

A Toxicological Review of the Ozone NAAQS

Michael Honeycutt, Ph.D. and Stephanie Shirley, Ph.D.
Toxicology Division, Texas Commission on Environmental Quality

The Texas Commission on Environmental Quality (TCEQ) strives to protect our state's public health and natural resources consistent with sustainable economic development. To accomplish this mission, we base decisions on the law, common sense, sound science, and fiscal responsibility and we strive to ensure that regulations are necessary, effective, and current. In accordance with this mission, the TCEQ agrees with EPA that the NAAQS for ozone should protect public health. However, we would like to emphasize that modeling presented in the Health Risk and Exposure Assessment (HREA) for ozone indicates a lower standard may result in additional premature mortality for some areas of the country, including Houston (figures 7B-2, 7B-4, and appendix 7).

EPA presented the information below in black text in Chapter 7 of the HREA, i.e. the core analysis. We added the red text, summing the total impact of ozone reductions on mortality in Houston to reflect the information presented in Appendix 7, but not the core analysis. According to EPA's modeling, the net result will be an *increase* in mortality in Houston for any of the alternative standards under consideration.

Number of Premature Mortalities Predicted by EPA to Occur in Houston		
	Presented by EPA in Chapter 7	Based on Full Analysis found in Appendix 7
Meeting Current Standard (75 ppb) from Present Day (2007) Ozone Levels	Not presented	47 More
Going from 75 ppb to 70 ppb	1 more	48 More
Going from 75 ppb to 65 ppb	3 Less	44 More
Going from 75 ppb to 60 ppb	12 Less	35 More
2009 Data from Final draft of HREA		

In addition, when considering alternative O₃ standards (60-70 ppb), the lower end of the proposed range is not well-supported. In fact, EPA states in its Policy Assessment (PA) for

ozone that at lower concentrations "...the likelihood and magnitude of a response becomes increasingly uncertain..." (PA p3-1) and elsewhere that the "...the relative importance of background O₃ would increase ...with a lower level of the O₃ NAAQS" (PA p2-27).

Our conclusions are summarized below and are based on a thorough evaluation of the relevant scientific literature as well as the analysis presented by EPA in its HREA and PA for ozone. This evaluation was conducted by our Toxicology staff, which consists of 9 PhD and 5 Master's level scientists, including 3 certified by the American Board of Toxicology, and collectively representing over 150 years of experience. These individuals specialize in toxicology and risk assessment related to air contaminants. The methods employed by our scientists are state of the science, peer reviewed, and published. These guidelines and resulting toxicity factors are used by several other states as well as other countries, including Canada, Australia, Israel, Taiwan, Austria, Belgium, Mexico, China, and the Netherlands. While the EPA sets NAAQS standards for 6 pollutants, the TCEQ establishes acceptable levels for thousands (>5000) of air contaminants.

It is our determination, based on an evaluation of the available scientific information, that EPA has not made the case that a lower standard will improve public health, especially in light of their prediction of *increased* mortality as a result of *lower* ozone levels, as shown in the table above.

A thorough weight of evidence is lacking in EPA's analysis.

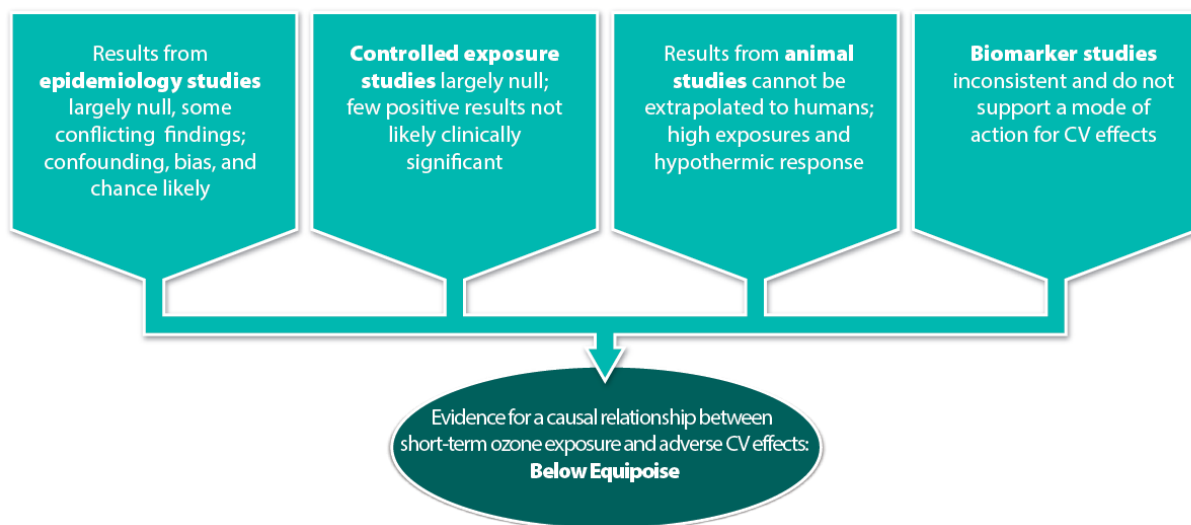
It is not clear how EPA has applied its weight of evidence framework to integrate results from human clinical studies, epidemiological studies, and animal studies. Throughout the draft document, studies are described as "positive" without indicating whether the results were statistically significant, biologically plausible, clinically meaningful, or consistent with other studies. For example, it is not clear how newer studies (Smith *et al.* 2009, Zanobetti and Schwartz 2008, and Jerrett *et al.* 2009) were weighed against other studies that reported "small associations or no associations" between ozone and mortality. In its consideration of weight of evidence, it is not clear how EPA evaluated consistency across studies or whether evidence evaluated across realms was ultimately considered.

A rigorous weight of evidence evaluation should be conducted, rather than giving positive results more weight than null results simply because they are positive. Based on EPA's incomplete evaluation of the evidence, it is not clear that there are causal relationships for health effects at ozone exposures below the current standard. EPA should use a rigorous weight of evidence as recommended by the National Academy of Sciences (NAS), and should not make policy judgments without assessing all of the available evidence.

The draft HREA uses endpoints previously determined to have "Suggestive," "Likely Causal" as well as "Causal" relationships with ozone exposure. Only endpoints with sufficient evidence to indicate a causal association should be used in setting a NAAQS. Therefore, only respiratory endpoints that can be demonstrated to be caused by short-term exposure to ozone should be used. It is especially problematic to use mortality supposedly related to long-term exposure to ozone as this was categorized as merely "Suggestive" in the ISA and lacks adequate evidence from scientific literature to be utilized in setting a standard. EPA should select endpoints that have clear biological plausibility and clinical significance.

The selection of endpoints is inappropriate in some cases, e.g. cardiovascular effects.

In the 2013 ISA, EPA stated that the epidemiology evidence for cardiovascular endpoints is inconsistent and lacks coherence across realms of evidence. Although EPA determined that the evidence was sufficient to conclude a “likely” causal relationship between short-term ozone exposure and cardiovascular-related endpoints, a thorough review of the literature reveals mixed results. In a soon-to-be-published report, Goodman *et al.* (2014) rigorously evaluated the studies reviewed by EPA as well as additional available literature. The authors reviewed 90 epidemiology studies, 8 controlled human exposure studies, 11 experimental animal studies, and 26 biomarker studies. Using a systematic weight of evidence approach it was determined that the available studies reported mixed results with positive, null and negative associations being reported. There was no consistent evidence that ozone affects biomarkers of inflammation, coagulation, oxidative stress, lipids and glucose metabolism, or overall cardiovascular health. There was no consistency in effects (e.g. increase versus decrease) and effects were often in the opposite direction of an adverse effect. Based on this information, the mode-of-action data do not support a biologically plausible mechanism for cardiovascular effects of ozone. Taken together, the weight of evidence (see figure below) indicates that a causal relationship between short-term exposure to ambient ozone levels and adverse effects on the cardiovascular system is not likely in humans. Put another way, while a few studies might have found a correlation between ozone concentrations and heart attacks, the overall weight of the evidence does not lead to the conclusion that low-level ozone exposure causes heart attacks. These results indicate that there is not adequate evidence of a causal relationship and therefore cardiovascular endpoints should not be included in the PA.



