TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

Protecting Texas by Reducing and Preventing Pollution

March 24, 2014

Air and Radiation Docket and Information Center
Mail Code: 2822T
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue NW.
Washington, DC 20460

Attn: Docket ID No. EPA–HQ–OAR–2008–0699

Re: Comments on the U.S. EPA Second External Review Draft Health Risk and Exposure Assessment for Ozone and Related Photochemical Oxidants EPA–452/P–14–004a

Dear Sir or Madam:

The Texas Commission on Environmental Quality (TCEQ) appreciates the opportunity to respond to the U.S. Environmental Protection Agency's (EPA) request for input in the notice published in the January 29, 2014, edition of the *Federal Register* entitled: "Second External Review Draft Health Risk and Exposure Assessment for Ozone and Related Photochemical Oxidants."

Enclosed, please find TCEQ's detailed comments to the EPA action referenced above. If you have any questions concerning the enclosed comments, please contact Michael Honeycutt, Ph.D., Toxicology Division, Office of the Executive Director, at michael.honeycutt@tceq.texas.gov.

Sincerely,

Richard A. Hyde, P.E.
Executive Director

Enclosure

Health Risk and Exposure Assessment Second Draft - 2014

In February of 2014, EPA released its second draft Health Risk and Exposure Assessment for Ozone for public comment closing on March 24th 2014. At the same time, the second draft Welfare Risk and Exposure Assessment and second draft Policy Assessment were released for public comment with the same closing date, allowing stakeholders 36 working days to review the three substantial documents and all associated appendices. This is simply impracticable and suggests that EPA is not interested in receiving meaningful and complete comments. If EPA genuinely wishes to receive the most useful input, advanced notice of some sort should be given to stakeholders paired with a reasonable timeframe for preparing comments. Nevertheless, in the time allowed, TCEQ has prepared the following comments on the second draft Health Risk and Exposure Assessment (HREA).

General Comments

The TCEQ agrees with EPA that the NAAQS for ozone should protect public health. We would like to emphasize that modeling presented in the HREA indicates a lower standard may result in additional premature mortality for some areas of the country, including Houston (figures 7B-2 and 7B-4).

In addition, we would like to emphasize that when considering alternative O_3 standards, the lower end of the proposed range is not well-supported. In fact, EPA states 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 O_3 would increase ...with a lower level of the O_3 NAAQS" (PA p2-27).

EPA has not made the case that a lower standard will improve public health and TCEQ urges EPA to retain the current standard.

A true weight of evidence is lacking.

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 or 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. The TCEQ urges EPA to use a rigorous weight of evidence as recommended by the National Academy of Sciences (NAS), and believes that EPA should not make policy judgments without assessing all of the available evidence.

The selection of endpoints is inappropriate in some cases.

The draft HREA uses endpoints previously determined to have "Suggestive," "Likely Causal" as well as "Causal" relationships with ozone exposure. TCEQ believes 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 ISA and lacks adequate evidence from scientific literature to be utilized in setting a standard.

In the 2013 ISA, EPA stated that the epidemiology evidence for cardiovascular endpoints is inconsistent and lacks coherence across realms of evidence. In addition, Goodman *et al.* (2014) rigorously evaluated the studies reviewed by EPA as well as additional available literature. The authors utilized a systematic weight of evidence approach and determined that the available studies reported mixed results with positive, null and negative associations being reported. These results indicate that there is not adequate evidence of a causal relationship and therefore cardiovascular endpoints should not be included in the PA.

The TCEQ urges EPA to only use causal endpoints and to select endpoints that have clear biological plausibility and clinical significance.

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 O_3 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.

Lung function decrements are not likely to be adverse.

The EPA has selected hypothetical lung function decrements over specific cutoff values (≥10%, 15%, or 20%) in one year. However, this approach overstates the significance of individual responses, which are highly variable. Moreover, determining the percent or number of individuals that experience at least one hypothetical FEV_1 decrement over a particular cutoff likely overestimates the significance of individual responses, particularly at lower ozone exposure levels because of the individual variability of FEV_1 when measured by spirometry. Indeed, Pellegrino *et al.* 2005 noted that FEV_1 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 FEV_1 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 ≥ 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 FEV_1. 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. Thus, while FEV_1 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 TCEQ urges EPA to only use causal endpoints and to select endpoints that have clear biological plausibility and clinical significance. Moreover, the available data indicate that adverse respiratory effects do not occur at ozone concentrations below the current NAAQS.

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 as single pollutant CRFs were utilized in the core analysis.

