COMMENTS BY THE TEXAS COMMISSION ON ENVIRONMENTAL QUALITY REGARDING THE EXTERNAL REVIEW DRAFT INTEGRATED SCIENCE ASSESSMENT FOR PARTICULATE MATTER

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I. Summary of Proposed Action

On October 23, 2018, the United States Environmental Protection Agency (EPA) published in the *Federal Register* (83 FR 53471) notice of the availability and public comment period for the External Review Draft of the Integrated Science Assessment for Particulate Matter.

The Integrated Science Assessment (ISA) is the first in a series of technical and policy assessments that provide the basis for the primary particulate matter (PM) National Ambient Air Quality Standard (NAAQS). The EPA last revised the primary PM NAAQS in 2012 based on the available scientific literature supporting that standard. The draft ISA summarizes available scientific evidence and provides causal determinations for various health effects, the incidence of which are later modeled to evaluate the health protectiveness of the existing standard and support either the retention of the existing NAAQS or the setting of a new NAAQS.

II. General Comments

A. General Comments Related to Ambient PM

The ISA is inconsistent in its definition of seasons.

The EPA should be more consistent in how it defines seasons in the ISA. For example, in Figure 2-12, winter is defined as DJF (December-January-February), whereas in Table 2-4 winter is January-February-March. Given the importance of seasonal heterogeneity, it is important that this definition be consistent.

The EPA should be clearer about the availability of measurement data.

Chapter 2 of the ISA frequently states that measurements of PM between 10 and 2.5 micrometers in diameter ($PM_{10-2.5}$) have only recently been available. However, $PM_{10-2.5}$ data should have been available, even retroactively, anywhere there was both a federal reference method (FRM) $PM_{2.5}$ and an FRM measuring PM of less than 10 micrometers in diameter (PM_{10}) operating at the same time at the same monitoring site, regardless of differences in sampler type and design flow rate. If $PM_{10-2.5}$ data are of interest, the EPA should be able to calculate them from existing data or provide a more detailed explanation why such a retroactive calculation is inappropriate.

The EPA should provide more discussion on background and international transport of PM.

The EPA should describe how the "regional background" is determined/quantified (see page 2-67 line 21). The general discussion in Section 2.5.4 is useful but does not explain how statements like "...urban concentrations are on average 3.9 to 5 $\mu g/m^3$ higher than regional background..." are made with such precise figures. Numerical comparisons between sites against "backgrounds" were also present in several other locations in Chapter 2.

In addition, Section 2.5.4.2 related to Intercontinental Transport appears incomplete as it pertains to Texas. The paragraph discussing African dust does not mention the annual and

significant transport of Saharan Dust into the Gulf of Mexico and gulf states, including Texas, but only states that the dust "can affect the eastern U.S." (line 13). Additionally, while not technically intercontinental but instead *international* transport, a discussion regarding how PM originating from agricultural burning in Mexico and Central America can impact the gulf states would also be appropriate in this section.

B. General Comments Related to Exposure

The ISA needs to better evaluate exposure and measurement error, including their impact on concentration-response functions, and consider the resulting impact in the final evidence integration and causal determinations.

The most basic measure of exposure is typically monitoring data collected on a person, near their home, or at an ambient air monitoring site. This monitoring data is prone to known interferences, including humidity and mechanical issues influencing flow through the instrument. The most consistent application of quality control procedures is found in the ambient monitoring network under the direction of rules in 40 Code of Federal Regulations Part 58 by the EPA. Even in these tightly controlled networks, the data can vary by +/- 10% and still be considered valid. An evaluation of collocated federal reference $PM_{2.5}$ monitors across the United States indicates that duplicates of the same equipment, operated in the same manner, in the same location, and sampling at the same time and duration can have annual average concentrations that are different by +/- 4 $\mu g/m^3$ (Attachment A). Wade et al. (2006) further states that "...differences between instruments and analytical procedures that affect the precision of assessment of temporal variation are sources of error. Factors that affect the spatial heterogeneity of air pollution include the distribution of emission sources, as well as meteorological phenomena, topological features, and pollutant volatility and reactivity." Yang et al. (2018) also notes that misclassification may occur for participants who reside far away from the monitoring stations. Unfortunately, rather than considering how well exposure was evaluated as part of study selection or how exposure error could affect subsequent health effect estimates, the ISA (as well as many study authors) appears to have disregarded this known uncertainty out of convenience and assumes that measured ambient concentrations represent true ambient conditions and even personal exposure with complete accuracy.