Lung function decrements are not likely to be adverse.

The EPA has selected hypothetical lung function decrements over specific cutoff values ($\geq 10\%$, 15% , or 20%) in one year. However, determining the percent or number of individuals that experience at least one hypothetical FEV₁ decrement over a particular cutoff likely overestimates the significance of individual responses, particularly at lower ozone exposure levels because of the individual variability of FEV₁ when measured by spirometry. Indeed, Pellegrino *et al.* 2005 noted that FEV₁ decrements can vary by as much as 5% in healthy adults within a single day and by 15% or more from year to year. Moreover, this same study noted that changes in FEV₁ correlate “poorly with symptoms and may not, by itself, accurately predict clinical severity or prognosis for individual patients.” In addition, because the selected model estimates individuals with at least one hypothetical lung function decrement over each of the cutoffs, it is possible that many of the selected individuals have only a single occurrence of effect which is of questionable clinical significance.

The draft HREA does not accurately reflect the available data addressing the selected lung function endpoint of FEV₁ decrements. The low concentration studies by Adams *et al.* (2002 and 2006), Schelegle *et al.* (2009), and Kim *et al.* (2011) all indicate a threshold below 70 ppb at which there are no statistically significant adverse effects associated with ozone. EPA should explain its rationale for modeling risks below 70 ppb ozone levels when controlled human exposure studies do not indicate effects at these exposure levels.

In the HREA, EPA describes the exercise patterns in the clinical studies examining lung function as “moderate” when individuals exercised 50 minutes of each hour for a prolonged period of 6.6 hours. However, as noted in Folinsbee *et al.* 1988 and McDonnell *et al.* 1991, this simulates work performed during a day of heavy manual labor in outdoor workers. In fact, exercise at this level for 6 to 8 hours should be considered as “heavy” or “strenuous” instead. We would like to point out that CASAC commented on this in the first draft HREA, saying the clinical studies cited by EPA used “...unrealistic elevated minute ventilations” and that “overall ventilations are \geq mean ventilations that might be encountered during a day of heavy severe manual labor and represents the higher end of ventilations that might be encountered in the normal population for this prolonged period (6.6 h).”

Finally, EPA has focused much of its attention on small hypothetical changes in FEV₁. Other endpoints, such as respiratory symptoms, are generally required to determine if an individual is truly experiencing an adverse effect. In fact, the American Thoracic Society (2000) guidelines for identifying adverse effects link pulmonary changes with respiratory symptoms, clearly stating that reversible loss of lung function *in conjunction with* symptoms should be considered adverse. Thus, while FEV₁ may be a useful and sensitive biomarker, taken alone, it likely overestimates the number of individuals experiencing adverse effects. In addition, these lung function decrements would be transient, reversible, would not interfere with normal activity and would not result in permanent injury or respiratory dysfunction (Goodman *et al.* 2013).

The table below was taken from Pellegrino *et al.* 2005, an American Thoracic Society/European Respiratory Society joint publication, describes severity of FEV₁ decrements. Note that a change in FEV₁ of less than 30% is considered mild. This is in contrast with EPA’s analysis which designates changes in FEV₁ of 10% as adverse.

TABLE 6 Severity of any spirometric abnormality based on the forced expiratory volume in one second (FEV₁)

Degree of severity	FEV ₁ % pred
Mild	>70
Moderate	60–69
Moderately severe	50–59
Severe	35–49
Very severe	<35

% pred: % predicted.

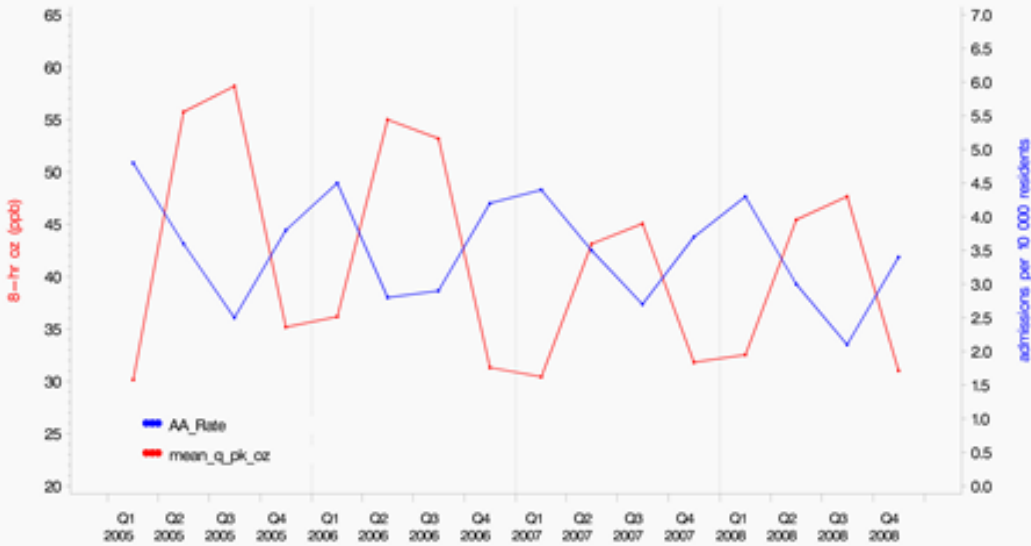
The evidence for ozone-caused new-onset asthma is insufficient.

Throughout the draft HREA, EPA indicates its belief that ozone causes asthma. In fact, CASAC has repeatedly indicated that the limited evidence on new-onset asthma should not contribute greatly to the consideration of the strength of evidence for respiratory-related effects. In addition, the draft HREA states that “[i]n the case of respiratory symptoms, the evidence is most consistently supportive of the relationship between short-term ambient O₃ metrics and respiratory symptoms and asthma medication use in children with asthma...” However, it is not clear that the findings of two multi-city studies, Schildcrout *et al.* (2006) and O’Connor *et al.* (2008) have been considered. In fact, it is more accurate to say that the evidence for this endpoint is mixed.

The TCEQ analyzed data in 2000 to determine if asthma hospitalizations correlated with ozone concentrations. It was determined that there was an inverse relationship; that is, when ozone levels were high (red lines), asthma-related hospitalizations (blue lines) were low and when ozone levels were low, asthma-related hospitalizations were higher. These results suggest that ambient ozone concentrations are not the primary cause of asthma-related hospital admissions. The full results are included as an attachment. For the purposes of illustration, results for Dallas and Denton Counties are presented below.

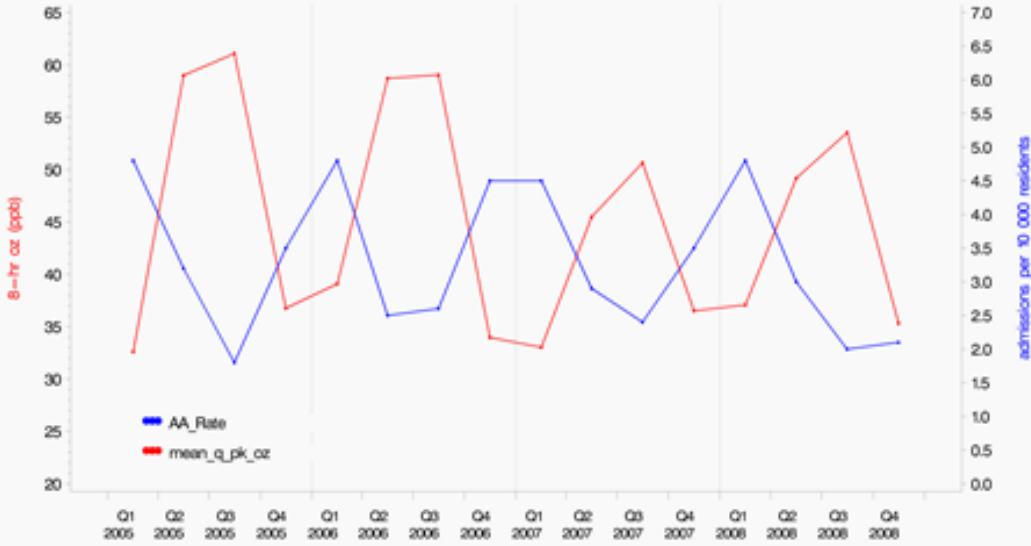
Dallas County

Quarterly Average Peak 8-hr Ozone vs Quarterly Hospital Age-Adjusted Admission Rate, Dallas County