The TCEQ would like to emphasize that important information 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 PM_{10} 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 draft 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 2009. We would like to point out that long-term mortality was not listed on page 7-17 and 18 under ozone attributable effects nor is it listed as a causal endpoint in ISA. The use of this 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 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 O_3; Lipfert *et al.* 2006; Wang *et al.* 2009; Jerrett *et al.* 2005). Moreover, it is inappropriate to combine data across cities for a national risk estimate, given the known geographic heterogeneity of these estimates (Goodman 2013; Smith *et al.* 2009). Finally, data relating to potential confounders 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.

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."

We read with interest the statement by EPA on page 7-69 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 agrees with EPA that lowering the ozone standard will not result in appreciable health benefits.

The classification of "at risk" groups is not adequately supported.

EPA extrapolated data from 18 to 35 year old volunteers to younger age groups and support this decision by saying that change in lung function in children is similar to adults. It is therefore unclear how this observation supports classifying children as an "at risk" group.

EPA has classified asthmatics as an "at risk" group despite previous advice from CASAC indicating that the evidence suggesting asthmatics are more sensitive than non-asthmatics is weak. Epidemiology studies cited by EPA in the ozone ISA are inconsistent, with some studies reporting statistically significant effects in asthmatics (Escamilla-Nunez *et al.* 2008, Alexeeff *et al.* 2007, Thaller *et al.* 2008, Lewis *et al.* 2005) and others reporting no difference (Barraza-Villarreal *et al.* 2008, Berhane *et al.* 2011, Khatri *et al.* 2009, Hernandez-Cadena *et al.* 2009, Liu *et al.* 2009). In addition, human controlled exposure studies have reported inconsistent results in asthmatics, with only mild, transient, and reversible effects being observed. Based on these inconsistent findings it is unclear that asthmatics truly constitute an "at risk" group.

There is evidence for effect thresholds that is not utilized in the draft HREA.

There are four controlled exposure studies that have played a key role in the HREA (Adams *et al.* 2002, 2006, Schelegle *et al.* 2009, and Kim *et al.* 2011). Taken together, these studies indicate that there are no statistically significant adverse effects associated with ozone exposure below 70 ppb. Effects that might be expected to occur at these low levels are not adverse and any decrements in hypothetical lung function in individuals at this exposure level cannot reliably be attributed to ozone.

EPA incorporates the McDonnell *et al.* 2012 study in the MSS model described in Chapter 6. However, we have concerns regarding the interpretation of a threshold from this study. The authors did indicate a concentration threshold and it is unclear why EPA chose to incorporate this as a delay in response rather than a concentration threshold below which effects do not occur. This is especially confusing because EPA also states on p 7-30 "...clinical studies have suggested the presence of a threshold for respiratory effects..."

EPA indicates that it does not believe there to be a population threshold for effects of ozone based on its review of relevant epidemiology. However, there are a number of factors that limit the ability to detect thresholds in such studies. It has long been recognized that measurement error can bias results, which tends to flatten and linearize exposure-response curves in epidemiological studies (Rhomberg *et al.* 2011). Brauer *et al.* (2002) have also evaluated exposure misclassification for ozone where ambient concentrations are very poor approximations of personal exposure. The authors find that it is not possible to determine whether or not an effect threshold exists. Therefore, the conclusion that there is no evidence to support a threshold for ozone exposure and mortality is not supported, and the evidence from controlled human exposure studies as well as proposed modes of action should be used to support the existence of a threshold for purported mortality effects.

CASAC provided EPA with advise that is in agreement with the above comments: "...the recent paper by McDonnell *et al.* 2012 clearly establishes the statistical significance of a threshold model for O_3 FEV_1 responses...the model would also be directly applicable to functional changes seen in...epidemiology studies." The commenter continued "[j]ust because the epidemiology studies are not able to define a threshold for O_3 effects for the mortality, hospital admissions, and other effects does not mean that a 'biologically effective threshold' does not exist. This issue becomes a statistical one that epidemiology studies have a difficult time trying to establish. However, most biomedical scientists would argue that there is a threshold." The TCEQ agrees with this member of CASAC and encourages EPA to appropriately incorporate thresholds into their analysis.

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 (p3-5 and 3-6). In fact the CHAD results presented indicate that the surveyed individuals spend an average of 4.3 hours per day outdoors but that this estimate is highly variable and somewhat dated. Notably, EPA focused on individuals spending >2 hours outdoors, but it is not clear what proportion of population fits this assumption. These limitations are especially important when estimating percent of population expected to experience hypothetical lung function decrements, which is a key component of the HREA and anticipated to contribute to the estimated benefits for the proposed NAAQS.

Similarly, it is unclear how the results of APEX modeling in Chapter 5 were paired with the information from the DEARS (Meng *et al.* 2012) and Xue *et al.* 2004 and Geyh *et al.* 2000 studies which indicate that daily personal exposure is well below any of the benchmarks suggested.

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% 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 draft HREA when deriving quantitative estimates of risk.

