-stages with potential ambient ozone exposures above the current and proposed alternative ozone NAAQS, while at moderate or greater exertion levels;
- Number of people in the general population and in at-risk populations and life-stages with impaired lung function, ostensibly resulting from exposures to ozone; and
- Potential magnitude of premature mortality and selected short-term morbidity health effects (symptoms in asthmatics and hospital admissions/Emergency Department visits) in the population, including at-risk populations and life-stages, where data are available to assess these groups.

For each of the analyses, estimates for recent ambient levels of ozone (defined as baseline) and for air quality conditions simulated to just meet the existing ozone standard and alternative standards are provided.

Lung function decrements were predicted in all 15 Urban Areas based on a model (McDonnell et al., 2012) fit to data from 23 controlled human exposure studies. In addition, concentration-response functions were obtained from the studies listed in **Table 1** (separate document, Attachment 1 to TPA's comments) for use in predicting the following in a subset of 12 Urban Areas (excluding Chicago, Dallas, and Washington):

- Short-term hospital admissions for chronic obstructive pulmonary disease, and other respiratory diseases in a few cities;
- Respiratory-related Emergency Department visits;
- Respiratory symptoms;
- Short-term mortality; and
- Long-term mortality.

To estimate hospital admission/Emergency Department visit risks, EPA used concentration-response functions from nine epidemiology studies that were discussed previously and shown in

Table 1 (separate document, Attachment 1 to TPA's comments). To estimate the risk of respiratory symptoms, EPA used a concentration-response function from one epidemiology study (Gent et al., 2003). A concentration-response function from Smith et al. (2009) was used to estimate core short-term mortality risks and a concentration-response function from Zanobetti and Schwartz (2008) was used to conduct an additional set of short-term mortality sensitivity analyses. The concentration-response function from Jerrett et al. (2009) was used to estimate long-term mortality risks.

4.1.3 A Shift from Scientific Uncertainty to Presumptive Adversity

A shift in the discussion of the scientific evidence occurs in the HREA. In the ISA, there are deliberations surrounding interpretation of the health effects literature that center on the question of "whether" certain studies indicate a particular type of physiological response to exposure, and whether an observed response has medical relevance. However, while much debate continues regarding the level at which truly "adverse" health effects occur and the relationship between monitored ozone concentrations and hospitalization/mortality reported in epidemiology studies, EPA presumes that adverse effects occur at ozone concentrations as low as 60 ppb and that ozone causes the hospitalizations/deaths for the sake of estimating numerical risks in the HREA (McClellan, et al., 2009).

In calculating the number of people with impaired lung function, the HREA focuses on inconsistent and infrequent lung function changes observed in human exposure studies that are often too mild to be considered clinically relevant to identify the alternative ozone levels for consideration in the HREA. Furthermore, in calculating the potential magnitude of hospital admissions risks and premature mortality, EPA relies on epidemiological studies that neither measure actual exposures nor adequately control other factors that can confuse or confound study results. EPA cites these studies as additional evidence that health effects occur at concentrations below the current ozone NAAQS, despite the fact that the relationships between ambient ozone concentrations and health effects reported in the studies are uniformly weak, inconsistent, and mostly statistically insignificant. In these epidemiology studies, the role of ozone must be separated from other factors that can influence health such as, other pollutants, population characteristic (age, sex, race), health status (pre-existing conditions, obesity, blood pressure, lack of exercise), and living conditions. Unfortunately, this can only be done with complex statistical models and determining the accuracy of these models is difficult, if not impossible. Despite their flaws, the results from these health studies provide the starting point for EPA's HREA.

In addition, because there are relatively few air monitors, mathematical procedures are used to estimate ozone concentrations for un-monitored areas and models are used to predict the response to reductions in ozone precursors. However, the HREA fails to effectively integrate key uncertainties associated with its risk estimates at current ozone levels and risk reductions associated with concentrations predicted to occur in response to the alternative NAAQS levels. Despite acknowledgement that the risk estimates are highly dependent on the numerous assumptions made in the HREA, EPA continues to perform only qualitative uncertainty analyses rather than performing probabilistic assessments to better account for the many uncertainties.

Reporting a distribution of all of the possible risk estimates would be far more transparent than the approach taken in the HREA of biasing the discussions of uncertainty toward the potential for underestimated risks and burying the uncertainty analyses in appendices.

4.2 RISKS ARE OVERESTIMATED

4.2.1 EPA's Exposure Model Overestimates Exposure Used to Estimate Lung Function Risk

Modeling of personal exposure for the lung function risk assessment is implemented using APEX. APEX models differences in physiological parameters due to age, and these result in age-dependent predictions of ventilation rates, which are used to estimate risk. For several reasons, described in more detail below, personal exposure modeled by the APEX model is likely to be overestimated. Based on a personal monitoring study conducted using a miniaturized UV absorption monitor (PEM) to measure ozone concentrations in a series of microenvironments in Raleigh, North Carolina, Long et al. (2005) found that the APEX model underestimates concentrations in indoor and in-vehicle microenvironments when windows are open (modeled concentrations are approximately ½ the measured concentrations) and results in an 8-fold overestimate of concentrations when windows are closed. The median ratio of indoor PEM concentrations to APEX concentrations was 1.87 for open windows and 0.13 for closed windows. In addition, according to the HREA (Pg. 5-64), APEX ventilation rates can be overstated by 2-3 m^3/day, which is a significant overestimation in comparison to typically assumed daily inhalation rates of 20 m^3/day (i.e. 10-15%).

4.2.2 EPA's Lung Function Risks are Overstated

EPA uses the McDonnell-Stewart-Smith (MSS) model (McDonnell et al., 2012) to estimates FEV_1 responses for individuals associated with short-term exposures to ozone. The MSS model gives results that are higher than the Exposure-Response model used in previous reviews. The HREA goes to considerable lengths to describe why the MSS model represents an improvement over the Exposure Response model. However, both models predict responses to changes in ozone concentrations only in terms of decreases in FEV_1 (i.e., they do not determine if the FEV_1 decrement will be accompanied by respiratory symptoms).

The HREA defines an equivalent ventilation rate of 13 L/min-m^2 (Pg. 5-18 of HREA) as the lower-bound equivalent ventilation rate to categorize persons engaged in moderate exertion activities for an 8-hr period. Yet, lung function decrements are calculated for individuals with daily 8-hour average equivalent ventilation rates greater than 13 L/min/m^2 using concentration-response functions developed from controlled human exposure study data conducted at significantly higher equivalent ventilation rates of approximately 20 L/min/m^2 (23 in some studies). The 95th percentile 8-hour equivalent ventilation rate is between 14 and 15 L/min/m^2, while the equivalent ventilation rates used in the clinical studies of 20 L/min/m^2 is about the 99th percentile. Thus, the resulting headcounts and risks from the lung function risk assessment are overestimated (Heuss, 2012).

4.2.2.1 EPA Considers Lung Function Decrements by Themselves as "Adverse"

Reversible loss of lung function is only considered "adverse" when it is accompanied by respiratory symptoms (ATS, 2000). However, the models used in the HREA are not capable of predicting whether the predicted FEV_1 decrements will also be accompanied by respiratory symptoms. While estimating the magnitude of FEV_1 decrements associated with specific levels of short-term ozone exposure is a step in the right direction, it is insufficient for estimating the risk of "adverse" effects since it is incapable of estimating whether lung function decrements will be accompanied by respiratory symptoms. Therefore, the FEV_1 decreases predicted using these models, particularly given their small magnitude, are not a sufficient basis for concluding that "adverse" effects occur at levels below the current NAAQS.

4.2.2.2 EPA Applies 10% FEV_1 Threshold across all Populations Despite Application to Asthmatics Only in Last Review

According to the HREA (Pg. 6-5), "For this lung function risk assessment, a focus on the mid- to upper-end of the range of moderate levels of functional responses and higher (FEV_1 decrements ≥ 15%) is appropriate for estimating potentially adverse lung function decrements in active healthy adults, while for people with asthma or lung disease, a focus on moderate functional responses (FEV_1 decrements down to 10%) may be appropriate." However, rather than applying this rule of thumb in the evaluations conducted, the HREA indiscriminately applies a 10% FEV_1 decrement threshold across all evaluated populations (see Figure 6-7 and 6-8 of the HREA for school-aged children). This introduces an element of confusion into the HREA that makes the magnitude of the health impacts associated with short-term ozone exposure appear larger than they actually are. Interestingly, the 2007 *Ozone Health Risk Assessment for Selected Urban Areas* (EPA, 2007) only applied the ≥ 10% FEV_1 decrement threshold to asthmatic children. For non-asthmatic children, a ≥ 15% FEV_1 decrement threshold was used, as it should have been in the current review.

Pg. 6-46 of the HREA states that "these levels of impact (≥ 10%, 15%, and 20% decrease in FEV_1) were selected based on the literature discussing the adversity associated with increasing lung function decrements (EPA, 2012, Section 6.2.1.1; Henderson, 2006)." However, neither reference is provided in the HREA. Other places in the HREA reference back to the ISA (EPA, 2013) in justifying that these FEV_1 decreases represent clinically meaningful responses. The ISA in turn references Pellegrino (2005) and ATS (1991). However, as discussed in Section 3.0, neither of these references states that a ≥10% FEV_1 decrement represents a clinically meaningful result.

As discussed in detail in Section 2.0, there is still a question of whether a decrease in FEV_1 of ≥ 10% should be used as a threshold for considering a lung function decrement clinically meaningful, given that this lower level appears to have been selected primarily out of concern for the fact that asthmatic test subjects were not used in the controlled human exposure studies conducted to evaluate the effects of short-term ozone and CASAC's concern that asthmatics

may be more sensitive to the effects health effects associated with ozone exposure. However, the evidence that asthmatics are more sensitive than healthy people with normal lung function is mostly negative in controlled human studies and inconsistent, but often negative, and mostly statistically insignificant in epidemiology studies.

4.2.2.3 The HREA Provides Evidence that Asthmatics are not More Sensitive

On Pg. 6-21 of the HREA, EPA states that "Table 6-4 and Table 6-5 present summary results (ranges over cities and years) of FEV_1 decrements ≥ 10 and 15% estimated by the MSS model for the different age groups. The results for asthmatic school-aged children are very similar to the results for all school-aged children and are not presented here." Therefore, the HREA itself provides evidence in this section of the report that asthmatics do not appear to respond more dramatically to ozone than healthy children. Although the MSS model predictions do not rely on data from any of the controlled human exposure studies that were conducted in asthmatics, differences in activity patterns (participation in outdoor activities, percent waking hours outdoors at varying activity levels, etc.) between asthmatic children and adults and their healthy counterparts were investigated and showed that there was little difference in the in outdoor time, participation, or activity levels of asthmatics and non-asthmatics.

It is unclear why lung function data from controlled human studies, which directly evaluated the effect of ozone on asthmatics, were not used in the modeling exercise. One cannot help but wonder if it was because they do not provide supportive evidence for EPA's contention that asthmatics may be more sensitive. Nevertheless, the similarity in the modeled results for school-aged children and asthmatic school-aged children, which did consider differences in activity patterns, provides further support that asthmatics do not appear to be more responsive to the adverse effects of ozone.

4.2.2.4 The ≥ 10% FEV_1 decrement threshold was Indiscriminately Applied to All Populations Despite the Fact that it was Only Intended for Asthmatics

Table 6-4 of the HREA (Pg. 6-25) shows percent of population experiencing one or more days during the ozone season with a lung function decrement (decrease FEV_1) of more than 10%. However, consistent with the statement made on Pg. 6-5, estimating potentially adverse lung function decrements in active healthy adults should focus on the mid- to upper-end of the range of moderate levels of functional responses and higher (i.e., FEV_1 decrements ≥ 15%), not FEV_1 decrements ≥ 10%, as done here. Indiscriminately applying the ≥ 10% FEV_1 decrement as a threshold for all study populations is inappropriate and creates the impression that the modeled lung function decrements are more adverse than they actually are. This was not done in the risk assessment for the 2008 ozone NAAQS review and there is no discussion regarding why the protocol was changed for this review.