The ISA appears to attempt to partially justify its omission of exposure and measurement error through its use of studies that rely on modeling data. While modeling data may provide more geographically continuous concentrations with which to pair health endpoints in an epidemiologic analysis, the use of models does not reduce exposure and measurement error but compounds it, often in ways that are poorly evaluated or represented in publications. Several studies used land use regression model in which predictors (e.g., emission sources, traffic intensity, population density, land use, etc.) are extracted from Geographic Information Systems (GIS) to estimate PM exposure in assessing health effects (Raaschou-Nielsen et al. 2016, Eeftens et al. 2014, Gehring et al. 2015, Hampel et al. 2015, Wang et al. 2014, Adhikari et al. 2016). However, land use regression fails to separate impacts of pollutants clearly and transferability accuracy is relatively low in areas where topography and land use are quite different. For example, there may be large overlaps between the predictors for different PM components, since many of them share the same source. In addition, land use regression does not provide much information on seasonal variability. As the ISA acknowledges, model validation is not performed consistently across the literature and in some studies included in the ISA, model correlation with ambient concentrations can be quite low (Beckerman et al. 2013b, Hu 2009, Bentayeb et al. 2014). By using conclusions and concentration-response functions from such studies, the EPA has actually injected an unknown and possibly substantial amount of uncertainty into its analysis.

Further, the use of model predictions of ground-level PM does not resolve the disparity between personal and ambient exposure concentrations. Unlike most other criteria pollutants, PM has many sources, including those inside the home (e.g., cooking, cleaning, environmental tobacco smoke, and the "personal cloud") that are likely not captured by outdoor monitors (Wallace 1996, Abt et al. 2000, Ferro et al. 2004). Over 40 studies have evaluated the differences in personal and ambient PM concentrations and meta-analyses of available data have been unable to determine a consistent trend. For example, Avery et al. (2010a, b) conducted a systematic review of studies that concurrently measured PM concentrations on participants and either at an ambient or outdoor residential location. The authors noted that only approximately 24% of the 29 ambient/personal r values were greater than 0.7. Only approximately 19% of the 16 outdoor/personal r values were greater than 0.7. In other words, ambient monitors predicted at least 70% of the personal exposure concentrations less than 25% of the time. Importantly, 7 of the 29 personal/ambient measurement pairs (24%) differed by more than 10 $\mu g/m^3$. This 10 $\mu g/m^3$ measurement difference in personal versus ambient $PM_{2.5}$ not only comprises almost the entire level of the current annual NAAQS of 12 $\mu g/m^3$, but it is also the normalized incremental exposure used throughout the EPA's analysis in the ISA.

Many factors seem to affect the relationship between ambient concentrations and personal exposures, as well as the resulting risk estimate. Housing characteristics like heating source, ventilation, and cooking preferences, in addition to local weather, local emission sources, personal activity patterns, and particle composition (Sarnat et al. 2006, Breen et al. 2018, Brown et al. 2009) all impact personal exposure and ambient concentrations differently. Although the ISA does acknowledge a "moderate" correlation (0.3–0.7) between median personal exposures and ambient concentrations measured at fixed site monitors, it subsequently ignores the importance of this correlation in its evaluation of the accuracy of effect estimates. The personal-ambient relationship is important, complex, and, unfortunately, poorly considered in the health effect chapters of this ISA.