Denton County

Quarterly Average Peak 8-hr Ozone vs Quarterly Hospital Age-Adjusted Admission Rate, Denton County



It is important to emphasize that although the causes of asthma are not fully understood, there are many factors that influence the development and exacerbation of asthma. According to the World Health Organization, one of the strongest risk factors for developing asthma is genetic predisposition. In addition, indoor allergens (dust mites, pet dander, and presence of pests such as rodents or cockroaches) together with outdoor allergens (pollen and mold), tobacco smoke, or other triggers such as cold air, extreme emotions (anger or fear) and physical exercise can all provoke symptoms in those with asthma. The Centers for Disease Control and Prevention estimates that asthma prevalence has increased over recent years from 7.3% in 2001 to 8.4% in 2010¹. The reason for this increase is unknown, but some scientists have suggested changes in exposure to microorganisms (hygiene hypothesis) or the rise in sedentary lifestyle (affecting lung health) and obesity (which results in inflammation) may be to blame (Delgado et al. 2008).

Mortality analysis in the draft HREA is especially problematic.

EPA estimates short-term mortality impacts based on Zanobetti and Schwartz (2008) and Smith *et al.* (2009). However, the Concentration Response Functions (CRFs) vary from negative to positive for the same city, depending on which study is selected, ozone averaging time, model specifications, and ozone season. In fact, many of these estimates are indistinguishable from zero. It is not clear how these issues were considered by EPA or how the various choices of CRFs were weighed. In addition, these studies also indicate the confounding effects of co-pollutants such as PM and sulfate, which were not adequately considered by EPA because single pollutant CRFs were utilized in the core analysis.

The important information regarding the impact of co-pollutants which is presented in the appendix for Chapter 7 is not adequately communicated in the main text of the draft HREA. Namely, that for a number of cities, the sensitivity analysis indicates that upon inclusion of PM₁₀ in a co-pollutant model, virtually all of the risk estimates for short-term mortality become non-significant. In addition, use of an alternate CRF from the Zanobetti and Schwartz (2008) paper results in similar findings of largely non-significant ozone-attributable mortality.

In the HREA, Figure 7-2 presents heat maps for short-term ozone-attributable mortality. It is unclear how 149 ozone-attributable deaths occur at 40-45 ppb while no deaths are due to levels >65 ppb or that there is no discernable pattern for increased/decreased risk depending on concentration. This appears to be an artifact of assuming a linear, no-threshold relationship between mortality and ozone that leads to nonsensical results.

EPA also estimates long term mortality impacts based on Jerrett *et al.* 2009. Long-term mortality was not listed on page 7-17 and 18 of the HREA under ozone-attributable effects nor is it listed as a causal endpoint in ISA. This calls into question the appropriateness of including mortality as an endpoint in the HREA. In addition, the use of the Jerrett study is concerning, as other studies of this cohort reported no associations between long-term ozone exposure and cardiopulmonary mortality that are robust to adjustment for co-pollutants (e.g., Krewski *et al.* 2000; Pope *et al.* 2002). In addition, other long-term studies of ozone-related respiratory or cardiopulmonary mortality did not report positive associations (Goodman *et al.* 2013; Dockery *et al.* 1993; Beeson *et al.* 1998; Abbey *et al.* 1999; Chen *et al.* 2005; Miller *et al.* 2007; Lipfert *et al.* 2000 for mean O₃; Lipfert *et al.* 2006; Wang *et al.* 2009; Jerrett *et al.* 2005). Moreover, it is inappropriate to

¹ <http://www.cdc.gov/nchs/data/databriefs/db94.htm>

combine data across cities for a national risk estimate, given the known geographic heterogeneity of these estimates (Goodman *et al.* 2013; Smith *et al.* 2009). Finally, data relating to potential confounders, e.g. smoking rates, obesity rates, diet, medication usage, etc., was collected in 1982–1983 for the ACS study but never updated. For these reasons, the national risk estimate reported by Jerrett *et al.* (2009) should not be extrapolated throughout the U.S.

The tables below summarize the available evidence addressing long-term exposure to ozone and mortality. Overall, the results are not statistically significant (i.e. the confidence intervals include 1.0), especially in models that account for co-pollutants. Only one study (highlighted in pink) Jerrett *et al.* (2009), found a statistically significant effect of long-term ozone exposure on mortality when not corrected for co-pollutant exposure. Interestingly, the effect only occurred at temperatures above 82°F. It is well known that very warm or very cold temperatures are associated with increases in mortality (Ye *et al.* 2012). Paradoxically, the increased mortality was not observed in US regions with the highest ozone concentrations (southern California) nor in areas with the highest number of respiratory deaths (the northeastern US and the industrial Midwest). The Jerrett *et al.* (2009) study used the American Cancer Society (ACS) Cohort. Other researchers have examined the same cohort and have not found an effect of ozone on mortality.

Table 1 Epidemiology Studies of Long-term Ozone Exposure and Mortality

Study	Cohort	n	Time Period of		Seasonal or All Year	Ozone Metric	Outcome	Copolutant(s) in Model	Risk Measure	Unit of Measure	Estimate	95% Confidence Interval	
			Mortality Analysis	Ozone Data									
Dockery et al. (1993)	Harvard Six Cities cohort (US)	8.9 mil.	1974-1989	1977-1985	All year	NR	All-cause	None	Rate ratio	Varied	1.0-1.26 ^a	NR	
Abbey et al. (1999)	AHSMOG cohort of non-smokers (CA)	6,338	1982-1998	1982-1998	All year	Monthly avg.	Lung cancer	None	RR (M) RR (F)	Per 12 ppb; >100 ppb	4.19	1.81-9.69	
							NM lung				RR (M) RR (F)	1.39 1.20	0.52-3.67 0.88-1.47
							Cardiopulmonary				RR (M) RR (F)	1.20 1.01	0.77-1.33 1.06
							All natural causes				RR (M) RR (F)	0.88 1.14	0.75-1.02 0.98-1.32
											RR (M) RR (F)	0.90	0.80-1.02
											RR (M) RR (F)	1.10 ^d 1.00 ^d	1.00-1.20 0.99-1.01
Lipfert et al. (2000)	US veterans cohort, 31 cities	50,000	1975-1981	1975-1981	All year	Current peak ^b Peak, delayed ^b	All-cause mortality	None	RR	Per 1000 ppb	1.10 ^d 1.00 ^d	1.00-1.20 0.99-1.01	
Pope et al. (2002)	ACS cohort, 134 metropolitan areas	500,000	1982-1998	1980-1998	All year	1-hr max	All other causes ^d	None	RR	N/A	0.98	0.90-1.05	
					July-Sept						1.00	0.95-1.05	
					All year						1.01	0.95-1.10	
					July-Sept						1.05	0.98-1.11	
					All year						1.10	0.95-1.21	
					July-Sept						1.11	0.99-1.20	
					All year						0.90	0.80-1.10	
					July-Sept						0.95	0.85-1.10	
Chen et al. (2005)	AHSMOG cohort (CA)	3,239	1973-1998	1977-1998	All year	Monthly avg.	Coronary heart disease	None	RR (M) RR (F)	Per 10 ppb	0.89 0.97	0.60-1.30 0.68-1.38	
									RR (M) RR (F)	0.98 0.99	0.96-1.01 0.98-1.01		
Jerrett et al. (2005)	ACS, 86 metropolitan areas (US)	22,905	1982-2000	1999-2001	All year	Peak	None	RR	N/A	0.98	0.96-1.01		
						Max 8-hr ^a				0.99	0.98-1.01		
						Peak				0.97	0.93-1.02		
						Max 8-hr ^a				0.98	0.95-1.02		
						Peak				0.97	0.94-0.99		
						Max 8-hr ^a				0.99	0.96-1.01		
						Peak				0.99	0.91-1.07		
						Max 8-hr ^a				0.97	0.91-1.03		
Lipfert et al. (2006a)	US Veterans cohort, 31 cities	70,000	1997-2001	1997-2001	All year	Peak	None	RR	Per 1 ppb	1.25	NR		
						24-hr avg.				0.82	NR		
						Peak				1.18	NR		
Lipfert et al. (2006b)	US Veterans cohort, 31 cities	70,000	1989-2001	1989-1996	All year	Peak	None	RR	Per 40 ppb	1.094	1.03-1.16		
			1997-2001	1999-2001	All year, counties with NO ₂ data					TD	1.080	1.02-1.15	
										None	1.035	0.92-1.17	
										TD	1.033	0.92-1.16	