4.3 THE RISK ASSESSMENT PROCESS ADDS TO THE ALREADY SUBSTANTIAL UNCERTAINTY ASSOCIATED WITH THE SCIENCE

While uncertainty about the evidence for ozone-associated health effects at levels in the range of the proposed alternative NAAQS is high, the risk assessment process substantially adds to that uncertainty by ignoring evidence for thresholds below which ozone-attributable mortality occurs, using average mortality coefficients derived from highly variable city-specific estimates that are rarely statistically significant, and extrapolating the results from the studies to broader populations (i.e., the CBSA).

4.3.1 EPA's Use of "No Threshold" Models Led to Calculated Risks below Levels Affected by Lowering the NAAQS

In contrast to what has been done in previous ozone NAAQS reviews, and inconsistent with what is known about ozone's toxic mechanism, "No Threshold" models were used to predict ozone–attributable mortality, and in so doing, risks are calculated below levels that can reasonably be expected to be influenced by regulatory standards (i.e., below background concentrations). For example, background ozone concentrations between 2001 and 2013 have been estimated to be as high as 58 ppb (95th percentile 8-hour daily maximum for Houston-Galveston-Brazoria area) and 63 ppb (95th percentile 8-hour daily maximum for Dallas-Ft. Worth area) in Houston and Dallas, respectively (Estes, Smith, & Mercado, 2014). This assessment provides risk estimates for the Urban Areas for ozone concentrations down to zero, reflecting, what EPA concludes is a lack of evidence for a detectable threshold in the concentration-response functions, and the understanding that US populations may experience health risks associated with background levels of ozone.

The estimated contribution of background to ozone levels in the Urban Areas included in EPA's risk assessment ranges from 51% to 74%. Therefore, in many of the Urban Areas evaluated, most of the mortality risk estimated in EPA's risk assessment occurs at background concentrations and below.

4.3.2 Highly Variable Risk Estimates for Individual Cities Make Urban Area and National Risk Estimates Highly Uncertain

To minimize extrapolation uncertainty, EPA attempted to locate epidemiology studies performed in the 12 Urban Areas evaluated in the HREA so that estimated risk for the Urban Areas could be based on concentration-response functions derived from populations living in that same area.

4.3.2.1 EPA's Hospital Admissions/Emergency Department Visit Risk Estimates are Highly Uncertain

As discussed in Section 4.0, the two multi-city studies on hospital admissions reported negative or small, but inconsistent, overall increases in hospitalization (averaged across individual cities),

but hospital admissions for individual cities were highly variable (–30% to +40% for chronic obstructive pulmonary disease hospital admissions per 30 ppb increase in ozone). In addition, despite the fact that the two multi-city studies covered all 12 of Urban Areas evaluated in the Hospital Admission/Emergency Department visit risk assessment, EPA made a decision to evaluate hospitalizations for additional respiratory diseases in Los Angeles, New York City, and Detroit, additional respiratory-related hospital admissions and Emergency Department visits in Atlanta and New York City, and respiratory symptoms in Boston. No explanation of why the additional analyses were carried out was provided, but it required the use of single-city studies performed in these areas, which generally provide more variable results than multi-city studies. Not surprisingly, the effect estimates based on the single-city studies were generally larger than those from multi-city studies, but they were also much more variable.

4.3.2.2 EPA's Short-Term Urban Area Mortality Estimates are Highly Uncertain

Similarly, an average short-term mortality coefficient derived by averaging highly variable city-specific mortality coefficients, was used in estimating short-term mortality risk in the HREA. As discussed previously, **Figure 3-5** illustrates that the mortality estimates are positive for some cities and negative for others, cities included in both studies occasionally had widely disparate estimates in the different studies, and that the association between ozone and mortality in most cities is not statistically significant. Therefore, the variability in the individual city mortality coefficients make the average mortality coefficient used to estimate short-term mortality risk in the 12 Urban Areas in the HREA highly uncertain.

4.3.2.3 EPA's Long-Term National Mortality Estimate is Even More Uncertain

While the short-term mortality risk assessment was conducted for 12 Urban Areas that were included in the multi-city epidemiology studies on which they were based, the long-term mortality risk assessment includes full spatial coverage across the entire US but has less geographic specificity in the concentration-response functions used to calculate ozone-attributable mortality because the study on which it was based only included 96 MSAs (Metropolitan Statistical Areas), which covers only about 40% of the US.

In the face of clear evidence that there is substantial regional heterogeneity in the effects of ozone, the national risk assessments for long-term mortality is of limited value. The variability in the individual city long-term mortality coefficients from Jerrett et al. (2009) make the average mortality coefficient used to estimate the long-term mortality burden for the entire nation even more uncertain than those used to estimate hospital admissions/Emergency Department visits and short-term mortality in the 12 Urban Areas.

4.3.3 EPA Introduces Additional Error by Extrapolating Beyond Areas Covered in Studies

The HREA (Pg. 7-5 and 7-6) indicates that all core risk estimates were *modeled using* study areas based on the core-based statistical area (CBSA) regardless of whether the

epidemiological studies providing the effect estimates used the core-based statistical area spatial definition or a different spatial study area definition. EPA acknowledges that there is a degree of uncertainty introduced by applying effect estimates to study areas (i.e., CBSAs) that do not match those used in the underlying epidemiological studies. In fact, they state "we introduce an additional source of exposure measurement error, which goes beyond the impact that measurement error has on the effect estimate, and introduces additional uncertainty into the estimates of risk associated with simulating meeting existing and alternative standards." and conclude that "The sensitivity analysis related to using study-based spatial definitions for urban areas shows clearly that using the smaller urban areas biases downward the risk reductions across an urban area."

Use of the smaller Smith et al. (2009) based study area did result in a lower mortality incidence for all of the urban areas, but this does not mean that using the smaller Urban Areas on which the studies are based somehow "biases" the risk estimates. It is not at all surprising that the mortality incidence is increased when the risk coefficient is applied to a larger area (i.e., the CBSA), but that does not mean that the larger risks that result from using a larger population value in the calculation are somehow superior to the smaller risks estimated only the population actually evaluated in the study is included. Instead, it suggests that, as acknowledged, additional exposure measurement error was introduced into the evaluation as a result of expanding the area over which the concentration-response functions were applied to the core-based statistical areas. Even going from one community to another within a larger metropolitan area, different socioeconomic classes and a host of other environmental variables that may modify effects (e.g., racial makeup, presence of central air conditioning vs. window units, etc.) may be encountered. Therefore, there is no implication or reason to expect that the relationship derived in one community would be applicable to another.

4.4 EPA'S OWN RISK ASSESSMENT DOES NOT SUPPORT THAT A DECREASE IN THE NAAQS WILL HAVE A HEALTH BENEFIT

Several instances, although by no means all, where EPA's risk estimates in the HREA do not provide supportive evidence that lowering the ozone NAAQS will benefit health are described in the sections to follow.

4.4.1 Modeled Lung Function Results Suggest Limited Risk

Figure 4-2 below (reproduced from Table 6-13 of the HREA (Pg. 6-48) displays the incremental increases in risk at the current NAAQS and the proposed alternative levels, where risk is the highest value for the percent of school-aged children with at least one FEV_1 decrement ≥ 10% (over years 2006 - 2010).

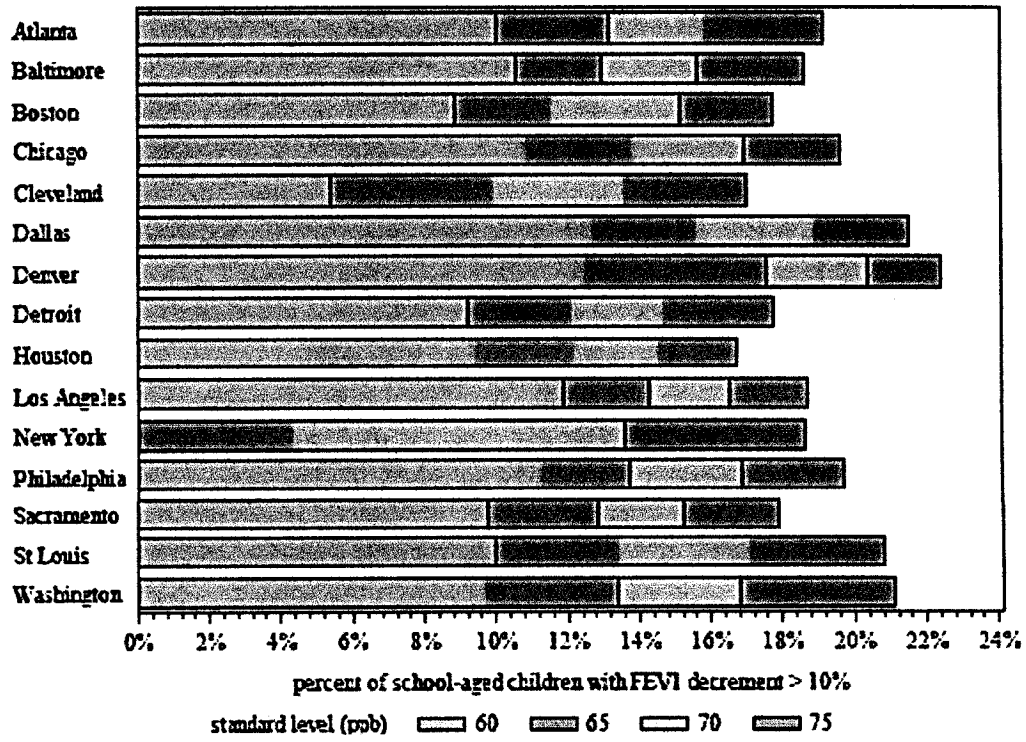
According to the HREA (Pg. 6-47), "This figure shows that there are significant increases in incremental risk for all 15 cities in the progression of alternative standard levels from 60 ppb to the level of the existing standard, 75 ppb ". This is an overstatement of the implications of these

results, to say the least. Although a minor point, the focus should be on the decrease in risk in the progression from the current NAAQS to the alternative levels.

As indicated in the title of **Figure 4-2**, the results represent the highest value for each study area over the four years evaluated, therefore, it is a near worst-case estimate. Second, a FEV_1 decrease of $\geq$ 10% is used as the lung function threshold, which represents the low-end of what is considered a moderate lung function decrement (at 9%, it would be considered mild). Lung function decrements such as decreases in FEV_1 are transient and completely reversible, resolving within 4 hours of exposure cessation. Therefore, a small decrement in lung function is not a serious health concern, and given the small magnitude of the decrement (i.e., 10%), it would not even be a significant concern for an asthmatic, although EPA persists in making unsupported statements that it would be. The focus on one-time lung function decrements $\geq$ 10%, despite the fact that there is no evidence that a one-time lung function deficit of this magnitude would have any lasting or serious health consequences is perplexing. However, this is one of many ways in which the results of the HREA are skewed toward giving the impression that a reduction in the NAAQS is necessary to protect public health.