Failing to adequately address exposure considerations can lead to faulty conclusions about the risk of PM exposure. This concept is illustrated in a recent cohort simulation study conducted by NERA Economic Consulting (Attachment B). Even using unrealistically pristine cohort data simulated in this study, the concentration-response functions tended to be distorted toward linearity or supra-linearity as measurement error increased. Any true threshold would be nearly impossible to find using more realistic data, which is subject to even greater noise and error. The NERA analysis is consistent with work by Rhomberg et al. (2011), which noted that exposure measurement errors can flatten and linearize a curve when there actually is a threshold. These analyses suggest that greater scrutiny should be applied to evaluating the linear concentration-response functions reported in epidemiologic studies, as well as blanket statements in the ISA such as, "Generally, the results of these analyses continue to support a linear, no-threshold relationship for total (nonaccidental) mortality, especially at lower ambient concentrations of $PM_{2.5}$."

Rather than ignoring key exposure evidence or relying on default assumptions made by the EPA or study authors, the EPA should conduct a more thorough, independent analysis of personal exposure and measurement error and the impact that it has on dose-response evidence. The EPA could do this by restricting its current assessment to those studies that first provide evidence that the monitor or model was a good predictor of personal exposures. Further, the EPA should carry this uncertainty through the rest of its assessment of the causal determinations in the ISA and the subsequent health protectiveness of the current standard. Currently available evidence is clear that at concentrations at and below 12 $\mu g/m^3$, there is little certainty that instruments or models are capable of distinguishing +/- 1 $\mu g/m^3$ or that ambient concentrations offer a suitable surrogate for personal exposures. Any policy decisions related to the health protectiveness of the NAAQS should be made with this understanding.

Exposure measurement error does not always bias effect estimates toward the null.

The ISA states that, "Bias toward the null, or attenuation of the effect estimate, indicates an underestimate of the magnitude of the effect, and is characteristic of nondifferential measurement error" (page 3-3). This statement is overly simplistic and not entirely true. Chang et al. (2014), for example, states that "In general, the exposure misclassification resulting from geographic models of environmental exposures can be differential and can result in bias away from the null even if non-differential." Jurek et al. (2005) also states that "additional conditions beyond non-differentiality are required to guarantee that bias is towards the null." Biasing risk estimates toward the null is, in fact, limited to simple, single-pollutant studies where: (1) the concentration-response is *genuinely* linear (Fuller 1987), (2) measured concentrations are good surrogates for personal exposure, and (3) differences between the measured and the personal exposures are constant (Zeger et al. 2000). Further, even when there is a bias toward the null the effect estimate is not necessarily underestimated, as stated in the ISA. Jurek et al. (2005) states that "it is incorrect to claim (as authors often do) that the estimate from a study must be an underestimate because the bias is towards the null." The EPA does not appear to have conducted any analysis of the assumption of a bias toward the null and does not provide any scientific citation that unconditionally supports it. Exposure and measurement error are highly complex and should be given more than a passive or default consideration in the ISA.

The ISA should be consistent in use of studies, particularly those in foreign nations.

The EPA states that studies examining associations in Asia have "limited generalizability due to high annual pollutant concentrations." (page 5-219). Further, Section 3.4.1.2 notes "Since PM levels, sources, and composition are likely to differ substantially in some areas from those typically encountered in the U.S., this section focuses on North American and European personal ambient studies." Yet it appears that studies conducted outside these regions are subsequently used in the ISA's health effects evaluations. For example, the only studies that showed a statistically-significant cardiovascular effect in Figures 6-8 through 6-11, which examined associations between short-term $PM_{2.5}$ exposure and cardiovascular effects in single-pollutant models and models adjusted for other pollutants, were conducted in Taiwan. The EPA should justify this discrepancy and provide a narrative discussion on why effect estimates for Taiwanese $PM_{2.5}$ are so high relative to $PM_{2.5}$ from other nations.