Study	Cohort	n	Time Period of		Seasonal or All Year	Ozone Metric	Outcome	Copolutant(s) in Model	Risk Measure	Unit of Measure	Estimate	95% Confidence Interval								
			Mortality Analysis	Ozone Data																
Jerrett et al. (2009)	ACS cohort, 86 metropolitan areas (US)	448,850	1982-2000	1977-2000; 1999-2000 (PM)	Summer only (April-Sept)	1-hr max	All-cause	None	RR [†]	Per 10 ppb	1.001	1.00-1.01								
								PM			0.989	0.98-1.00								
							Cardiopulmonary	None	RR		1.016	1.01-1.02								
								PM			0.992	0.98-1.00								
							Respiratory	None	RR		1.027	1.01-1.05								
								PM			1.040	1.01-1.07								
							CV	None	RR		1.014	1.01-1.02								
								PM			0.983	0.97-0.99								
							IHD	None	RR		1.017	1.01-1.03								
								PM			0.973	0.96-0.99								
Krewski et al. (2009)	ACS cohort, 116 metropolitan areas	1.2 mil	1982-2000	1980	8-hr max	All-cause	All year	HR	Per 10 ppb	1.00	0.99-1.01									
							Summer (April-Sept)			1.02	1.01-1.02									
						Cardiopulmonary	All year			HR	0.99	0.98-1.01								
							Summer (April-Sept)				1.01	1.00-1.03								
						IHD	All year			HR	1.03	1.02-1.04								
							Summer (April-Sept)				0.99	0.96-1.01								
						Lung cancer	All year			HR	1.01	0.98-1.03								
							Summer (April-Sept)				1.01	0.99-1.02								
						All other causes	All year			HR	0.98	0.95-1.02								
							Summer (April-Sept)				1.00	0.96-1.04								
						Smith et al. (2009)	ACS cohort, 66 cities			352,000	1982-2000	NR	Warm season (second and third quarters)	8-hr max	All-cause	None	RR	Per 10 ppb	1.01 [†]	1.00-1.23
																Carbon and sulfate			1.00 [†]	0.99-1.01
															Carbon	1.00 [†]			0.99-1.02	
															Cardiopulmonary	None			1.03 [†]	1.01-1.05
												2003-2005	Cardiopulmonary	Carbon and sulfate	1.02 [†]	1.01-1.04				
														Carbon	1.02 [†]	1.00-1.04				
Cardiorespiratory	None	RR	1.002	0.99-1.02																
	NO ₂ and SO ₂		0.999	0.99-1.01																
Wang et al. (2009)	Cohort in Brisbane, Australia	887,955	1996-2004	1996-2004	All year	1-hr max	Cardiorespiratory	None	RR	Per 1 ppb	1.002	0.99-1.02								

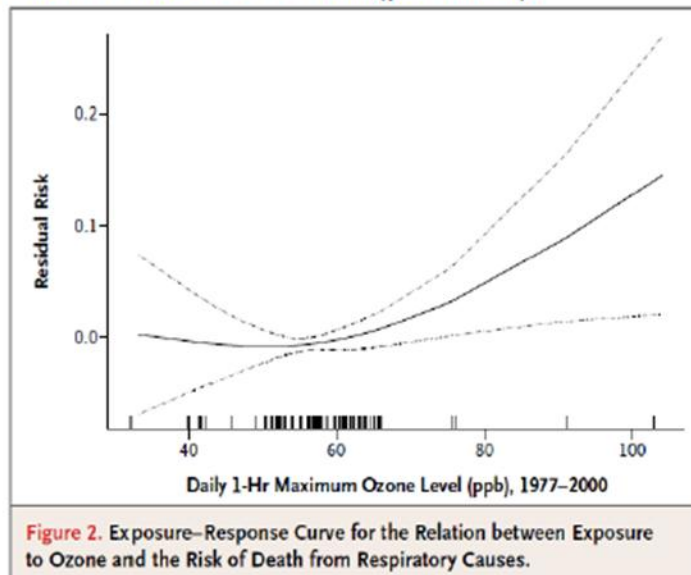
Only for temperatures >82°F, NOT in US regions with highest ozone concentrations (Southern CA) NOR in areas with highest respiratory deaths (NE and Industrial MW).

However, since EPA used the Jerrett study as the basis for their analysis, they should use the model that best fit the data. The figure below, taken from the Jerrett study, illustrates that a threshold model fits the data better than a non-threshold model. That is, there is a safe level of exposure to ozone. However, this was not the model that was utilized by EPA.

Figure 2 illustrates the shape of the relation between exposure to ozone and death from respiratory causes. There was limited evidence that a threshold model specification improved model fit as compared with a nonthreshold linear model ($P=0.06$) (Table 3S in the Supplementary Appendix).

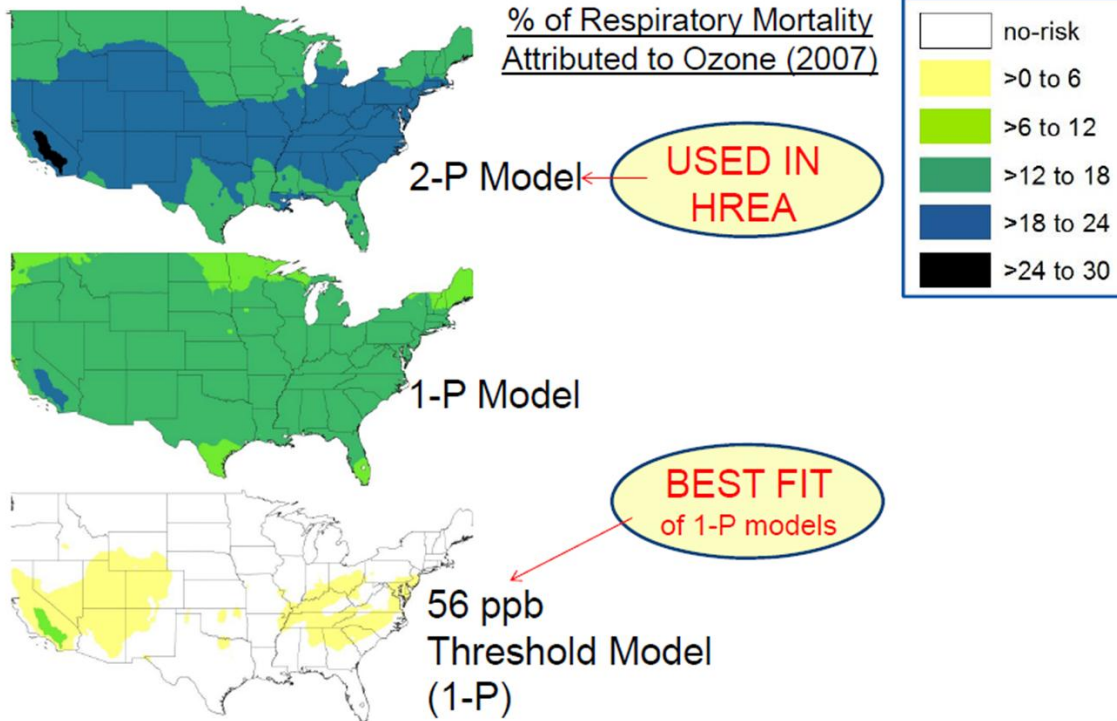
(p. 1091-1092)

Also from Jerrett *et al.* (p. 1094):