The TCEQ urges EPA to consider personal exposure in setting the ozone standard, which would lead to the conclusion that the current standard is more than adequately health–protective.

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 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 O_3 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, the TCEQ urges EPA to assess risk above background ozone levels, as these are the levels that can potentially be controlled by regulation.

There is substantial regional heterogeneity in effects estimates for ozone.

For mortality attributable long-term exposure to ozone, EPA chose to use the same concentration-response function from Jerrett *et al.* 2009 for all 12 urban case study areas despite mentioning regional heterogeneity many times throughout the draft. TCEQ would like to emphasize that in light of the substantial regional heterogeneity, it

is unclear how to interpret pooled estimates, particularly given the inconsistencies across studies. Indeed the authors of the NMMAPS analysis stated that "quoting a single value as a national average is misleading if there is substantial heterogeneity" (Smith *et al.* 2009).

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 PM_{10} in a co-pollutant model, virtually all of the risk estimates for short-term mortality become non-significant.

The TCEQ urges EPA to utilize multipollutant 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 HDDM 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." It is not clear how this observation supports lowering the NAAQS and what benefit cities such as Houston would be expected to gain.

The mortality estimates for alternative standards presented by EPA generate nonsensical results. Net mortality was estimated to increase in cities including Houston under alternative standards. In addition, it seems highly unlikely that ~75% of risk is estimated for ozone concentrations <60 ppb, which we would like to emphasize 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. It is therefore unclear that cities such as Houston would be expected to benefit from the alternative standards proposed.

Based on Table 5-7 it appears that the only significant potential exposures would be to 60 ppb ozone. At this concentration we 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, we read with interest the last line of the HREA: "[m]ortality from short-term and long-term O_3 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, therefore TCEQ urges EPA to retain the existing standard.

Comments on HDDM

General comment: The TCEQ appreciates EPA's efforts to improve the science used to quantify the effects of modifying the 2008 ozone NAAQS, specifically the replacement of the quadratic rollback with a model-based approach that more realistically portrays the anticipated resulting ozone concentrations, use of the Higher-order Direct Decoupled Method (HDDM). However, we have several specific comments on the analyses presented in the Appendices to Chapter 4:

The 2008 National Emissions Inventory (NEI) has been shown to have NO_2 biases in Texas and other states, perhaps due to non-road, area, and off-road sources. Researchers have found the 2011 NEI to have improved estimates. Back-casting to 2007 from 2011 may yield model performance improvements and higher confidence in the modeled sensitivities.

The reason for choosing a different Goddard Earth Observation System model with chemistry (GEOS-Chem) run for initial model conditions from that used for model boundary conditions was not documented.

The biogenic emission model used in the modeling analysis, Biogenic Emissions Inventory System (BEIS), does not appear to have been updated for some time. The EPA web pages for BEIS do not exist (links broken). The recently updated Model of Emissions of Gases and Aerosols from Nature (MEGAN) is more up-to-date and represents the current state-of-the-science.

The modeling shows higher mean normalized bias on both the East and West coasts of the U.S. (Northeast, Florida, Texas, California), which may be attributable to marine-influenced meteorology not captured by the model's relatively coarse resolution of 12 Km. To properly assess the effects of a new ozone standard in these regions, high resolution simulation (4 km or smaller) is necessary.

Treating emission reductions uniformly across all sectors and geographic areas is clearly unrealistic. Predicting the reductions which would actually be implemented to reach a new standard is obviously not possible, but some assessment of the uncertainties imparted through this approach should be undertaken.

The TCEQ's experience has been that reducing both NO_X and VOC emissions in Houston has proven extremely effective in reducing both modeled and ambient ozone levels. However, the results of EPA's analysis wherein both NO_X and VOC emissions were reduced simultaneously seem contradictory, because for many cities including Houston it appears that reducing both pollutants simultaneously would be less effective than reducing NO_X alone. This implies that should an area reduce NO_X emissions substantially, then increasing VOC emissions would be beneficial! While this might be true under very limited, specific chemical regimes, it is difficult to believe that this phenomenon would be as widespread as EPA's modeling indicates, and might be indicative of some underlying errors in the model formulation. Before we can have confidence in EPA's modeling analysis, EPA must explain these anomalous results.

Specific Comments

- P5-22 graphs should have the same scale
- P6-26, lines 7-8- please clarify what is meant here.
- P7-19, line 12 is missing a reference.
- Include confidence intervals in all Chapter 7 figures and tables.
- Figs 7-2 and 7-3 "total" columns for alternate standards should be re-labeled "total change" or something similar. As is, seems to imply that the 683 deaths for Houston would be reduced to 5 for the alternate standard of 70 ppb.
- Totals different for Table 7-7 versus Figures 7-2 and 7-3. For instance, for Houston, Figure 7-3 lists a total incidence of 683 whereas Table 7-7 lists 680 for 2007.
- Clarity needed on p9-35 L7-9. Which metrics are referred to by "those metrics incorporate thresholds" and is this correct, because EPA previously stated that a concentration threshold was not utilized, despite evidence for a such a threshold by McDonnell *et al* 2012.
- P9-46 line 4, please expand on "...there may be some reduction in the magnitude of the risk decrease..." this passage is unclear and hard to follow.