FIGURE 4-2
ESTIMATED PERCENT OF SCHOOL-AGE CHILDREN WITH FEV_1 DECREMENT $\geq$ 10% AT THE CURRENT NAAQS AND PROPOSED ALTERNATIVE LEVELS

Figure 6-13. Lung Function Risk Results, Incremental Increases In Risk For Increasing Standard Levels: Percent of All School-aged Children With FEV_1 Decrement $\geq$ 10%, Highest Value For Each Study area Over Years[a]

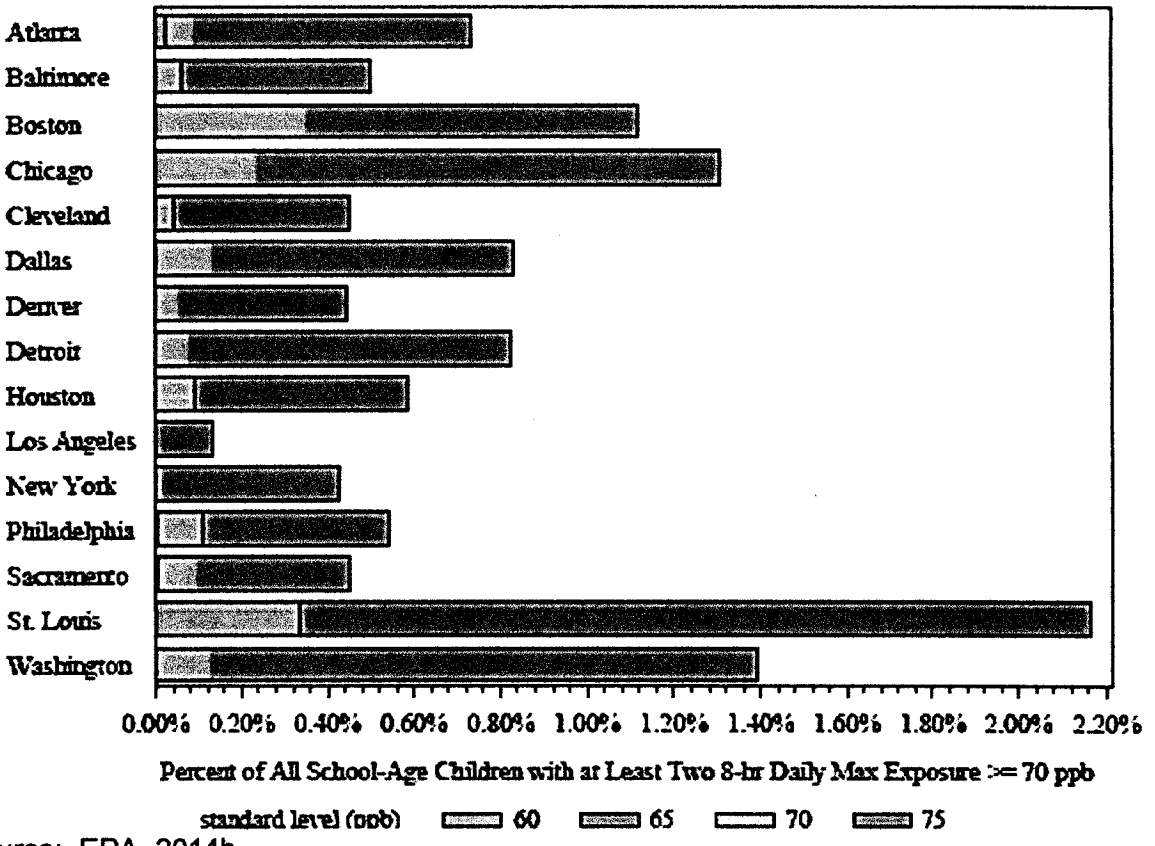


Source: EPA, 2014b

In addition, **Figure 4-2** above represents results for non-asthmatic children and, therefore, the percentage of children with FEV_1 decrements $\geq$ 15% should have been presented, rather than the percentage of children with FEV_1 decrements $\geq$ 10%. Had the $\geq$ 15% threshold been used as intended, the results would look very different. Although the percent of individuals $\geq$ 10% and 15% are provided in Appendix 6C, where EPA compares results from the current lung function model to the previous NAAQS review lung function model results, EPA applies the $\geq$ 10% FEV_1 decrement threshold to asthmatic children. The results for non-asthmatic children are compared to the $\geq$ 15% FEV_1 decrement benchmark (see Table 6C-1 of Appendix 6C of the HREA). As clearly stated in the text above Table 6C-1 of the HREA Appendix 6, "Table 6C-1 compares the estimated percent of asthmatic school-aged children with responses ≥ 10% and the estimated percent of all school-aged children with responses ≥ 15%." It is unclear why EPA presents results for school-age non-asthmatic children compared to the $\geq$ 10% FEV_1 in the report itself, but looking at Table 6C-1, it is apparent that there is a substantial decrease in the estimated percent of school-age children with $\geq$ 15% FEV_1 decrement. In Atlanta, for example, the estimated percent of school-age children with $\geq$ 15% FEV_1 decrement ranges from 0.9%-1.7% as compared to almost 20% estimated to have $\geq$ 10% FEV_1 decrement presented in **Figure 4-2** above.

Figure 4-3 below, which was reproduced from the HREA appendix, provides more meaningful results that can help answer the question of whether the ozone NAAQS needs to be lowered to protect public health. Rather than focusing on a single event for which there is no evidence of adversity, it shows the percent of school-age children that would experience at least two 8-hour daily maximum ozone exposures greater than 70 ppb (a level that has not produced clinically meaningful or clearly adverse group mean FEV_1 decrements in a single study and that completely resolves within 4 hours) at the current ozone NAAQS and the proposed alternative levels.

FIGURE 4-3
PERCENT OF SCHOOL-AGE CHILDREN WITH AT LEAST TWO 8-HOUR DAILY MAXIMUM EXPOSURES > 70 PPB AT CURRENT NAAQS AND ALTERNATIVE LEVELS



Source: EPA, 2014b

Figure 4-3 reveals that, if the current ozone NAAQS of 75 ppb were retained (brown bars), only about 2% of children are predicted to have two exposures greater than 70 ppb **in the city with the worst air quality**. In 10 out of the 15 Urban Areas evaluated, considerably less than 1% of children (e.g., ≈ 0.6% for Houston and 0.8% for Dallas) would be exposed to ozone concentrations greater than 70 ppb on two occasions if the current ozone NAAQS were retained. Therefore, **Figure 4-3** demonstrates that there is little need to lower the NAAQS to protect health.

4.4.2 EPA Acknowledges that Lowering the NAAQS will Not have Health Benefits

Pg. 7-71 of the HREA states "...despite considerable variability in absolute ozone-attributable risk, Figure 7-4 also suggests that most of the study areas display relatively limited reduction in ozone-attributable risk across the three alternative standards (with the exception of New York, which has a notable decrease in risk for the 70 to 65 ppb standard level). This suggests that a

substantial fraction of ozone-attributable risk would still remain, even after simulated attainment of the lowest alternative standard considered."

Although EPA does its best to "spin" the results to suggest that a reduction in the NAAQS is needed to protect public health, or as in this case, even a 60 ppb ozone NAAQS is not low enough, the last sentence in the paragraph above is a clear acknowledgement by EPA that reducing the ozone NAAQS will not have a health benefit.

Figure 7-4 from the HREA is reproduced as **Figure 4-4**.

4.4.3 Net Result of Lowering NAAQS Would Be to Increase Mortality or Hospital Admissions in Some Areas

The short-term mortality estimates for Houston suggest that the net result of lowering the ozone NAAQS would be to increase mortality, rather than decrease it. A portion of Table 7B-1 - Core Short-Term Ozone-Attributable Mortality (air quality data from 2007), from Appendix 7 of the HREA is reproduced in **Figure 4-5**.

FIGURE 4-4
PLOTS OF SHORT-TERM OZONE-ATTRIBUTABLE MORTALITY ASSOCIATED WITH MEETING EXISTING NAAQS AND ALTERNATIVE LEVELS

Figure 7-4 Plots of Short-Term o_3-attributable All-Cause Mortality for Meeting Existing standard and Alternative Standards (Smith et al., 2009) (Simulation year 2007 and 2009)

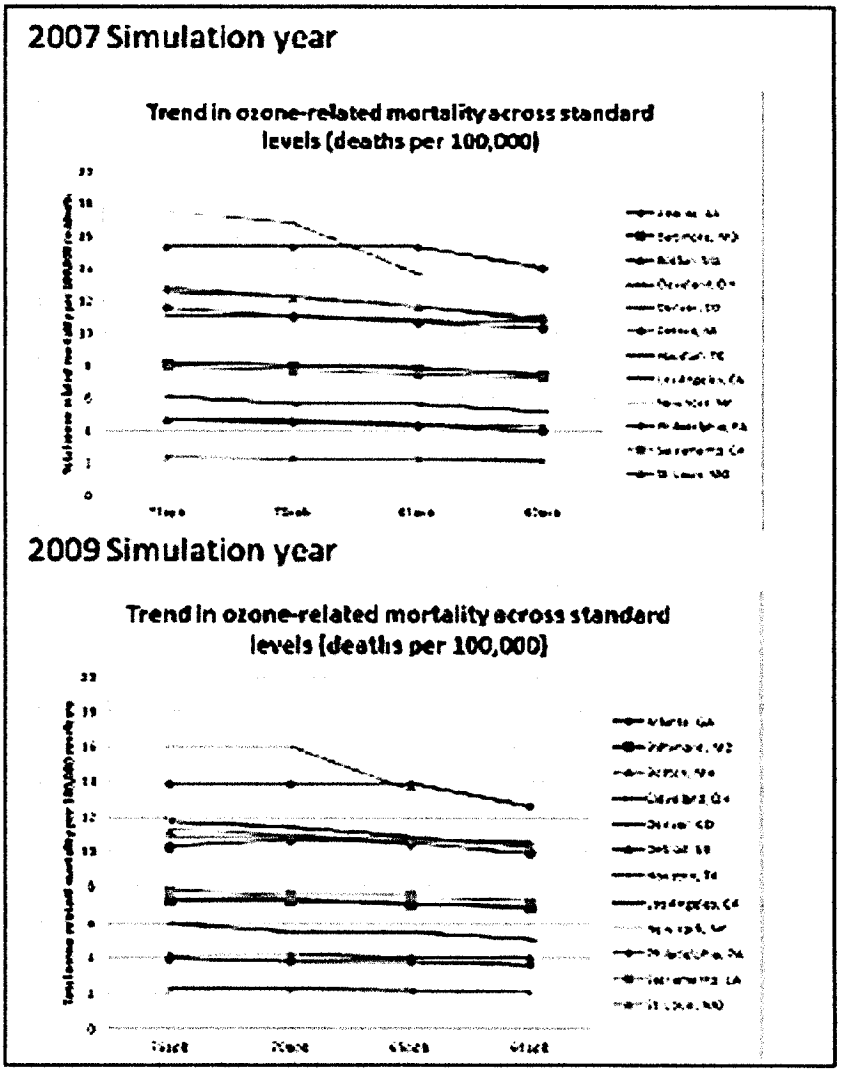


FIGURE 4-5
SHORT-TERM OZONE-ATTRIBUTABLE MORTALITY - HOUSTON

Table 7B-1 Core Short-Term Ozone-Attributable Mortality (2007) (incidence. percent of baseline mortality. incidence per 100.000) (Smith et al.. 2009)

	Air Quality Scenario								
	Absolute Ozone-Attributable Incidence					Change in Ozone-Attributable Incidence			
Study Area	Base	75ppb	70ppb	65ppb	60ppb	Base-75	75-70	75-65	75-60
Atlanta, GA	300	270	260	250	230	37	12	21	34
	(-430 - 1000)	(-370 - 890)	(-360 - 850)	(-340 - 820)	(-330 - 780)	(-51 - 120)	(-16 - 39)	(-30 - 72)	(-47 - 110)
Baltimore, MD	470	440	430	420	400	23	13	27	45
	(-260 - 1200)	(-250 - 1100)	(-240 - 1100)	(-230 - 1000)	(-220 - 1000)	(-12 - 57)	(-7 - 33)	(-15 - 68)	(-25 - 110)
Boston, MA	360	350	350	330	320	6	7	20	32
	(-510 - 1200)	(-500 - 1200)	(-490 - 1200)	(-470 - 1100)	(-460 - 1100)	(-8 - 19)	(-10 - 24)	(-28 - 67)	(-46 - 110)
Cleveland, OH	430	430	420	400	370	0	14	32	64
	(-41 - 890)	(-41 - 890)	(-40 - 860)	(-38 - 830)	(-35 - 760)	(0 - -1)	(-1 - 28)	(-3 - 67)	(-6 - 130)
Denver, CO	87	86	84	82	79	1	2	4	8
	(-290 - 440)	(-280 - 440)	(-280 - 430)	(-270 - 420)	(-260 - 400)	(-3 - 4)	(-6 - 10)	(-14 - 23)	(-25 - 40)
Detroit, MI	660	660	630	610	590	3	23	42	69
	(32 - 1300)	(32 - 1300)	(31 - 1200)	(30 - 1200)	(29 - 1100)	(0 - 5)	(1 - 44)	(2 - 81)	(3 - 130)
Houston, TX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Los Angeles, CA	1100	1300	1200	1200	1100	-180	43	87	160
	(-450 - 2600)	(-530 - 3000)	(-510 - 2900)	(-490 - 2800)	(-460 - 2600)	(77 - -450)	(-18 - 100)	(-36 - 210)	(-66 - 380)

Source: EPA, 2014a, Chapter 7, 8 and 9 Appendices, Pg. 7B-1.