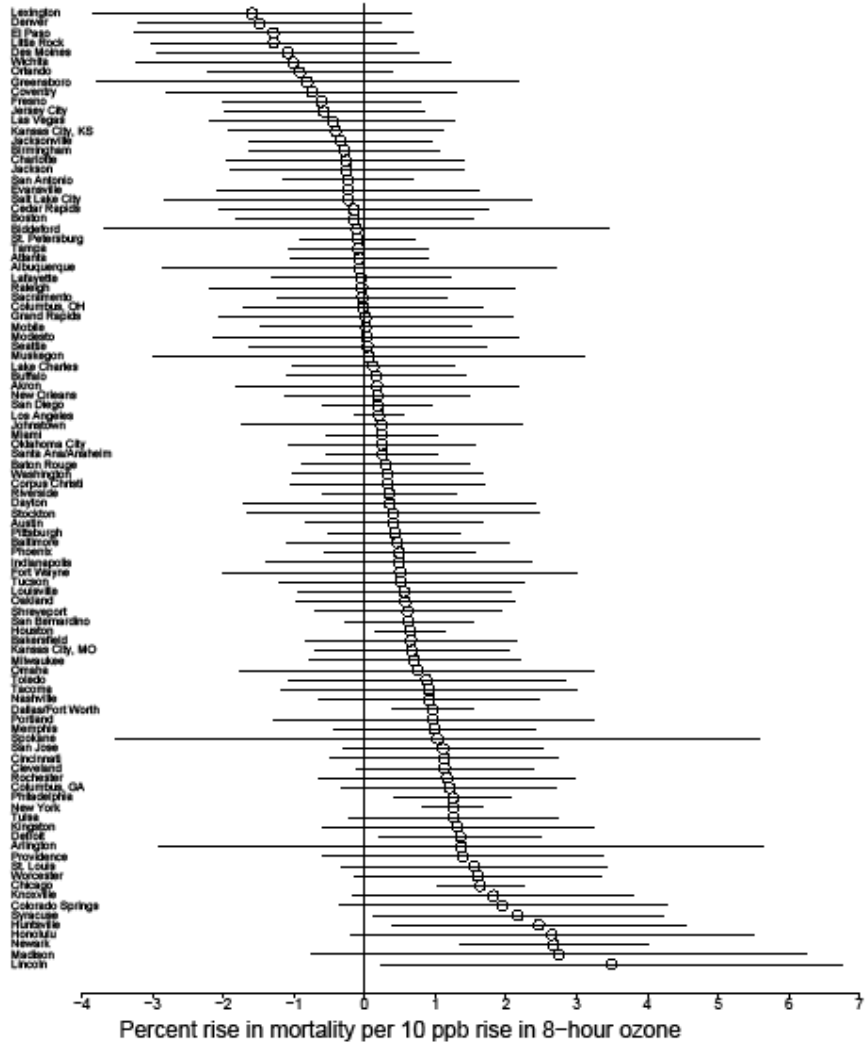
This is an important point because it has a tremendous impact on the calculation of risk attributed to ozone as illustrated below. Using the most scientifically-appropriate model indicates that most of the country has little to no risk from ozone, a substantially different finding than the EPA reported when using the inappropriate model.

**Long-Term Respiratory Mortality Risk:
HREA Risk Estimates Are Extremely Sensitive
to Alternative Models in Jerrett *et al.***



National estimates for mortality in the presence of substantial regional heterogeneity in effects estimates are especially problematic. Indeed, Smith *et al.* 2009 state "...quoting a single value as a national average is misleading if there is substantial heterogeneity." They continue "...the heterogeneity and sensitivity of ozone effect estimates to a variety of covariates leaves open the issue of whether or not ozone is causally related to mortality. Consequently the question arises whether any particular ozone-mortality effect estimate can reliably be used to predict mortality reductions that would ensue from specific ozone reductions." The figure below from Smith *et al.* 2009 illustrates the mean percent change in mortality per 10 ppb increase in 8-hour ozone concentration in 98 US cities. The vast majority show no association between ozone and mortality (cities where the horizontal bars touch the vertical, zero-effect line have no significant association). The data could also be interpreted as having a health-protective effect in some cities.

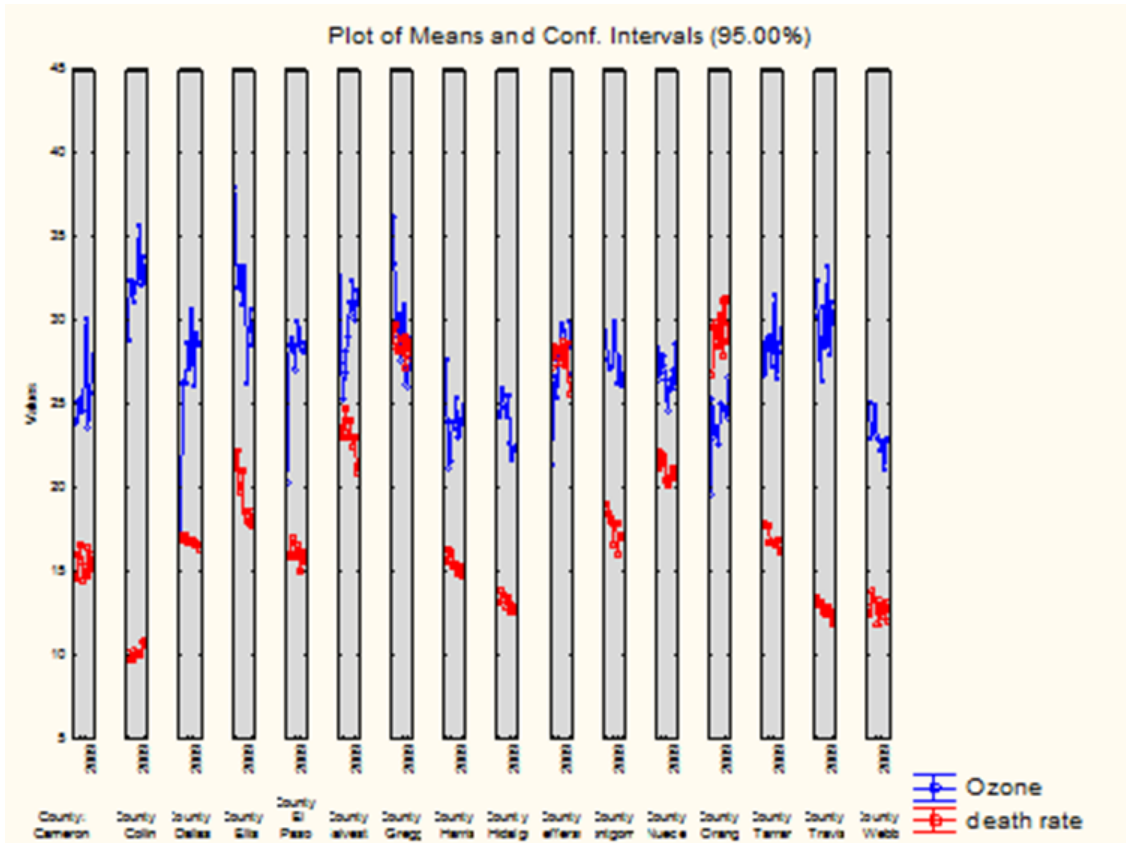
8-HOUR OZONE-MORTALITY COEFFICIENTS RAW ESTIMATES AND 95% CONFIDENCE INTERVALS



We read with interest the statement by EPA on page 7-69 of the HREA that mortality risk is generally not responsive to alternate standards. In other words, the proposed standards would not be expected to have a significant impact on mortality risk. It would then follow that EPA anticipates that there will be no appreciable benefits expected from the proposed alternative standards for this endpoint.