C. General Comments Related to Biological Plausibility and Causality

The ISA's discussion and presentation of biological plausibility does not objectively weigh the available scientific evidence and should be reconsidered.

The EPA's addition of a health endpoint-specific section on biological plausibility and diagram illustration are an improvement from previous ISAs; however, they also illustrate the extreme uncertainty in the current literature. The majority of pathways for each health system only indicate "proposed" relationships to health endpoints—that is, there is no experimental or epidemiologic evidence for the relationship. It is curious, then, how the EPA can determine that a causal relationship exists between PM exposure and these health endpoints when the evidence does not exist. Unlike traditional risk assessments, the EPA's biological plausibility analysis appears to begin with the presumption that the health endpoints are caused by exposure and then the EPA outlines potential ways such an effect could occur. A better, more objective and transparent approach would be to restrict the analysis to those pathways with evidence that lead to apical events using a strong weight-of-evidence approach, which includes weighing negative or null evidence and evaluating dose-response and temporal concordance (e.g., between hypothesized precursor events from experimental studies and apical outcomes from epidemiological studies). As currently presented, the biological plausibility diagrams and discussion are, at best, misleading.

For key endpoints, the EPA should also provide some discussion of the likelihood of the development of subsequent effects.

In addition to the biased approach to the biological plausibility assessment, the EPA puts an unwarranted amount of emphasis on small subclinical biological changes. For example, only three studies (Jacobs et al. 2012, Rich et al. 2012, Brook et al. 2011) discussed in the ISA showed any statistically significant association between elevated $PM_{2.5}$ and changes in blood pressure (although the studies did not show consistent associations across all participants). While the change in blood pressure was minor, the EPA's biological plausibility assessment and diagram indicate that these changes in blood pressure would then lead to exacerbation of conduction abnormalities or arrhythmia, which then lead to emergency department visits, hospital admissions, and/or mortality (the apical events). As is commonly known, blood pressure is constantly changing throughout the day, and not every change in blood pressure or subclinical biomarker leads to an adverse health event, much less hospitalization. Although true changes in health effects may lead to more serious effects, many people experience changes in blood pressure or biomarkers without experiencing hospitalizations or death. Therefore, if the EPA provides such discussion and illustration of potential biological pathways, it must also provide some context and evaluation of the likelihood that such effects would develop. Absent this clarification, the mode of action discussion is illogical and misleading.

The EPA should require stronger and more consistent evidence in determining the biological plausibility and potential causality of PM-induced health effects.

In its weighing of evidence, the ISA appears to prioritize positive effect estimates over negative or null effect estimates. Indeed, in several instances, the ISA considers a single positive result to be enough evidence that PM induced the effect, even if conflicting evidence is available from a high quality study. This approach is scientifically and logically flawed. Substantial differences exist in study design, variable control, and statistical evaluation, all of which impact the strength of any findings.

One specific problem is the lack of dose-response concordance between concentrations known to produce effects in high-dose animal studies and lower-concentration epidemiology or controlled human exposure studies. The ISA fails to provide any meaningful discussion on why this may occur or why the EPA chose to ignore it in its final causal determination. Dose-response is a cornerstone of toxicology and there is no scientific basis for the EPA's treatment of an effect that occurs at high doses in an animal model as a likely effect at all doses in a separate species, especially when there are negative results at lower doses in humans.