Figure 4-5 shows the short-term ozone-attributable mortality incidence estimates per 100,000 people based on Smith et al. (2009).

According to **Figure 4-5**, the baseline (based on recent monitored air quality) ozone attributable mortality incidence per 100,000 is 640. However, upon meeting the current ozone NAAQS of 75 ppb or upon reaching 70 ppb, the incidence would increase to 680/100,000 (an additional 40 deaths per 100,000 people if ambient ozone levels are decreased). The mortality incidence/100,000 would decrease to 670 upon reaching 65 ppb and would go down to 660/100,000 upon reaching 60 ppb, which is still higher than the baseline incidence (640/100,000). The fact that the short-term mortality incidence estimates for Houston were higher at the current NAAQS and each of the alternative levels than estimated for recent Houston air quality conditions does not make sense. Similar results are shown in Table 7B-2 (air quality data from 2009). Not only do these results suggest that lowering the NAAQS will not have a health benefit, they suggest that implementing the current NAAQS or reducing it will be harmful to the citizens of Houston.

Houston appears to be the only city for which the short-term mortality incidence estimates were consistently predicted to increase upon lowering ambient ozone concentrations, however, Table 7B-3 - Core Short-Term Ozone-Attributable Morbidity – Hospital Admissions (air quality data from 2007), which is reproduced in **Figure 4-6** below, using concentration-response functions from Linn et al. (2000) for

FIGURE 4-6
SHORT-TERM OZONE-ATTRIBUTABLE HOSPITAL ADMISSIONS – LOS ANGELES

Table 7B-3 Core Short-Term Ozone-Attributable Morbidity – Hospital Admissions (2007 and 2009)

Endpoint/Study Area/Descriptor	Air Quality Scenario								
	Absolute Ozone-Attributable Incidence					Change in Ozone-Attributable Incidence			
	Base	75ppb	70ppb	65ppb	60ppb	Base-75	75-70	75-65	75-60
2007 Simulation Year									
HA (respiratory); Detroit (Katsouyanni et al., 2009)									
1hr max, penalized splines	250	230	220	210	200	18	13	23	37
1hr max, natural splines	240	230	210	200	190	17	12	22	36
HA (respiratory); NYC (Silverman and Ito, 2010; Lin et al., 2008)									
HA Chronic Lung Disease (Lin)	130	120	120	95	95	12	6.7	29	29
HA Asthma (Silverman)	450	420	400	330	330	50	28	120	120
HA Asthma, PM2.5 (Silverman)	340	310	290	240	240	36	20	84	84
[redacted]									
[redacted]	[redacted]								

Source: EPA, 2014a, Chapter 7, 8 and 9 Appendices, Pg. 7B-7.

Los Angeles, shows similarly counter-intuitive results for respiratory hospital admissions. The results suggest that, rather than decreasing respiratory-related hospital admissions, decreasing the ozone NAAQS would increase them in Los Angeles. As shown in **Figure 4-6**, the baseline (risks predicted based on recent ambient air levels in Los Angeles) respiratory hospital admissions are 610 but would go up to 790 upon meeting the current NAAQS of 75 ppb, an increase of 180 hospital admissions. Respiratory hospital admissions are predicted to go down to 770 upon reaching 70 ppb ozone, to 750 upon meeting 65 ppb, and 730 upon reaching 60 ppb. However, even at 60 ppb, the predicted respiratory hospital admissions in Los Angeles using the Linn et al. (2000) data are still higher than the baseline level. Similarly, hospital admissions for chronic obstructive pulmonary disease in Houston, based on the Medina-Ramon et al. (2006) concentration-response functions (Table 7B-3, Appendix 7 of HREA), are predicted to increase (from the baseline) upon reaching the current NAAQS, after which hospital admissions begin to decrease, but don't reach a level lower than baseline until 60 ppb is reached. Needless to say, EPA's own risk estimates, which suggest that lowering the ozone NAAQS in Houston and Los Angeles has the potential to worsen public health, do not support EPA's contention that the ozone NAAQS needs to be lowered to protect public health.

4.4.4 Most of EPA's Estimated Mortality Risks are Associated with Ozone Levels in the Range of Background

EPA's current risk assessment predicts risk for ozone concentrations down to zero because EPA concludes that there is a lack of evidence for a threshold. There are at least two problems with EPA's approach: 1) concentrations that are below background levels will not be affected by lowering the NAAQS since they come from natural sources and from areas outside Federal

control; and 2) there is good evidence for a threshold below which mortality does not occur that EPA continues to ignore.

The estimated contribution of background to ozone levels in the Urban Areas included in EPA's risk assessment ranges from 51% to 74%. Therefore, in many of the Urban Areas evaluated, most of the mortality risk estimated in EPA's risk assessment occurs at background concentrations and below. For example, as much as 67% of the ozone in Houston is estimated to come from background sources that would not be affected by lowering the ozone NAAQS. Based on EPA's estimates of short-term mortality caused by ozone (Figure 7B-3 Core Short-Term Ozone-Attributable Mortality (2009), Appendix 7 of HREA), using recent ozone concentrations, 8 out of 642 ozone-related deaths in Houston (≈ 1%) are caused by ozone concentrations > 75 ppb, 7 deaths (≈ 1%) are attributed to concentrations between 75 ppb and 70 ppb, while 410 of the 642 deaths (≈ 65%) are predicted to occur at ozone concentrations of 45 ppb or less, which is equivalent to average background levels during the months of May and October.

4.5 OVERALL CONCLUSIONS DRAWN FROM EPA'S HEALTH RISK AND EXPOSURE ASSESSMENT

In conducting the HREA for ozone, EPA has focused on inconsistently and infrequently observed lung function changes in human exposure studies that are often too mild to be considered clinically relevant to justify lowering the 8-hour primary ozone NAAQS. In addition, epidemiological studies that neither measure actual exposures nor adequately control other factors that can confuse study results have been relied upon as additional evidence that health effects occur at concentrations below the current ozone NAAQS, despite the fact that the relationships between ozone and health effects reported in epidemiology studies are uniformly weak.

Based on Zephyr's review, each section of the HREA is significantly flawed. Some of the details of those flaws include:

- Because there are relatively few air monitors, mathematical procedures are used to estimate ozone concentrations for un-monitored areas and models are used to predict the response to reductions in ozone precursors-this introduces additional uncertainty into the HREA;
- Because it is well known that personal exposure concentrations are considerably lower than ambient ozone concentrations, EPA models personal exposure for the lung function risk assessment using an exposure model known to over-predict ozone exposures;
- While much debate continues regarding the level at which truly adverse health effects occur and the relationship between monitored ozone concentrations and mortality/hospitalization reported in epidemiology studies, EPA presumes that adverse effects occur at ozone concentrations as low as 60 ppb and that ozone causes the deaths/hospitalization for the sake of estimating numerical risks in the HREA;

- The HREA fails to adequately convey the degree of uncertainty associated with the risk estimates;
- Neither model used in the HREA to predict changes in lung function is capable of predicting whether decreases in FEV_1 will be accompanied by respiratory symptoms, a requirement for transient and reversible effects, such as mild decreases in FEV_1, to be considered adverse according to the adversity definition of the ATS (2000) that EPA has adopted;
- The HREA justifies using a $\geq$ 10% decrease in FEV_1 as the lower threshold for assessing lung function decrement based on the assumption that a ≥10% decrement in lung function may be a more adverse event in an asthmatic child even though, as acknowledged throughout this report, the evidence that asthmatics are more sensitive to the adverse health impacts of ozone is very limited;
- Despite clearly stating that a FEV_1 decrement ≥ 15% threshold is appropriate for estimating potentially adverse lung function decrements in active healthy adults, while for people with asthma or lung disease, a focus on FEV_1 decrements down to 10% may be appropriate, the HREA indiscriminately applies a $\geq$ 10% FEV_1 decrement threshold across all evaluated populations (in the 2007 HREA, a $\geq$ 10% FEV_1 decrement threshold was only applied to asthmatics);
- Inconsistent with most of what is known about ozone's toxic mechanism, a "No Threshold" model was used to predict ozone–attributable mortality, and in so doing, risks are calculated below levels that can reasonably be expected to be influenced by regulatory standards;
- In the face of clear evidence that there is substantial regional heterogeneity in the association of ozone and premature mortality, the value of the nationwide estimates of ozone-attributable mortality is questionable.

These flaws bring the entire document and its findings into question. Therefore, we conclude that the current HREA should not be relied upon for decision-making related to whether lowering the ozone NAAQS would provide demonstrably better protection of public health than does the current ozone NAAQS.

5.0 VEGETATIVE EFFECTS STUDIES

Ozone in the lower troposphere is a common phytotoxic air pollutant that can cause injury to plant tissue and reduce rates of photosynthesis, plant growth, and plant productivity. Ozone exposure can affect both tree growth and crop yields and damages are cumulative over the growing season. The primary pathway of ozone interaction with plant tissues is through stomata, small openings on plant leaves that allow for the transfer of gases such as oxygen, carbon dioxide, and water vapor. Upon entering stomata, ozone acts as an oxidizer, causing changes in biochemical and physiological processes and ultimately resulting in cell death and visible foliar injury. The secondary standard is set to protect public welfare, including protection against damage to crops and vegetation that provide both tangible and intangible health benefits for people. Currently, the impact of ozone on vegetation is assessed using a seasonal, cumulative exposure index known as the W126 index. The W126 index measures ozone exposure in vegetation by weighing ozone concentrations during peak hours in the three peak months of the ozone season and averaging over three years.

5.1 EVIDENCE ON VEGETATIVE EFFECTS DOES NOT SUPPORT A MOVE TO A LOWER OZONE NAAQS

EPA is proposing to revise the secondary standard to within the range of 65 to 70 ppb. However, based upon the analysis done by the EPA in Section 7 of the WREA, the existing data on ozone effect on plant communities in National Parks, Monuments, and Forrest does not support a move to a level below the current NAAQS of 75 ppb. Of the sites monitored for ozone exposure, the majority would be protected from aesthetically damaging foliar injury by meeting the existing standard of 75 ppb.