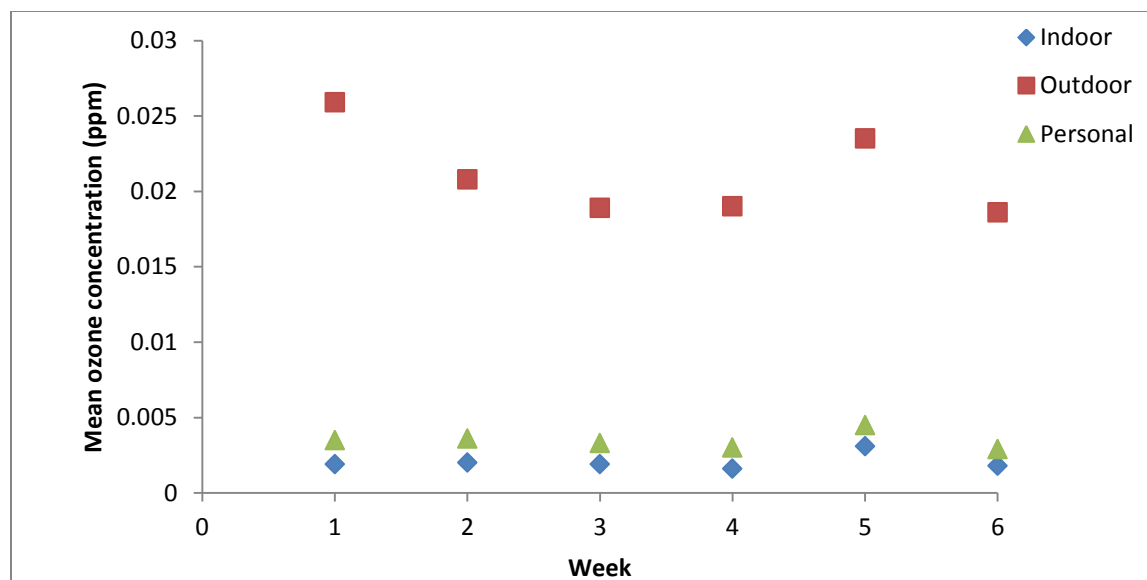
The TCEQ has worked with Louis Anthony Cox, Jr., a noted statistician and editor in chief of the journal *Risk Analysis* to examine the relationship between ozone and mortality in Texas. Between 1999 and 2010, levels of ozone in Texas varied substantially from year to year. This provides an opportunity to compare changes in ambient pollutant levels over time to changes in all-cause, cardiovascular, and respiratory mortality rates. We found that changes in historical ozone levels did not predict changes in mortality rates. Nonparametric tests also show no significant associations between yearly changes in ozone levels and corresponding changes in mortality rates. The figure below is a time series of mortality rates (deaths per million people per day) and average ozone concentrations from 2000 to 2010 by county. Note that there is no

correspondence between changes in ozone concentration (blue lines) and changes in the death rate (red lines). These findings suggest that the substantial short-term mortality benefits from reducing ozone predicted by the United States Environmental Protection Agency and others, based on statistical models of exposure-response associations elsewhere, may not hold in Texas counties.



Epidemiology studies are limited by their study design.

In EPA's discussion of the available epidemiological studies, there is inadequate discussion of personal exposure and indoor versus outdoor ozone concentrations. The graph below reproduced from Lee *et al*, 2004 illustrates results similar to numerous other studies. Because people spend much of their time indoors and indoor concentrations of ozone are extremely low, people are actually exposed to much lower ozone concentrations than those measured at outdoor monitoring stations.



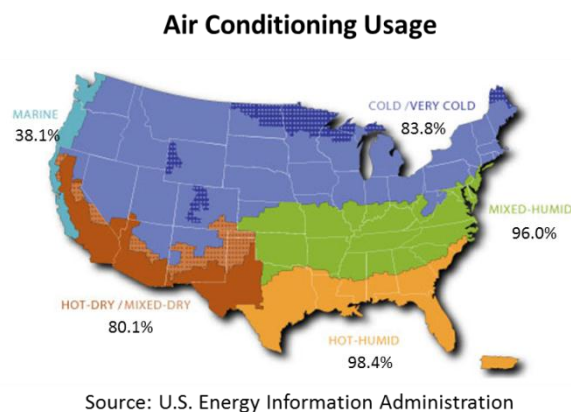
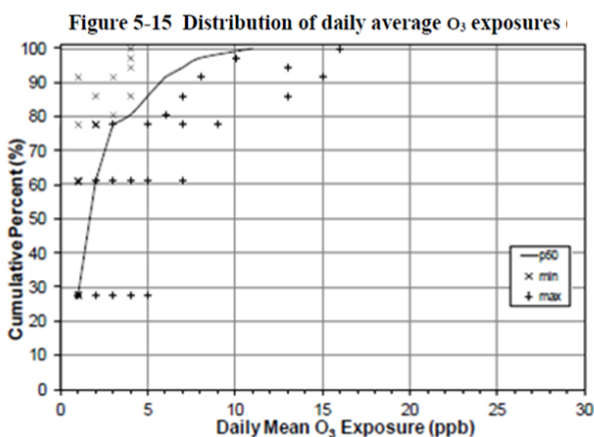
EPA should consider such differences when interpreting studies reporting associations between health effects and ambient ozone concentrations. How likely are these associations to be plausible given estimates of personal exposure? Were the *all* of the hundreds of thousands of people in the epidemiology studies outside for at least 8 hours each day immediately prior to their deaths? It is highly unlikely that these associations are plausible. In fact, in a June 5, 2006 letter to EPA from the CASAC ozone review panel, EPA’s scientific advisors stated, “The Ozone Staff Paper should consider the problem of exposure measurement error in ozone mortality time-series studies. It is known that personal exposure to ozone is not reflected adequately, and sometimes not at all, by ozone concentrations measured at central monitoring sites. . . . Therefore, it seems unlikely that the observed associations between short-term ozone concentrations and daily mortality are due solely to ozone itself.”

In addition, EPA introduces the topic of regional heterogeneity and states that “a national or combined analysis may not be appropriate. . .” in the context of discussion thresholds. However, this also calls into question the appropriateness of a one-size-fits-all standard. The observed city to city heterogeneity strongly implies such a standard would be more or less stringent than necessary, depending on location.

In conclusion, the available epidemiology studies have reported substantial heterogeneity between cities that range from positive to null or negative (i.e. higher ozone levels are correlated with reduced mortality). Therefore, a pooled nation-wide estimate is misleading and overestimates the risk of ozone. Ecological epidemiology studies are not rigorous enough to use as the basis for setting the ozone standard. EPA should use a quantitative weight-of-evidence approach that includes all available information.

Ambient concentrations are not representative of personal exposures.

EPA should explain the limitations of setting standard for ambient air based on clinical exposures when HREA states that most people spend the majority of their time indoors (see quote from CASAC above). Presumably, the patients in the epidemiology studies used by EPA to propose lowering the standard also spent much of their time indoors. Similarly, it is unclear how the results of APEX modeling in the HREA were paired with the information from the DEARS (Meng *et al.* 2012, see figure below), Xue *et al.* 2004 and Geyh *et al.* 2000 studies which indicate that daily personal exposure is well below any of the benchmarks suggested. In addition, the U.S. Energy Information Administration estimates that for many areas of the country, as much as 98.4% of the population utilizes air conditioning units, which would remove the vast majority of ambient ozone (see figure below).²



EPA considers outdoor workers to be an “at risk” population that may be exposed to levels of ozone reported at ambient monitors. A study by O’Neill *et al.* 2003 reported that outdoor workers in Mexico City experienced average personal ozone exposures that were 60 percent lower than ambient monitor levels. EPA also suggests that children playing outside for extended periods of time may be exposed to levels of ozone reported at ambient monitors. In a study by Lee *et al.* 2004, children in the top 25% of time spent outdoors experienced personal ozone exposures 80% lower than levels measured at ambient monitors. This difference between ambient ozone concentrations and personal exposures is key for interpreting both epidemiological studies as well as clinical exposure studies. In fact, EPA is aware that there are differences between ambient concentrations of ozone and personal exposure, but effectively ignores this difference in the HREA when deriving quantitative estimates of risk.

EPA points out in figure 5-15 of the HREA that the upper end of daily average ozone personal exposure are well less than 20 ppb, well below the current standard and the range of proposed alternate standards. EPA should consider personal exposure in setting the ozone standard, which would lead to the conclusion that the current standard is more than adequately health-protective.

² <http://www.eia.gov/consumption/residential/reports/2009/air-conditioning.cfm>

Risk is calculated below background and lowest measured levels of relevant studies.