One of the more extreme examples of this is shown in associations between short-term $PM_{2.5}$ exposures and asthma exacerbations (although this method was also used for other endpoints). The EPA admits that exposure studies in humans, inarguably *the* most relevant species for evaluating the biological plausibility of similar effects in the United States population, are inconsistent with respect to lung function effects and pulmonary inflammation in asthmatics. The ISA specifically discusses Urch et al. (2010), which found no sensitive subclinical effects underlying asthma exacerbation in human volunteers exposed to concentrated air particles (CAPs) at concentrations up to four-fold higher than the level of the current short-term NAAQS. Rather than conclude that such effects were then unlikely in the population, the EPA turns to much less relevant data in animals that were exposed to high doses (>350 $\mu g/m^3$) that are not relevant to typical ambient concentrations. It is unclear why the EPA would dismiss the most directly relevant and informative data and ignore the lack of dose-response concordance between human and animal studies. Dose-response concordance needs to be more thoroughly analyzed and discussed for the sake of making any scientifically credible assertions about health effect associations at low exposure concentrations.

In addition, the EPA frequently acknowledges the presence of inconsistent results, only to conclude that evidence exists for an effect due to results from another study. For example, Figure 11-14 illustrates that four of six studies are not statistically significantly associated with mortality. The ISA provides little meaningful discussion about why results from the two studies showing an effect are enough to outweigh the results from other reviewed studies. The ISA does try to rationalize inconsistent results in Lanzinger et al. (2016), for example, by stating that the study only uses a few years of data. However, Janssen et al. (2013) only uses data from 2008-2009 and found statistically significant results. An alternative and entirely plausible reason for these inconsistent study results is that the results are due to chance alone.

Finally, the EPA needs to consistently apply its causal framework. For example, the ISA states that the causality determination for short-term $PM_{10-2.5}$ exposure and total mortality was "suggestive of, but not sufficient to infer causality" because the magnitude of the association along with the width of the 95% confidence intervals vary across studies. However, this same scenario occurs in both long-term and short-term exposure to $PM_{2.5}$ yet the EPA determined that $PM_{2.5}$ was causally related to mortality.

For all of these reasons, the EPA needs to reevaluate its method for evaluating biological plausibility and overall causality determinations. Better, more scientifically rigorous methods already exist and are even in use within other EPA offices. For example, the EPA's Integrated Risk Information System (IRIS) recently began implementing systematic review methods in its chemical assessments.

Epidemiology studies are inappropriate for the basis of causal determinations.

PM is quickly becoming one of the most densely-studied pollutants. There are numerous controlled human exposure studies, which are superior to epidemiologic or animal toxicology studies due to their design, ability to control many potential variables within the study, and use of the most relevant species. The EPA has acknowledged that not all evidence is suitable for risk assessment and, for example, deferred to evidence from controlled human exposure studies in the Risk and Exposure Assessments for ozone, sulfur dioxide, and carbon monoxide (USEPA 2010a, 2014, 2018). Consistent with these assessments and as detailed elsewhere in these comments, it makes little sense for EPA to dismiss the evidence from controlled human exposure studies in favor of epidemiology study findings. Due to ambient PM characteristics (especially its regional heterogeneity) and known exposure measurement errors, epidemiology study designs are particularly prone to errors and biases. Exposure measurement error, in particular, can result in an exaggeration of risks at low concentrations and tend to make a linear response appear supralinear (Crump 2005, Zeger et al. 2000).

Therefore, whenever possible, the EPA should rely on the most relevant data available to it. Epidemiology studies are better suited for hypothesis generation than for determinations of biological plausibility or causality. Consequently, the EPA should evaluate epidemiology studies in this limited light and base mode of action and causality decisions on data from controlled exposure studies that actually critically evaluate these exposure-response processes. The EPA should also include a thorough discussion of whether a supralinear concentration-response function is biologically plausible for PM and, if so, what specific evidence and mechanisms support this determination, especially at environmentally-relevant concentrations.

The EPA's causality framework states that there should be no risk that the association of exposure and effect is due to chance alone, though the EPA is unable to link exposure with most of the effects in its biological plausibility diagram.