According to an air quality analysis conducted by EPA, a standard between 65 and 70 ppb would provide air quality, in terms of 3-year average W126 index values, at or below a range of 13–17 ppm-hours. The most recent set of data concerning ozone exposure in National Parks, Monuments, and Forests is the USDA's Forest Service's Ozone Biomonitoring Program (OBP). This data set is based upon monitoring for ozone and its effects at 214 Forest Health Monitoring (FHM) sites or "biosites" across the nation focusses on the National Park Service's (NPS) list of ozone-sensitive plant species. The EPA's analysis focused on measurements taken from 2006 to 2010.

Three National Parks were looked at in depth: Great Smokey Mountains National Park, Rocky Mountain National Park, and Sequoia/Kings Canyon National Park. Under recent air quality conditions, 44%, or 959 km^2, of the Great Smokey Mountains National park has W126 index values above 15 ppm-hours. If just the existing ozone NAAQS of 75 ppb is met at Great Smokey Mountains National Park, W126 index values are reduced such that no area is over 7 ppm-hours (just meeting the alternative of 15 ppm-hours produces the same result as meeting the existing standard). Rocky Mountain National Park is home to a handful of species that are more ozone-sensitive than those in the Great Smokey Mountains, especially the Quaking Aspen. Under recent ozone air quality conditions, the entirety of the Rocky Mountain National

Park (1067 km^2) has W126 index values over 15 ppm-hours. Meeting the existing 75 ppb NAAQS would bring about 59% of Rocky Mountain National Park into the 7-5 ppm-hours. Under recent conditions, all areas of the Sequoia/Kings Canyon National Park experience W126 index values of over 15 ppm-hours. Meeting the existing ozone standard would move entirety of Sequoia/Kings Canyon National Park to under 7 ppm-hours. .

5.2 OZONE EXPOSURE IN SENSITIVE PLANT SPECIES AND COMMUNITIES ARE GENERALLY MARKED BY FOLIAR INJURY

There are many studies that examine the effects of ozone exposure on vegetation in relation to crop yields and losses and rural plant communities (such as National Parks of wildlife areas). Most of the available studies targeted specific crops or plant species at limited intervals of time within or near certain sites. For the most part, these studies support governmental regulations designed to limit tropospheric ozone, but many disagree on the best method for assessing ozone exposure.

5.2.1 Effects of Ozone on Crop Yield

A number of efforts have been made to define the impact of ozone on crop productivity, predict crop losses, and set air quality standards that keep crop losses to economically acceptable levels. There is clearly a negative relationship between the yield of a wide range of crops and exposure to ozone, although sensitivities do vary between species and cultivars.

Upon interaction of plant tissue with ozone in the stomata, a complex chain of chemical and biochemical responses occurs, producing reactive oxidized species and initiating physiological responses from the plant. Such responses include cell death and accelerated senescence (the process of deterioration). Cellular antioxidant systems that evolved to handle the oxidative stress encountered from metabolic and external factors can assist in ozone tolerance when present. Other than decreased crop yield and visible injury, plant responses to ozone include decreased photosynthetic carbon assimilation due to a loss of Rubisco (a carbon-fixation enzyme) activity from oxidation. Ozone exposure may also damage the stomata's ability to control carbon dioxide and water vapor levels within the leaf and is implicated in damaging the electron transport chain needed to complete photosynthesis.

5.2.2 Effects of Ozone on Rural Plant Communities

Multiple studies on the effects of ozone on rural plant communities have been conducted at National Parks and Wildlife Refuges (NWRs) in conjunction with the National Park Service (NPS) and the United States Fish and Wildlife Service (USFWS). While most ozone effect studies have focused on crops, native plant communities can also be sensitive to ozone exposure. Studies in the Southern Appalachian Mountains, Shenandoah National Park, Great Smokey Mountains National Park, the Sierra Nevada Mountains, and multiple NWRs have shown instances of premature leaf loss, reduced photosynthesis, reduced radial growth, and reduced leaf, root, and total dry weight (biomass) in sensitive plant species. Most cases of

ozone exposure in sensitive plant species and communities are marked by foliar injury. Damages due to ozone exposure may be exacerbated by levels of soil moisture, elevation, weather, the presence of other air pollutants, insects, diseases, and other environmental stressors.

Ozone uptake can vary greatly by species and within species, with some being more sensitive to exposure at lower concentrations and uptake being highly variable across the same species.

6.0 CONCLUSIONS

6.1 THE CURRENT NAAQS IS REQUISITE TO PROTECT PUBLIC HEALTH AND WELFARE WITH AN ADEQUATE MARGIN OF SAFETY

Taken together, the evidence and studies evaluated in this report indicate that the current ozone NAAQS is protective of public health and welfare with an adequate margin of safety. This conclusion is supported by EPA's own risk assessments (the HREA and WREA) as well as the scientific studies that provide input for the assessment.

6.1.1 EPA's Premise for Recommending a Revision to the Current NAAQS is Faulty

The Clean Air Act (CAA) requires that primary NAAQS that are protective of public health, with an adequate margin of safety, and secondary NAAQS that are protective of public welfare to be established. "Public welfare" is defined as including "effects on soils, water, crops, vegetation, man-made materials, animals, wildlife, weather, visibility and climate." Examples of what is intended by "public health" are not similarly provided, nor is a definition of what constitutes an "adequate margin of safety."

EPA concludes (Pg. 75236 of the proposed rule) that the current primary ozone standard set at a level of 75 ppb is not requisite to protect public health with an adequate margin of safety, and that it should be revised to provide increased public health protection. EPA is proposing this revision to increase public health protection, including for "at-risk" populations such as children, older adults, and people with asthma or other lung diseases, against an array of ozone-related adverse health effects. However, the literature does not support that any of these so called "at-risk" populations are in fact more sensitive to ozone than healthy people. Therefore, EPA's entire rationale for recommending that the ozone NAAQS be revised is based on a faulty premise.

6.1.2 EPA's Risk Assessment Does Not Support that a Reduction in the NAAQS Will Benefit Health

The goal of EPA's risk assessments is to provide information that is helpful in answering questions about the adequacy of the existing NAAQS but the misrepresentation of the risk assessment *results* by EPA suggests that the assessment was not so much exploratory as it was a "means to an end".

EPA overestimates exposure in the HREA by using models known to overestimate personal exposure indoors, assuming unreasonably high activity levels, and substituting higher outdoor air concentrations for lower personal exposure levels. EPA overpredicts risk by selectively using only positive responses from studies suggesting that increased ozone concentrations lead to increased health effects (ignoring negative results) and estimating hospital admission and mortality risks associated with all ozone concentrations (down to zero), despite evidence that

there is a threshold below which adverse effects do not occur. Despite the overpredictions and modeling assumptions that are based on false premises, the HREA results not only fail to support that a reduction in the NAAQS will have health benefits, the net result of the risk assessment is that mortality and hospital admissions will actually be increased in some areas. Furthermore, the majority of the estimated risk occurs at ozone concentrations in the range of background levels, which will not be affected by lowering the NAAQS.

6.1.3 Scientific Studies Do Not Support that Effects with Relevance to Human Health Occur at Levels below the Current Ozone NAAQS

There are major concerns about the scientific rigor of EPA's evaluation of the scientific literature, as well as EPA's process for establishing "causality" classifications for ozone health endpoint relationships. Furthermore, the method by which EPA selected the studies from which response relationships were derived for use in predicting risks remains a mystery.

6.1.3.1 Laboratory Studies Show that Effects Do Not Occur below Ozone Concentrations of 88 ppb

Recent laboratory studies that evaluate the association between ozone and lung function at exposures below the current NAAQS of 75 ppb indicate that there are no statistically significant adverse effects with clinical relevance to human health below 88 ppb. Nonetheless, EPA summarizes the information as providing positive evidence for effects at levels below the current NAAQS by ignoring widely recognized definitions of what constitutes an "adverse" effect and the criterion for judging the clinical relevance of effects that they themselves developed.

6.1.3.2 Population Studies Fail to Show that Effects Occur At Concentrations Below 75 ppb

Review of population studies that examined associations between short-term ambient ozone exposure and respiratory effects report inconsistent results and small effects across all health endpoints. EPA does not reveal or appear to adequately consider factors that biased those study results, such as measurement error, choice of latency period, and failure to adjust results for the confounding influence of other pollutants (especially PM). Instead, EPA repeatedly provides summaries of the available scientific literature that emphasizes only positive associations.

The few positive and statistically significant associations reported in mortality studies are very weak and likely completely swamped by the large error introduced by not adequately adjusting the estimates for confounding variables (especially PM) and regional differences. EPA appears to ignore the undeniable evidence for significant confounding by PM and enormous regional variability in the size of the association, with both positive and negative associations reported in individual cities, in its mortality estimates.

EPA's reliance on one weakly positive study with many limitations for estimating the national mortality burden flies in the face of every aspect of EPA's formal framework for evaluating the weight of scientific evidence, which requires consistency in the observations used to infer causality.

6.1.4 Overall Conclusions Drawn from Review of EPA's Evidence for Lowering Current Ozone NAAQS

Following an exhaustive review of the evidence that EPA has provided in support of its recommendation that the ozone NAAQS be reduced, the only possible conclusion is that the evidence fails in every way to support such a recommendation.

When environmental policy makers and regulators are tasked with making regulatory decisions on the basis of scientific studies, they should consider the uncertainties associated with the available evidence. Regulatory actions should be based on a high level of certainty about the causal nature of the association.

Although two controlled human studies reporting lung function decrements following exposures to lower concentrations were available in the 2008 ozone NAAQS review, an important uncertainty that lead to EPA's decision not to establish the NAAQS at a concentration below 75 ppb was the extent to which exposures to ozone concentrations below 80 ppb result in lung function decrements. The paucity of studies, their uniformly small sample sizes, small effect sizes, large measurement errors, and high variation, combine to give less reliable results. In addition, there appears to be evidence of data fishing in two cases (Brown et al., 2008; Kim et al., 2011). In light of these factors, the extremely weak evidence from controlled human exposure studies for lung function decrements at concentrations below 75 ppb is no better today than it was in 2008

In the litigation that arose from the lawsuit challenging the 2008 ozone standards, the DC Circuit upheld (2013) EPA's 2008 primary standard of 75 ppb. In upholding EPA's primary standard of 75 ppb, the court rejected arguments from environmental groups that EPA should have adopted a lower standard, stating that it accepted EPA's argument that there was legitimate uncertainty that a "causal" relationship between 8-hour exposures less than 75 ppb exists, such that associations reported in epidemiology studies at lower levels did not necessitate a more stringent standard.

The *epidemiology studies* that EPA is relying on for this rulemaking report uniformly small associations that are: 1) inconsistently observed across studies; 2) inadequately controlled for confounding influences; and 3) statistically insignificant as often as not. Moreover, EPA consistently ignores evidence for thresholds in ozone-related effects, fails to properly acknowledge the uncertainties associated with its risk estimates, and relies on a single unsubstantiated study for it's for long-term mortality estimates. Therefore, there is no more certainty today regarding whether the associations reported in epidemiology studies for concentrations below the current NAAQS are "causal" with respect to observed health effects than there was in 2008.

Taken together, the evidence and studies evaluated in this report indicate that the current ozone NAAQS is protective of public health and welfare. This conclusion is supported by EPA's own risk assessment as well as the scientific studies that provide input for the assessment.

7.0 REFERENCES

79 Federal Register 75234 (2014, December 17). National Ambient Air Quality Standards for Ozone; Proposed Rule.

Abbey, D., Nishino, N., McDonnell, W., Burchette, R., Knutsen, S., Beeson, W., & Yang, J. (1999). Long-term inhalable particles and other air pollutants related to mortality in nonsmokers. *Am J Respir Crit Care Med, 159*, 373-382.