In the draft HREA, EPA acknowledges that there is uncertainty in extrapolating health risks from ozone exposures that go beyond the ozone levels measured in the relevant epidemiology. However, EPA presents analysis on “total” risk modeled down to zero, outside of the range of available data. This is problematic because there is no way to determine the uncertainty surrounding the risk estimates for the alternative standards under consideration.

In reviewing the studies cited by EPA in the HREA, associations between ozone and selected endpoints generally became weaker and not significant at lower ozone levels. EPA did not incorporate these findings in its risk assessment. Instead, risks were extrapolated below the Lowest Measured Levels (LMLs) of the selected studies and to zero ozone, even though the data from the underlying studies did not report effects at low levels of ozone.

Perhaps more importantly, in assigning risk below background levels of ozone, EPA is suggesting risk below levels that can be potentially modified by implementation of the ozone NAAQS, as pointed out by CASAC in its review of the first draft HREA. In fact, one member of CASAC stated “The C-R function which goes down to zero makes little sense. First of all, such levels are never obtained... Secondly, this zone has little value since it cannot be influenced by the regulatory process.” This commenter continues “...we should have a vision of what levels/cut offs are scientifically sound and contribute to standard setting in a practical way.” A second commenter added “[g]iven the background levels of O₃ that cannot be controlled by U.S. regulatory actions, this reviewer endorses applying the C-R function down to the LML and does not support obtaining risk estimated down to zero.”

Given the uncertainty surrounding risks calculated at low levels of ozone, EPA should assess risk above background ozone levels, as these are the levels that can potentially be controlled by regulation.

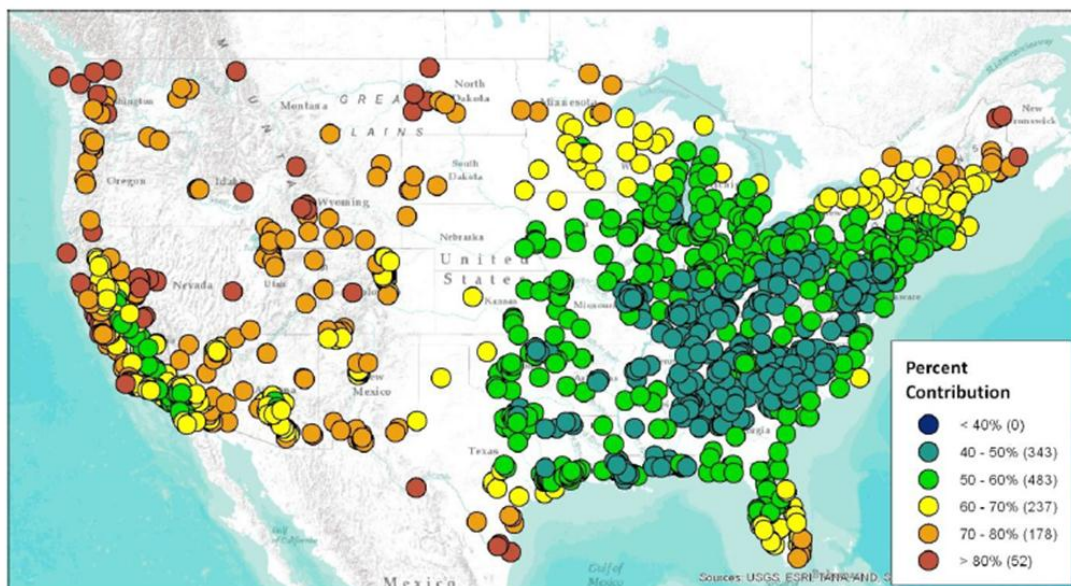


Figure 2-12. Map of apportionment-based U.S. background percent contribution to seasonal mean O₃ based on 2007 CAMx source apportionment modeling.

There is substantial evidence for confounding by co-pollutants.

The core analysis presented in the draft HREA includes estimates for single pollutant models. However, EPA noted in the first draft HREA that confounding by co-pollutants reduces the effect estimates for ozone. Therefore EPA should acknowledge that risk estimates may well be overestimated by not using multi-pollutant models. In fact, CASAC also commented on this point: “[t]o this reviewer, no results should be presented that have not taken into account PM_{2.5} at a minimum.” This topic is especially troubling as the additional analysis presented in Appendix 7 demonstrates that upon inclusion of PM₁₀ in a co-pollutant model, virtually all of the risk estimates for short-term mortality become non-significant.

EPA should utilize multi-pollutant models that account for the confounding effects of co-pollutants and better capture the potential contribution of ozone to health effects.

The rationale for lower ozone standard is inadequate.

The draft HREA presents hypothetical health effects that are based on one or two 8-hour theoretical exposures above the various benchmarks. However, the ozone standard is based on the 4th highest 8-hour exposure averaged over 3 years. It is not clear how this analysis supports a lower standard that would not necessarily capture a single exposure over a given benchmark.

The draft HREA presents modeling results for Houston stating that “seasonal average values ...remained nearly constant relative to the existing standard when air quality were [sic] further adjusted to meet the 65 ppb standard.” This observation does not support lowering the NAAQS.

The mortality estimates for alternative standards presented by EPA generate surprising, nonsensical results. Net mortality was estimated to *increase* in cities including Houston under alternative standards. In addition, it seems highly unlikely that the majority of the risk calculated for ozone (~75%) is attributable to low ozone concentrations (<60 ppb, which is the lower bound for the proposed alternative standards). Furthermore, for Houston <1% of mortality risk is estimated for ozone concentrations >60 ppb, based on Figures 7-2 and 7-3. We fail to see how cities such as Houston would be expected to benefit from the alternative standards proposed because EPA estimates *increased* mortality from lowering the standard.

Based on Table 5-7 of the HREA it appears that the only significant potential exposures would be to 60 ppb ozone. According to the scientific literature, at this concentration one would expect only mild, reversible, transient effects on lung function that are of unclear clinical importance. Furthermore, based on the confidence intervals presented in this table, no significant exposure to 70 or 80 ppb would be expected even if the current standard were to be retained. Therefore, it is not clear how this information supports a more stringent NAAQS.

Finally, the last line of the HREA states: “[m]ortality from short-term and long-term O₃ exposures and respiratory hospitalization risk is not greatly affected by meeting lower standards...” This observation does not support the necessity of a lower standard. EPA’s own modeling shows either adverse or little to no public health benefit from lowering the current standard.

EPA does not present a clear rationale for the necessity of a lower standard. For instance, the evidence presented by for respiratory endpoints EPA appears to cast doubt on the lower end of the proposed range of alternative standards. In addition, EPA indicates “...a *mostly consistent*

positive association between O₃ exposure and respiratory-related hospital admissions and ED visits...” “Mostly consistent” is not strong enough evidence for using these endpoints for setting a lower NAAQS.

In addition, the three observations on page 3-112 of the HREA are based on mortality over the full range of ozone concentrations. Based on figure 3-16, the choice of a 60—70 ppb standard will not appreciably change any of these key observations. Moreover, the final line of the HREA states “[m]ortality from short-term and long-term O₃ exposures and respiratory hospitalization risk is not greatly affected by meeting lower standards...” We agree with EPA that the proposed alternate standards will not have an impact on respiratory hospitalization risk, therefore there is no scientific reason to lower the existing standard.

Finally, on page 3-115 of the PA and elsewhere in discussion of uncertainty related to effects at low concentrations of ozone EPA makes contradictory statements. EPA calculates increases in theoretical mortality resulting from alternative standards leading to potentially substantial disbenefits. However, EPA argues that the decreases in health effects estimated for higher ozone concentrations are real whereas the increases in those same health effects at lower concentrations are uncertain. It can't be both ways. This illustrates the impact of choosing a linear model and calculating risks below both the LMLs of available studies as well as background O₃. This also highlights the tenuous connection between the ozone and mortality, especially at concentrations below the current standard.

EPA's own modeling shows either adverse or little to no public health benefit from lowering the current standard, therefore EPA should retain the existing standard.