The causality framework provides guidelines for consistently and objectively determining the causal nature of the pollutant-response relationship. Categories showing a stronger causal

relationship necessarily require stronger evidence. Indeed, for the "causal" determination, the framework states that "the pollutant has been shown to result in health effects in studies in which chance, confounding, and other biases could be ruled out with reasonable confidence. For example: (1) controlled human exposure studies that demonstrate consistent effects, or (2) observational studies that cannot be explained by plausible alternatives or that are supported by other lines of evidence" (USEPA 2015). Unfortunately, as detailed in comments below, the evidence presented in the ISA chapters related to respiratory and cardiovascular endpoints and particularly in the biological plausibility diagrams for each of the evaluated health endpoints do not appear to provide this level of confidence. The EPA should reconsider many of its causal determinations with better adherence to its causal framework. Further, the TCEQ strongly encourages both the CASAC and the EPA to reevaluate the state of the science with respect to the causal framework. Quantitative causality assessments and systematic reviews have received greater attention and acceptance as best practices in recent years. Improving the scientific rigor, transparency, and objectivity of the EPA's evidence integration, weight of evidence, and causal analyses will ensure greater reliability of subsequent analyses.

The EPA should use dosimetry models to evaluate animal toxicology studies to determine if concentrations are relevant to humans before using them to inform causal determinations.

Although in some instances the EPA correctly relies upon animal toxicology studies to support understanding of potential effects pathways, the EPA fails to also evaluate the relevance of study exposures to humans. Extrapolation of animal toxicological data is necessary to estimate human equivalent concentrations and health outcomes. Even assuming similarity between animal models and their corresponding human diseases, interspecies differences in physiology, behavior, toxicokinetics, toxicodynamics, and genetics may significantly limit the reliability of animal studies. For instance, a 2013 study reported that the mouse models often used in the study of human inflammatory diseases have been misleading because mice differ significantly from humans in their responses to inflammatory conditions. Mice varied from humans regarding the genes which were turned on and off, as well as in the timing, and duration of inflammatory gene expression. Worse still, the mouse models exhibited intraspecies variation in their responses (Seok et al. 2013). The notion that animal toxicological studies, especially those involving environmental pollutants, may be a poor predictor of human health risk/hazard is not new. Undoubtedly, Alexander Pope's dictum stating that, "The proper study of mankind is man" is well known and has been widely cited (Gold 1952). Numerous studies on a variety of chemical exposures, as well as some systematic reviews of animal study literature, stress the difficulty and uncertainties of extrapolating from animal toxicological studies to human experiences (Bebarta et al. 2003, Florey and Abraham 1951, Nau 2001, Needs and Brooks 1985, Lepper et al. 2006).

Dosimetric adjustment is commonplace in chemical risk assessment and is even well discussed in EPA's 1994 guidance on Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (USEPA 1994). Since 2011, the EPA has also published a method for developing data-derived extrapolation factors for inter- and intra-species extrapolation. Further, one of the most common tools for dosimetric adjustment was actually created by the EPA and is in use by the IRIS program. With so much attention paid to dosimetric adjustments and so much existing institutional knowledge and expertise in dosimetry models, it is unclear why the ISA failed to conduct this assessment to determine whether high-dose animal results are truly relevant for humans at environmentally-relevant concentrations.

D. General Comments Related to Uncertainty Analysis

EPA should address uncertainty in use of models, study design, and confounders controlled for in individual studies.

As stated elsewhere in these and previous comments to the EPA, there are numerous areas of uncertainty within scientific studies that should be better considered and, if possible, quantified prior to using them to inform such an important standard. Exposure concentrations, either monitored or modeled, are subject to inherent variability. Health effect classifications by health care providers are similarly subject to mis-classification error and variability as changes occur in personnel, hospital, and insurance coding procedures[1]. These variables can lead to distortions in resulting concentration-response functions. The EPA should also consider important uncertainties that arise due to differences in study design and conduct. The strength of the study design and how well the authors controlled for extraneous variables have great impact on the confidence in the final results.