Adams, W. (1998). Dose-response effects of varied equivalent minute ventilation rates on pulmonary function responses during exposure to Ozone.

Adams, W. (2002). COMPARISON OF CHAMBER AND FACE-MASK 6.6-HOUR EXPOSURES TO OZONE ON PULMONARY FUNCTION AND SYMPTOMS RESPONSES. *Inhal Toxicol, 14*, 745-764.

Adams, W. (2003). Comparison of chamber and face mask 6.6-hour exposure to 0.08 ppm ozone via square-wave and triangular profiles on pulmonary responses. *Inhal Toxicol, 15*, 265–281.

Adams, W. (2006). Comparison of Chamber 6.6-h Exposures to 0.04-0.08 PPM Ozone via Square-wave and Triangular Profiles on Pulmonary Responses. *Inhal Toxicol, 18*, 127-136.

Alexis, N., Urch, B., Tarlo, S., Corey, P., Pengelly, D., O'Byrne, P., & Silverman, F. (2000). Cyclooxygenase metabolites play a different role in ozoneinduced pulmonary function decline in asthmatics compared to normals. *Inhal Toxicol, 12*, 1205–1224.

ATS. (1991). American Thoracic Society. Lung Function Testing: Selection of Reference Values, and Interpretative Strategies. *Am Rev Respir Dis, 144*, 1202-1218.

ATS. (2000). American Thoracic Society. What Constitutes an Adverse Health Effect of Air Pollution? *Am J Respir Crit Care Med*, 665–673.

Balmes, J., Aris, R., Chen, L., Scannell, C., Tager, I., Finkbeiner, W., & Christian, D. (1997). *Part I: Airway Inflammation and Responsiveness to Ozone in Normal and Asthmatic Subjects.* Research Report No. 78, Health Effects Institute.

Basha, M., Gross, K., Gwizdala, C., Haidar, A., & Popovich, J. J. (n.d.). Bronchoalveolar lavage neutrophilia in asthmatic and health volunteers after controlled exposure to ozone and filtered purified air. *Chest, 106*, 1757–1765.

Bates, D. (1987). *Overview on Characterizing Study Groups and Their Responses in Susceptibility to Inhaled Pollutants.* American Society of Testing and Materials. Utell, M.J.; Frank, R.

Bell, M., McDermott, A., Zeger, S., Samet, J., & Dominici, F. (2004). Ozone and Short-term Mortality in 95 US Urban Communities, 1987–2000. *JAMA, 292*, 2372–2378.

Brown, J., Bateson, T., & McDonnell, W. (2008). Effects of Exposure to 0.06 ppm Ozone on FEV1 in Humans: A Secondary Analysis of Existing Data. *Environ Health Persp, 116*(8), 1023-1026.

Chen, L., Jennison, B., Yang, W., & Omaye, S. (2000). Elementary school absenteeism and air pollution. *Inhal Toxicol., 12*, 997-1016.

Cowie, R., Underwood, M., & Feld, S. (2007). Asthma symptoms do not predict spirometry. *Can Respir J, 14*(6), 339-342.

Darrow, L., Klein, M., Sarnat, J., Mulholland, J., Strickland, M., Sarnat, S., . . . Tolbert, P. (2011). The use of alternative pollutant metrics in time-series studies of ambient air pollution and respiratory emergency department visits. *J Exposure Sci Environ Epidemiol, 21*, 10-19.

Delfino, R., Gone, H., Linn, W., Pellizzari, E., & Hu, Y. (2003). Asthma symptoms in Hispanic children and daily ambient exposures to toxic and criteria air pollutants. *Environ Health Perspect*, 647-656.

Dockery, D., Pope, C. I., Xu, X., Spengler, J., Ware, J., Fay, M., . . . Speizer, F. (1993). An association between air pollution and mortality in six US cities. *N Engl J Med, 329*.

Dominici, F., McDermott, A., Daniels, M., Zeger, S., & Samet, S. (2005). Revised analyses of the National Morbidity, Mortality, and Air Pollution Study: mortality among residents of 90 cities. *J Toxicol Environ Health A., 68*(13-14), 1071-92.

Enarson, D., & Yeung, M. (1985). Determinants of changes in FEV1 over a workshift. *Br J Indust Med, 42*, 202-204.

EPA. (1996). Air Quality Criteria for Ozone and Related Photochemical Oxidants. EPA/600/P93/004aF. July.

EPA. (2006). *Air Quality Criteria for ozone and related photochemical oxidants. EPA 600/R-05/004aF. February.*

EPA. (2007). *Ozone health risk assessment for selected urban areas. EPA 452/R-07-009. July.*

EPA. (2008). *Integrated Science Assessment for Oxides of Nitrogen — Health Criteri. EPA/600/R-08/07.*

EPA. (2009). *Risk and Exposure Assessment to Support the Review of the SO2 Primary National Ambient Air Quality Standards: Final Report. EPA-452/R-09-007.*

EPA. (2013). *Integrated Science Assessment for Ozone and Related Photochemical Oxidants. EPA 600/R-10/076F. February.*

EPA. (2014a). Policy Assessment for the Review of the Ozone National Ambient Air Quality Standards. EPA–452/P–14–002. January.

EPA. (2014b). *Health Risk and Exposure Assessment for Ozone. EPA-452/P-14-004a. February, 2014.* EPA.

EPA. (2014c). Welfare Risk and Exposure Assessment for Ozone. EPA-452/P-14-003a. February.

Estes, M., Smith, J., & Mercado, F. (2014, October 29). *Regional background ozone in the eastern half of Texas.* Retrieved March 3, 2015, from Community Modeling and Analysis System: https://www.cmascenter.org/conference/2014/agenda.cfm

Gent, J., Triche, E., Holford, T., Belanger, K., Bracken, M., Brackett, W., & Leaderer, B. (2003). Association of low-level ozone and fine particles with respiratory symptoms in children with asthma. *JAMA, 290*, 1859-1867. Retrieved from http://dx.doi.org/10.1001/jama.290.14.1859

Gilliland, F., Berhane, K., Rappaport, E., Thomas, D., Avol, E., Gauderman, W., . . . Margolis, H. (2001). The effects of ambient air pollution on school absenteeism due to respiratory illnesses. *Epidemiol., 12*, 43-54.

Goldberg, M., Burnett, R., Yale, J., Valois, M., & Brook, J. (2006). Associations between ambient air pollution and daily mortality among persons with diabetes and cardiovascular disease. *Environ Res., 100*(2), 255-267.

Goodman, J., & Pruitt, R. (2011). *Comments to the CASAC Ozone Review Panel on the First Draft Ozone Integrated Science Assessment.*

Goodman, J., Prueitt, R., Chandaliaa, J., & Sax, S. (2013a). Evaluation of adverse human lung function effects in controlled ozone exposure studies. *J. Appl. Toxicol.* doi:DOI 10.1002/jat.2905

Goodman, J., Prueitt, R., S.N., S., Bailey, L., & Rhomberg, L. (2013b). Evaluation of the causal framework used for setting National Ambient Air Quality Standards. *Crit Rev Toxicol, 43*(10), 829–849.

Heuss, J. (2012). Oral Comments on the First External Review Draft of the "Health Risk and Exposure Assessment for Ozone".

Horstman, D., Folinsbee, L., Ives, P., Abdul-Salaam, S., & McDonnell, W. (1990). Ozone concentration and pulmonary response relationships for 6.6-hour exposures with five hours of moderate exercise to 0.08, 0.1, and 0.12 ppm. *Am. J. Respir. Crit. Care Med., 142*, 1158-1163.

Huang Y, D. F. (2005). Bayesian hierarchical distributed lag models for summer ozone exposure and cardio-respiratory mortality. *Environmetrics, 16*, 547–562.

Huang, Y., Dominici, F., & Bell, M. (2005). Bayesian hierarchical distributed lag models for summer ozone exposure and cardio-respiratory mortality. *Environmetrics, 16*, 547–562.

Ito, K., Thurston, G., & Silverman, R. (2007). Characterization of PM2.5, gaseous pollutants, and meteorological interactions in the context of time-series health effects models. *J Exposure Sci Environ Epidemiol, 17*, S45–S60.

Jerrett, M., Burnett, R., Pope, C. A., Ito, K., Thurston, G., Krewski, D., . . . Thun, M. (2009). Long-Term Ozone Exposure and Mortality. *N Engl J Med, 360*(11), 1085-1095.

Johannes, H. W., Sznitman, J., Harpes, P., Straub, D., Moller, A., P., B., & Sennhauser, F. (2007). Correlation of Spirometry and Symptom Scores in Childhood Asthma and the Usefulness of Curvature Assessment in Expiratory Flow-Volume Curves. *Respir Care, 52*(12), 1744–1752.

Juniper, E., Guyatt, G., Epstein, R., Ferrie, P., Jaeschkl, R., & Miller, T. (1992). Evaluation of impairment of health-related quality of life in asthma: development of a questionnaire for use in clinical trials. *Thorax, 47*(2), 76-83.

Just, J., Segala, C., Sahraoui, F., Priol, G., Grimfeld, A., & Neukirch, F. (2002). Short-term health effects of particulate and photochemical air pollution in asthmatic children. *Eur Respir J, 20*, 899-906.

Katsouyanni, K., & Samet, J. (2009). *Air Pollution and Health: A European and North American Approach (APHENA).* Health Effects Institute Research Report No. 142.

Khatri, S., Holguin, F., Ryan, P., Mannino, D., Erzurum, S., & Teague, W. (2009). Association of ambient ozone exposure with airway inflammation and allergy in adults with asthma. *J Asthma, 46*, 777-785.

Kim, C., Alexis, N., Rappold, A., Kehrl, H., Hazucha, M., Lay, J., . . . Diaz-Sanchez, D. (2011). Lung Function and Inflammatory Responses in Healthy Young Adults Exposed to 0.06 ppm Ozone for 6.6 Hours. *Am J Respir Crit Care Med, 183*, 1215–1221.

Larsson, K., Hedenstrom, H., & Maimberg, P. (n.d.). Learning effects, variation during office hours and reproducibility of static and dynamic spirometry. *Respir, 51*, 214-222.

Lefohn, A., Hazucha, M., Shadwick, D., & WC., A. (2010). An alternative form and level of the human health ozone standard. *Inhal Toxicol, 22*, 999–1011.

Lin, S., Liu, X., Le, L., & Hwang, S. (2008). Chronic Exposure to Ambient Ozone and Asthma Hospital Admissions among Children. *Environ Health Persp, 116*, 1725-1730.

Linn, W., Szlachcic, Y., Gong, H. J., Kinney, P., & Berhane, K. (2000). Air pollution and daily hospital admissions in metropolitan Los Angeles. *Environ Health Perspect, 108*, 427-434.

Lipfert. (1997). *Technical Comments on EPA's Proposed Revisions to the National Ambient Air Quality Standard for Particulate Matter. BNL-64310. March.* US Department of Envergy.

Lipsett, M., Ostro, B., Reynolds, P., Goldberg, D., Hertz, A., Jerrett, M., & Smith, D. (2011). Long-Term Exposure to Air Pollution and Cardiorespiratory Disease in the California Teachers Study Cohort. *Am J Respir Crit Care Med, 184*, 828–835.

Lipsett, M., Ostro, B., Reynolds, P., Goldberg, D., Hertz, A., Jerrett, M., . . . and Bernstein, L. (2011). Long-Term Exposure to Air Pollution and Cardiorespiratory Disease in the California Teachers Study Cohort. *Am J Respir Crit Care Med, Am J Respir Crit Care Med*, 828–835.