References

Abbey, DE; Nishino, N; McDonnell, WF; Burchette, RJ; Knutsen, SF; Lawrence Beeson, W; Yang, JX. 1999. “Long-term inhalable particles and other air pollutants related to mortality in nonsmokers.” *Am. J. Respir. Crit. Care Med.* 159(2):373-382.

Adams, WC. 2002. “Comparison of chamber and face-mask 6.6-hour exposures to ozone on pulmonary function and symptoms responses.” *Inhal. Toxicol.* 14(7): 745-764.

Adams, WC. 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(2): 127-136.

American Thoracic Society. 2000. “What constitutes an adverse health effect of air pollution?” *Am. J. Respir. Crit. Care Med.* 161: 665-673.

Beeson, WL; Abbey, DE; Knutsen, SF. 1998. “Long-term concentrations of ambient air pollutants and incident lung cancer in California adults: Results from the AHSMOG study.” *Environ Health Perspect.* 106: 813-823.

Chen, LH; Knutsen, SF; Shavlik, D; Beeson, WL; Petersen, F; Ghamsary, M; Abbey, D. 2005. "The association between fatal coronary heart disease and ambient particulate air pollution: Are females at greater risk?" *Environ Health Perspect.* 113: 1723-1729.

Delgado, J; Barranco, P; Quirce, S. 2008. "Obesity and asthma." *J. Investig. Allergol. Clin. Immunol.* 18(6):420-425.

Dockery, DW; Pope, CA; Xu, X; Spengler, JD; Ware, JH; Fay, ME; Ferris, BG Jr.; Speizer, FE. 1993. "An association between air pollution and mortality in six U.S. cities." *N. Engl. J. Med.* 329(24):1753-1759.

Folinsbee, LJ; McDonnell, WF; Horstman, DH. 1988. "Pulmonary function and symptom responses after 6.6-hour exposure to 0.12 ppm ozone with moderate exercise." *J. Air Poll. Control Assoc.* 38(1):28-35.

Geyh, AS; Xue, J; Ozkaynak, H; Spengler, JD. 2000. "The Harvard Southern California chronic ozone exposure study: Assessing ozone exposure of grade-school-age children in two southern California communities." *Environ Health Perspect.* 108: 265-270.

Goodman, JE; Prueitt, RL; Chandalia, J; Sax, SN. 2013. "Evaluation of adverse human lung function effects in controlled ozone exposure studies." *J. Appl. Toxicol.* 34(5):516-524.

Goodman, JE; Prueitt, RL; Sax, SN; Lynch, HN; Zu, K; Lemay, JC; King, JM; Venditti, FJ. 2014. "Weight-of-evidence evaluation of short-term ozone exposure and cardiovascular effects." *Crit. Rev. Toxicol.* 44(9):725-90.

Jerrett, M; Burnett, RT; Ma, R; Pope, CA; Krewski, D; Newbold, KB; Thurston, G; Shi, Y; Finkelstein, N; Calle, EE; Thun, MJ. 2005. "Spatial analysis of air pollution and mortality in Los Angeles." *Epidemiology* 16(6):727-736.

Jerrett, M; Burnett, RT; Pope, CA; Ito, K; Thurston, G; Krewski, D; Shi, Y; Calle, E; Thun, M. 2009. "Long-term ozone exposure and mortality." *N. Engl. J. Med.* 360(11):1085-1095.

Kim, CS; Alexis, NE; Rappold, AG; Kehrl, H; Hazucha, MJ; Lay, JC; Schmitt, MT; Case, M; Devlin, RB; Peden, DB; 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.

Krewski, D; Burnett, RT; Goldberg, MS; Hoover, K; Siemiatycki, J; Jerrett, M; Abrahamowicz, M; White, WH. 2000. "Reanalysis of the Harvard Six Cities study and the American Cancer Society study of particulate air pollution and mortality." Health Effects Institute. <http://pubs.healtheffects.org/view.php?id=6>

Lee, K; Parkhurst, WJ; Xue, J; Ozkaynak, AH; Neuberg, D; Spengler, JD. 2004. "Outdoor/indoor/personal ozone exposures of children in Nashville, Tennessee." *J. Air Waste Manag. Assoc.* 2004 Mar;54(3):352-9.

Lipfert, FW; Baty, JD; Miller, JP; Wyzga, RE. 2006. "PM2.5 constituents and related air quality variables as predictors of survival in a cohort of U.S. military veterans." *Inhal. Toxicol.* 18: 645-657.

Lipfert, FW; Perry, HM; Miller, JP; Baty, JD; Wyzga, RE; Carmody, SE. 2000. "The Washington University-EPRI veterans' cohort mortality study: preliminary results." *Inhal. Toxicol.* 12(Suppl. 4):41-73.

McDonnell, WF; Kehrl, HR; Abdul-Salaam, S; Ives, PJ; Folinsbee, LJ; Devlin, RB; O'Neil, JJ; Horstman, DH. 1991. "Respiratory response of humans exposed to low levels of ozone for 6.6 hours." *Arch. Environ. Occup Health.* 46:145-150.

Meng, Q; Williams, R; Pinto, J.P. 2012. "Determinants of the associations between ambient concentrations and personal exposures to PM2.5, NO2, and O3 during DEARS." *Atmospheric Environment.* 63:109-116.

Miller, KA; Siscovick, DS; Sheppard, L; Shepherd, K; Sullivan, JH; Anderson, GL; Kaufman, JD. 2007. "Long-term exposure to air pollution and incidence of cardiovascular events in women." *N. Engl. J. Med.* 365 (5):447-58.

O'Connor, GT; Neas, L; Vaughn, B; Kattan, M; Mitchell, H; Crain, EF; III, ER; Gruchalla, R; Morgan, W; Stout, J; Adams, GK; Lippmann, M. 2008. "Acute respiratory health effects of air pollution on children with asthma in US inner cities." *J. Allergy Clin. Immunol.* 121: 1133-1139.

O'Neill, MS; Ramirez-Aguilar, M; Meneses-Gonzalez, F; Hernandez-Avila, M; Geyh, AS; Sienra-Monge, JJ; Romieu, I. 2003. "Ozone exposure among Mexico City outdoor workers." *J. Air Waste Manag. Assoc.* 53:339-346.

Pellegrino, R; Viegi, G; Brusasco, V; Crapo, RO; Burgos, F; Casaburi, R; Coates, A; van der Grinten, CP; Gustafsson, P; Hankinson, J; Jensen, R; Johnson, DC; MacIntyre, N; McKay, R;

Miller, MR; Navajas, D; Pedersen, OF; Wanger, J. 2005. Interpretative strategies for lung function tests. *Eur. Respir. J.* 26(5): 948-968.

Pope, CA; Burnett, RT; Thun, MJ; Calle, EE; Krewski, D; Ito, K; Thurston, GD. 2002. "Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution." *JAMA.* 287: 1132-1141.

Schelegle, ES; Morales, CA; Walby, WF; Marion, S; Allen, RP. 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(3):265-272.

Schildcrout, JS; Sheppard, L; Lumley, T; Slaughter, JC; Koenig, JQ; Shapiro, GG. 2006. "Ambient air pollution and asthma exacerbations in children; An eight-city analysis." *Am. J. Epidemiol.* 164(5):505-517.

Smith, RL; Xu, B; Switzer, P. 2009. "Reassessing the relationship between ozone and short-term mortality in U.S. urban communities." *Inhal. Toxicol.* 21(Suppl. 2):37-61.

Wang, XY; Hu, W; Tong, S. 2009. "Long-term exposure to gaseous air pollutants and cardio-respiratory mortality in Brisbane, Australia." *Geospat. Health.* 3: 257-263.

Xue, J; McCurdy, T; Spengler, J; Ozkaynak, H. 2004. "Understanding variability in time spent in selected locations for 7-12-year old children." *J. Expo. Anal Environ. Epidemiol.* 14: 222-233.

Ye, X; Wolff, R; Yu, W; Vaneckova, P; Pan, X; Tong, S. 2012. "Ambient temperature and morbidity: a review of epidemiological evidence." *Environ. Health Perspect.* 120:19-28.

Zanobetti, A; Schwartz, J. 2008. "Is there adaptation in the ozone mortality relationship: A multi-city case-crossover analysis." *Environ. Health.* 7:22.