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.

Alexeeff, SE; Litonjua, AA; Suh, H; Sparrow, D; Vokonas, PS; Schwartz, J. 2007. "Ozone exposure and lung function: Effect modified by obesity and airways hyperresponsiveness in the VA Normative Aging Study." Chest. 132: 1890-1897.

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

Barraza-Villarreal, A; Sunyer, J; Hernandez-Cadena, L; Escamilla-Nunez, MC; Sienra-Monge, JJ; Ramirez-Aguilar, M; Cortez-Lugo, M; Holguin, F; Diaz-Sanchez, D; Olin, AC; Romieu, I. 2008. "Air pollution, airway inflammation, and lung function in a cohort study of Mexico City schoolchildren." Environ Health Perspect. 116: 832-838.

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.

Berhane, K; Zhang, Y; Linn, WS; Rappaport, EB; Bastain, TM; Salam, MT; Islam, T; Lurmann, F; Gilliland, FD. 2011. "The effect of ambient air pollution on exhaled nitric oxide in the Children's Health Study." Eur Respir. J 37: 1029-1036.

Brauer, M; Brumm, J; Vedal, S; Petkau, AJ. 2002. "Exposure misclassification and threshold concentrations in time series analyses of air pollution health effects." Risk Anal. 22: 1183-1193.

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.

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.

Escamilla-Nuñez, MC; Barraza-Villarreal, A; Hernandez-Cadena, L; Moreno-Macias, H; Ramirez-Aguilar, M; Sienra-Monge, JJ; Cortez-Lugo, M; Texcalac, JL; del Rio-Navarro, B; Romieu, I. 2008. "Traffic-related air pollution and respiratory symptoms among asthmatic children, resident in Mexico City: The EVA cohort study." Respir Res. 9: 74.

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 Waste Manag Assoc. 38: 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. Jul 9. doi: 10.1002/jat.2905. [Epub ahead of print]

Goodman, JE; Lunch, HN; Zu, K; Sax, SN; Venditti, FJ; Prueitt, RL. 2014. "Weight-of-evidence evaluation of long-term ozone exposure and cardiovascular effects." Submitted.

Hernández-Cadena, L; Holguin, F; Barraza-Villarreal, A; Del Río-Navarro, BE; Sienra-Monge, JJ; Romieu, I. 2009. "Increased levels of outdoor air pollutants are associated with reduced bronchodilation in children with asthma." Chest. 136: 1529-1536.

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.

Khatri, SB; Holguin, FC; Ryan, PB; Mannino, D; Erzurum, SC; Teague, WG. 2009. "Association of ambient ozone exposure with airway inflammation and allergy in adults with asthma." J Asthma. 46: 777-785.

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.

Lewis, TC; Robins, TG; Dvonch, JT; Keeler, GJ; Yip, FY; Mentz, GB; Lin, X; Parker, EA; Israel, BA; Gonzalez, L; Hill, Y. 2005. "Air pollution-associated changes in lung function among asthmatic children in Detroit." Environ Health Perspect. 113: 1068-1075.

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.

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.

Liu, L; Poon, R; Chen, L; Frescura, AM; Montuschi, P; Ciabattoni, G; Wheeler, A; Dales, R. 2009. "Acute effects of air pollution on pulmonary function, airway inflammation, and oxidative stress in asthmatic children." Environ Health Perspect. 117: 668-674.

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.

McDonnell, WF; Stewart, PW; Smith, MV; Kim, CS; Schelegle, ES. 2012. "Prediction of ozone-induced lung function responses in humans." Inhal Toxicol. 22(2);160-168.

Meng, Q; Williams, R; Pinto, J.P. 2012. "Determinants of the associations between ambient concentrations and personal exposures to $PM_{2.5}$, NO_2, and O_3 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, III; 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.

Rhomberg LR, Chandalia JK, Long CM, Goodman JE. 2011. "Measurement error in environmental epidemiology and the shape of exposure-response curves." Crit Rev Toxicol. 41(8):651-671.

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.

Thaller, EI; Petronella, SA; Hochman, D; Howard, S; Chhikara, RS; Brooks, EG. 2008. "Moderate increases in ambient PM2.5 and ozone are associated with lung function decreases in beach lifeguards." J Occup Environ Med. 50: 202-211.

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.

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