McClellan, R., Frampton, M., Koutrakis, P., McDonnell, W., Moolgavkar, S., North, D., . . . Utell, M. (2009). Critical considerations in evaluating scientific evidence of health effects of ambient ozone: a conference report. *Inhal Toxicol, 21*(S@), 1-36.

McDonnell, W., Kehrl, H., Abdul-Salaam, S., Ives, P., Folinsbee, L., & DevlinR., B. (1991). Respiratory response of humans exposed to low levels of zone for 6.6 hours. *Arch. Environ. Occup. Health, 46*.

McDonnell, W., Stewart, P., & Smith, M. (2007). The temporal dynamics of ozone-induced FEV1 changes in humans: an exposure-response model. *Inhal Toxicol, 19*, 483–494.

McDonnell, W., Stewart, P., Smith, M., Kim, C., & and Schelegle, E. (2012). Prediction of lung function response for populations exposed to a wide range of ozone conditions. *Inhal Toxicol, 24*(10), 619–633.

Medina-Ramon, M., Zanobetti, A., & Schwartz, J. (2006). The Effect of Ozone and PM10 on Hospital Admissions for Pneumonia and Chronic Obstructive Pulmonary Disease: A National Multicity Study. *Am J Epidemiol, 163*(6), 579–588.

Mortimer, K., Neas, L., Dockery, D., Redline, S., & Tager, I. (2002). The effect of air pollution on innercity children with asthma. *Eur Respir J, 19*, 699-705.

Mudway, I., Stenfors, N., Blomberg, A., Helleday, R., Dunster, C., & Marklund, S. (2001). Differences in basal airway antioxidant concentrations are not predictive of individual responsiveness to ozone: A comparison of healthy and mild asthmatic subjects. *Free Radic. Biol. Med, 31*, 962-974.

Nicolich, M. (2007). *Attachment A: Some Additional Statistical Analyses of the FEV1 Pulmonary Response Data From the W.C. Adams Data (2006). EPA-HQ-OAR-2005-0172-4163.* Retrieved from http://www.regulations.gov

O'Connor, G., Neas, L., Vaughn, B., Kattan, M., Mitchell, H., Crain, E., . . . Morgan, W. (2008). Acute respiratory health effects of air pollution on children with asthma in US inner cities. *J Allergy Clin Immunol, 121*, 1133-1139.

Ostro, B., Lipsett, M., Mann, J., Braxton-Owens, H., & White, M. (2001). Air pollution and exacerbation of asthma in African-American children in Los Angeles. *Epidemiol, 12*, 200-208.

Park, J., Lim, Y., Kyung, S., An, C., Lee, S., Jeong, S., & Ju, S. (2005). Effects of ambient particulate matter on peak expiratory flow rates and respiratory symptoms of asthmatics during Asian dust periods in Korea. *10*, 470-476.

Pellegrino, R., Viegi, G., Brusasco, V., Crapo, R., Burgos, F., Casaburi, R., & Coates, A. (2005). Interpretative strategies for lung function tests. *Eur Respir J, 26*, 948–968.

Pope, C. I., Burnett, R., Thun, M., Calle, E., Krewski, D., Ito, K., & Thurston, G. (2002). Lung cancer cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *JAMA, 287*, 1132-1141.

Romieu, I., Ramirez-Aguilar, M., Sienra-Monge, J., Moreno-Macias, H., Del Rio-Navarro, B., & David, G. (2006). GSTM1 and GSTP1 and respiratory health in asthmatic children exposed to ozone. *Eur Respir J, 28*, 953-959.

Ross, M., Persky, V., Scheff, P., Chung, J., Curtis, L., Ramakrishnan, V., . . . Hryhorczuk, D. (2002). Effect of ozone and aeroallergens on the respiratory health of asthmatics. *Arch Environ Occup Health, 57*, 568-578.

Santanello, N., Barber, B., T.F., R., Friedman, B., Juniper, E., & J., Z. (1997). Measurement characteristics of two asthma symptom diary scale for use in clinical trials. *Eur Respir J, 10*, 646-651.

Scannell, C., Chen, L., Aris, R., Tager, I., Christian, D., Ferrando, R., . . . Balmes, J. (1996). Greater ozone-induced inflammatory responses in subjects with asthma. *Am. J. Respir. Crit. Care Med., 154*, 24-29.

Schelegle, E., Morales, C., Walby, W., Marion, S., & Allen, R. (2009). 6.6-Hour Inhalation of Ozone Concentrations from 60 to 87 Parts per Billion in Healthy Humans. *Am J Respir Crit Care Med, 180*, 265–272.

Schwartz, J. (2005). How sensitive is the association between ozone and daily deaths to control for temperature? *Am J Respir Crit Care Med., 171*, 627-631.

Shingo, S., Zhang, J., & Reiss, T. (2001). Correlation of airway obstruction and patient-reported endpoints in clinical studies. *Eur Respir J*, 220–224.

Silverman, R., & Ito, K. (2010). Age-related association of fine particles and ozone with severe acute asthma in New York City. *J Allergy Clin Immunol*, 367-373.

Smith, A. (2014). *Comments Regarding Effects Thresholds for Long-Term Mortality Risk (for the May 28, 2014 CASAC teleconference on the Ozone NAAQS).*

Smith, R., Xu, B., & Switzer, P. (2009). Reassessing the relationship between ozone and short-term mortality in U.S. urban communities. *Inhal Toxicol, 21*(S2), 37-61.

Spengler, C., & Shea, S. (2000). Endogenous Circadian Rhythm of Pulmonary Function in Healthy Humans. *Am J Respir Crit Care Med, 162*, 1038-1046.

Sridevi, G., & Sembulingam, P. (2013). Impact of diurnal rhythm on pulmonary functional Status in Normal Subjects. *Unique J Med Dental Sci , 01*(01). Retrieved from www.ujconline.net

Strickland, M., Darrow, L., Klein, M., Flanders, W., Sarnat, J., Waller, L., & Sarnat, S. (2010). Short-term Associations between Ambient Air Pollutants and Pediatric Asthma Emergency Department Visits. *Am J Respir Crit Care Med, 182*, 307-316.

Teeter, J., & Bleecker, E. (1998). Relationship Between Airway Obstruction and Respiratory Symptoms in Adult Asthmatics. *Chest, 113*(2).

Tolbert, P., Klein, M., Peel, J., Sarnat, S., & Sarnat, J. (2007). Multipollutant modeling issues in a study of ambient air quality and emergency department visits in Atlanta. *J Exposure Sci Environ Epidemiol, 17*, S29–S35.

Wang, X., Hu, W., & Tong, S. (2009). Long-term exposure to gaseous air pollutants and cardio-respiratory mortality in Brisbane, Australia. *Geospat Health, 3*, 257-263.

Wiwatanadate, P., & Liwsrisakun, C. (2011). Acute effects of air pollution on peak expiratory flow rates and symptoms among asthmatic patients in Chiang Mai, Thailand. *215*, 251-257.

Zanobetti, A., & Schwartz, J. (2008). Mortality Displacement in the Association of Ozone with Mortality: An Analysis of 48 Cities in the United States. *Am J Respir Crit Care Med*, 184-189.

TABLE 1: STUDIES USED BY EPA TO ESTIMATE RISK IN THE HEALTH RISK AND EXPOSURE ASSESSMENT (HREA)

Study	EPA Claims	Effects Evaluated	Age of Participants Cities Represented in Risk Assessment	Interpretation
Lung Function Decline				
Adams, 2002	EPA claims that "Taken together, these data indicate that mean FEV_1 is clearly decreased by 6.6-hour exposures to 60 ppb ozone and higher concentrations in subjects performing moderate exercise."	FEV_1 Decrements	19 – 35 yrs Atlanta Baltimore Boston Chicago Cleveland Dallas Denver Detroit Houston Los Angeles Philadelphia New York City Sacramento St. Louis Washington DC	Laboratory studies consistently demonstrate that statistically significant lung function decrements that meet the accepted definition of "adverse" (FEV_1 decrease accompanied by respiratory symptoms) and the threshold EPA uses for judging clinical relevance (i.e., $\geq$ 10% decrease in FEV_1) do not occur until ozone concentrations of 88 ppb or higher are reached. • Adams (2002) observed a statistically significant decrease in FEV_1 accompanied by respiratory symptoms at 80 ppb but the FEV_1 decrease did not reach a level considered clinically relevant by EPA (i.e., $\geq$ 10% decrease in FEV_1) until concentrations reached 120 ppb. • Adams (2006) reported a statistically significant decrease in FEV_1 accompanied by respiratory symptoms at 80 ppb but the FEV_1 decrease did not reach the 10% level considered clinically relevant by EPA at any of the concentrations tested (i.e., 40, 60, or 80 ppb). • Schelegle et al. (2009) observed a statistically significant decrease in FEV_1 accompanied by respiratory symptoms (i.e., meets definition of "adverse") at 72 and 81 ppb, but the decrease in FEV_1 did not reach the 10% level considered clinically relevant by EPA until a concentration of 88 ppb was reached. • Kim et al. (2011)observed a statistically significant decrease in FEV_1 and an increase in inflammation of the airways at 60 ppb, but the decrease in FEV_1 was small (< 2%; i.e., not clinically meaningful) and not accompanied by respiratory symptoms (i.e., not "adverse"). Statistical significance achieved at 60 ppb is likely the result of omitting data on concentrations other than 60 ppb and time intervals other than 6.6 hours, which likely biased the analysis toward detecting a difference between the filtered air control and 60 ppb ozone exposure scenarios.
Schelegle et al., 2009				
Kim et al., 2011 [a]				
Hospital Admissions				
Medina-Ramone et al., 2006[a]	EPA uses this study to support an association between short-term ozone exposure and chronic obstructive pulmonary	Hospital Admissions for chronic obstructive pulmonary disease	$\geq$ 65 yrs Atlanta Baltimore Boston	Reporting of same day decreases in hospital admissions is biologically implausible and casts doubt on the reliability of the study. • The study found that increased ozone causes : - Decrease in same day chronic obstructive pulmonary disease hospital admissions;

Study	EPA Claims	Effects Evaluated	Age of Participants Cities Represented in Risk Assessment	Interpretation
	disease hospital admissions		Chicago Cleveland Detroit Houston Los Angeles Philadelphia New York City Sacramento St. Louis	- Increase in next day chronic obstructive pulmonary disease hospital admissions; and - When summed across 2 days, there was a small increase in chronic obstructive pulmonary disease hospital admission – this was used in EPA risk assessment and conceals counter-intuitive result for same day hospital admissions. • City-specific results were highly variable. Individual-city associations for chronic obstructive pulmonary disease and hospital admissions ranged from –30% to +40% for a 30 ppb increase in the summer 8-hour ozone concentration. Therefore, EPA's use of a single point estimate conceals observed variation in results. • The cities included in the study were not randomly selected and do not provide good geographic coverage of the US, despite that this was one of EPA's primary stated goals in selecting epidemiology studies for use in the HREA. Therefore, combining results across cities is not representative of national response.
Linn et al., 2000	EPA relies upon this study as evidence of association between short-term ozone concentrations and cardiovascular Emergency Department visits or hospital admissions	Hospital Admissions and Emergency Department visits for Pulmonary conditions	All Ages Los Angeles	Use of study in EPA risk assessment produced results suggesting that public health in Los Angeles will suffer if the NAAQS is reduced - a counter-intuitive result. This and the additional findings below suggest this study is unreliable and should not have been relied upon by EPA. For example, the study found: • Only a few equivocally positive relationships with increased ozone levels and hospital admissions or emergency department visits and only when other pollutants and heat stress confounded results. • Increased ozone level was associated with either negative (increased ozone associated with decreased hospital admissions) or non-significant positive relationships with cardiovascular, pulmonary, and cerebrovascular hospital admissions in year-round and single season analyses. • Only positive associations occurred when normal model parameters were not included (i.e., temperature or other meteorological variables) – study does not support that ozone causes an increase in hospital admissions. • Summer ozone did not present higher risk of hospital admissions, which is inconsistent with other studies.
Lin et al., 2008	EPA uses this study to support an association between short-term ozone concentrations and	Hospital admissions for Respiratory conditions (primarily	< 18 yrs	This study found mixed results for the association between ambient ozone level and respiratory hospital admissions in different regions of New York (New York City is only region included in EPA risk assessment). • Associations were statistically significant in only 5 of 11 regions in New York.

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	pediatric respiratory hospital admissions in New York state	asthma)	New York City	• Found relatively small increases in respiratory-related hospital admissions that were highly variable (i.e., uncertain). • This study produced much lower risk estimates than Silverman and Ito for New York City, possibly due to slightly different latency periods assumed, and control for more confounding effects (e.g., PM10). • It is unclear how the addition of this study added any clarity to EPA's risk assessment since NYC was included in the Medina-Ramon et al. (2006) study and produced higher estimated hospital admissions (COPD) than this study (lung disease).
Silverman and Ito, 2010	EPA relies upon this study as evidence that children are at increased risk of ozone-induced asthma hospital admissions, as compared to adults.	Hospital admissions for Asthma – ICU/non-ICU	< 6 yrs 6-18 yrs 19 – 49 yrs New York City	The study found: • Increase in relative risk for ICU admissions in 6-18 yr group. • Increase in relative risk for non-ICU admissions in all age groups. • Control for PM2.5 caused risk for ICU admissions in 6-18 yr group to become insignificant • Same associations not observed for adults. • It is unclear how the addition of this study added any clarity to EPA's risk assessment since NYC was included in the Medina-Ramon et al. (2006) study, although it produced lower estimated hospital admissions (COPD) than this study (asthma).
APHENA; Katsouyanni et al. 2009[a]	EPA relies upon this study to support ozone-related increase in respiratory hospital admissions.	Hospital admissions for cardiovascular and Respiratory conditions	≥ 65 yrs Detroit	Study does not provide good support for an association between ozone and increased hospital admissions. • US estimates became statistically insignificant when controlled for PM10. • EPA only used the positive results (showed an association with increased hospital admissions) that were not corrected for PM10 in its risk assessment-example of hand-picking data that support EPA's position. • EPA limited the study's use to Detroit only, despite fact that its inclusion would have resulted in better geographic coverage. - Only 2 of the 14 US cities included in this study coincide with 12 Urban Areas evaluated in EPA risk assessment; - Additional cities from this study could have been included in risk assessment to provide better geographic coverage across US.

Study	EPA Claims	Effects Evaluated	Age of Participants Cities Represented in Risk Assessment	Interpretation
Emergency Department Visits				
Tolbert, 2007[a]	EPA relies upon this study to provide evidence of an association between short-term ozone concentrations and asthma-related emergency department visits	Emergency Department visits for Respiratory conditions	All Ages Atlanta	Original Atlanta Study – evaluated air quality data and respiratory emergency department visits in Atlanta from 1993 – 2004. • Looked at the effects on all age groups; • Air quality data were averaged across multiple monitors; • In EPA's risk assessment, hospital admission estimates were significantly reduced by correction for PM10 (PM10 corrected estimates similar to Darrow et al. [2011] estimates); • By comparison to Strickland et al., (2010) and Darrow et al. (2011) illustrates sensitivity of results to: - Populations evaluated; - Inclusion of secondary variables that can affect the association between ozone and emergency department visits; - Averaging of ambient pollutant concentrations; and latency periods (period between ozone exposure and hospital admission) chosen. • It is unclear how the inclusion of 3 studies using the same data for the same city, but producing widely variable results, added any clarity to EPA's risk assessment (see discussion of Strickland et al. (2010) and Darrow et al. (2011).
Strickland et al., 2010[a]			5-17 yrs Atlanta	Reanalysis of original Atlanta Study by Tolbert et al. (2007) – evaluated same air quality data and respiratory emergency department visits as Tolbert et al. (2007) in Atlanta from 1993 – 2004. • Looked at the effects on children in 5 – 17 yrs; • Air quality data were population weighted instead of simply averaging across multiple monitors as in Tolbert et al. (2007); • In EPA risk assessment, estimates of emergency department visits were similar to those from Tolbert et al. (2007) and Darrow et al. (2011) when 2-day latency period (period between ozone exposure and emergency department visit) was selected; • In EPA risk assessment, estimates of emergency department visits were much higher than those from Tolbert et al. (2007) and Darrow et al. (2011) when 7-day latency period was chosen - it is not biologically plausible that an emergency department visit for asthma would be associated with previous 7 days of ozone concentrations (ozone causes effects soon after exposure) and these results should not have been relied upon by EPA;

Study	EPA Claims	Effects Evaluated	Age of Participants Cities Represented in Risk Assessment	Interpretation
				• By comparison to Tolbert et al., (2007) and Darrow et al. (2011) illustrates sensitivity of results to: - Populations evaluated; - Inclusion of secondary variables that can affect the association between ozone and emergency department visits; - Averaging of ambient pollutant concentrations; and latency periods (period between ozone exposure and hospital admission) chosen.
Darrow et al., 2011[a]	EPA relies on this study as evidence for an association between short-term ozone concentrations and respiratory emergency department visits in Atlanta		All Ages Atlanta	Reanalysis of original Atlanta Study by Tolbert et al. (2007) – evaluated same air quality data and respiratory emergency department visits as Tolbert et al. (2007) in Atlanta from 1993 – 2004. • Looked at all ages (same as Tolbert et al. [2007]); • Air quality data obtained from single central monitor instead averaging across multiple monitors as in Tolbert et al. (2007) or taking population weighted average as in Strickland et al. (2010); • Produced lowest hospital admission estimates of three Atlanta studies, even without correcting for any co-pollutants; • By comparison to Tolbert et al., (2007) and Strickland et al. (2010) illustrates sensitivity of results to: - Populations evaluated; - Inclusion of secondary variables that can affect the association between ozone and emergency department visits; - Averaging of ambient pollutant concentrations; and latency periods (period between ozone exposure and hospital admission) chosen
Ito, 2007[a]	EPA relies upon this study to provide evidence of association between short-term ozone concentrations and asthma-related emergency department visits	Emergency Department visits for Asthma	All Ages New York City	• Study showed:Increases in asthma-related emergency department visits, but the results were uncertain (i.e., variable); • Ambient concentrations were not associated with their corresponding personal exposures for any of the pollutants, except for PM2.5.

Study	EPA Claims	Effects Evaluated	Age of Participants Cities Represented in Risk Assessment	Interpretation
Respiratory Symptoms				
Gent 2003	EPA relies upon this study as evidence of an association between short-term ozone concentrations and respiratory symptoms, and medication use in children with asthma	Respiratory symptoms: wheeze, persistent cough, chest tightness, shortness of breath	< 12 yrs asthmatic) Boston	The study found that increased ozone concentrations did not increase respiratory symptoms or medication use in asthmatics. This study does not support EPA's position that ozone increases symptoms/medication use in asthmatics. The only statistically significant result was in co-pollutant model with PM2.5, indicating that ozone was not capable of causing the increase in symptoms/medication use by itself. The study had these flaws: • It relied on subjective symptom reporting by subject's mothers, which may have biased the effect estimates; • It covered a relatively small population (271) of children born into families with at least one child that already had asthma (genetic predisposition toward asthma); • It included symptoms and medication use recorded on symptom/medication calendars by child's mother (i.e., non-standard reporting); • Results were obtained for Connecticut and Springfield, MA and used for Boston - errors were likely introduced by extrapolating relationships identified in one population to a completely different population.
Short-Term Mortality				
Smith et al., 2009	EPA relies upon this study as evidence of suggesting increased mortality risks in northeastern cities due to exposure to ozone.	Non-accidental deaths due to Respiratory and Cardiovascular problems	All Ages Atlanta Baltimore Boston Chicago Cleveland Detroit Houston Los Angeles Philadelphia New York City Sacramento St. Louis	While EPA uses an average mortality coefficient derived from this study (by averaging across cities included) to estimate increased mortality risk in association with ozone, the study found a negative association between ozone concentrations and mortality in some cities (e.g., Southwest, Urban Midwest). EPA's use of these results was inappropriate because: • Cities included in the study cover about 40% of the US and their selection was not based on a random nationally-based sample. Therefore, combining results across cities is not representative of national response. • Results were extremely variable across cities, and the mortality coefficient was statistically significant for only 6 of 95 cities, making the combining of results across cities even more problematic. • EPA ignored evidence presented in the study for a threshold, or at least different slopes within different concentration intervals. EPA's use of a "No Threshold" model to predict short-term mortality in its risk assessment using the Smith et al. (2009) results, which likely resulted in a significant overestimate of short-term mortality. "No Threshold" models assume that there is no ozone concentration

Study	EPA Claims	Effects Evaluated	Age of Participants Cities Represented in Risk Assessment	Interpretation
				too low to cause mortality. However, there is evidence that there is an ozone mortality threshold and EPA continually ignores it.
Zanobetti and Schwartz, 2008[a]	EPA relies upon this study as additional support for an association between short-term ozone concentrations and respiratory mortality	Non-accidental deaths due to Respiratory and Cardiovascular problems	All Ages Atlanta Baltimore Boston Chicago Cleveland Detroit Houston Los Angeles Philadelphia New York City Sacramento St. Louis	EPA's use of these results was inappropriate because: • Cities included in study only cover about 20% of the US and were not selected based on a random nationally-based sample. Therefore, combining results across cities is not representative of national response. • Results across cities were extremely variable, and the mortality coefficient was only statistically significant for 4 of 48 cities, making the combining of results across cities even more problematic.
Long-Term Mortality				
Jerrett et al., 2009	EPA relies upon this study as providing the strongest evidence for association between long-term ozone concentrations and mortality, which remained robust after adjusting for PM2.5 concentrations	Respiratory, cardiovascular, cardio-pulmonary conditions	≥ 30 yrs Atlanta Baltimore Boston Chicago Cleveland Detroit Houston Los Angeles Philadelphia New York City Sacramento St. Louis	EPA placed its focus entirely on this study in its assessment of the association between long-term ozone exposure and mortality. No other long-term studies have reported associations with cardiopulmonary mortality that remained positive once other pollutants were accounted for (i.e., ozone was not the culprit). EPA's use of these results was inappropriate because: • This study does not provide clear evidence of an association with long-term mortality. • This study did not adequately control for PM2.5. It used only 2 years of annual PM2.5 data, but 24 years of daily maximum hourly ozone data and the potential for confounding by other co-pollutants was not evaluated at all. • Cities covered in the study were not randomly selected and, therefore, combining results across cities is not representative of national response. • The study showed inverse associations between ozone and cardiovascular and all-cause mortality, which is counter-intuitive and casts doubt on the validity of the results. • EPA's used a "No Threshold" model to predict long-term mortality in its risk assessment using the Jerrett et al. (2009) results and this likely resulted in a

Study	EPA Claims	Effects Evaluated	Age of Participants Cities Represented in Risk Assessment	Interpretation
				significant overestimate of long-term mortality. "No Threshold" models assume that there is no ozone concentration too low to cause mortality. However, there is evidence that there is an ozone mortality threshold and EPA continually ignores it.

[a] Partly or full funded by EPA

Acronyms:

EPA – Environmental Protection Agency
FEV_1 – Forced expiratory volume in 1 second
HREA – Health Risk and Exposure Assessment for Ozone (EPA, 2014a)
ICU – Intensive Care Unit
NAAQS – National Ambient Air Quality Standard