Further, the EPA should be more thorough when evaluating the potential for confounding in individual studies. The only evaluation of confounding in the ISA is for co-pollutant confounding in some individual studies. However, confounding is a much broader issue than a single co-pollutant. On page A-7 the ISA acknowledges that failure to account for confounders can produce artifactual associations; thus, "studies that statistically adjust for multiple factors or control for them in the study design are emphasized." Although the TCEQ agrees that residual confounding makes it difficult to determine the presence and magnitude of a pollutant-mediated effect, the EPA needs to further discuss if/how it applied this idea in the ISA. For example, how many factors and which factors should researchers control and in what way? Clarifying this information would lead to a more transparent analysis in the ISA, as well as provide guidance for future analyses and research.

A study by Pun et al. (2017) showed there was residual confounding, especially for the national effect estimate, after adjusting for neighborhood behavioral covariates. A study by Greven et al. (2011) also found confounding of the national estimate. These studies and the idea of confounding of the national estimate should be more fully discussed in the mortality section to illustrate the importance of controlling for confounding.

In its summary and integration of study results, the EPA should consider the validation of the model used by the study authors and the uncertainty that the model may contribute to the conclusions.

The ISA states, "attention must be given to the strengths and limitations of individual exposure models and their appropriateness for a given scenario (e.g., urban vs. rural, where monitoring for use in model training and validation may be sparse in the latter case) rather than assuming that the predicted $PM_{2.5}$ exposure concentration is accurate if it includes satellite data" (page 3-39). The TCEQ agrees with this statement and believes that it should factor into future risk estimates and analyses, especially because satellite models are relatively new and many factors appear to affect their performance. In fact, a recent study by Zhang et al. (2018) conducted in Texas using satellite models was not mentioned in the ISA but illustrates some of the complexities involved in predicting daily $PM_{2.5}$ concentrations. The model performance varied

[1] According to the National Institute of Health and the National Heart, Lung, and Blood Institute, "Limitations of cause-of-death statistics, other than those associated with revisions in the ICD, are well-known. Inaccuracies in death certification and inconsistencies in selecting and coding the underlying cause of death create uncertainties about the true mortality from a specific cause compared with other causes. These limitations must be kept in mind when comparing the same cause of death over time or the same cause of death between demographic groups or countries."

greatly by region, season, and study years. Such uncertainties need to be considered if risk estimates from these studies are to be used in forming a causal determination and especially if they are used to inform the Risk and Exposure Assessment.

E. General Comments Related to Health Effect Estimates

The EPA's methods for evaluating the shape of the dose-response curve essentially ensure that the shape will appear linear. The EPA needs to better consider key assumptions and the impact that they have on the shape of the dose-response curve.

As described previously in these comments, existing errors can alter the shape of the dose-response curve. Exposure measurement error, in particular, can result in an exaggeration of risks at low concentrations and tend to make relationships appear linear or supralinear (NERA 2018, Rhomberg et al. 2011, Crump 2005). Further, epidemiology studies generally assume a linear dose-response shape (Lepeule et al. 2012). Relying solely on epidemiology studies, then, tacitly assumes a linear dose-response shape without consideration of the necessary mode of action data to support such a model choice. Indeed, the limited evidence provided in the ISA is difficult to interpret, given both the lack of empirical evaluations of alternatives to linearity, as well as the results from cut-point analyses that provide some evidence for a non-linear relationship between $PM_{2.5}$ exposure and many of the endpoints evaluated in the ISA. The TCEQ urges the EPA to reconsider available data more objectively through evaluation of known errors as well as evaluating how those errors may impact the appearance of the dose-response.

The EPA should place more emphasis on the statistical significance of results, rather than general trends of point estimates.

In the past, the EPA has correctly expressed concern that statistical significance could be fabricated in an attempt to attain publication (e.g., p-hacking). However, this reason alone is not sufficient to disregard statistical significance altogether. As further detailed below, a study quality evaluation would likely mitigate these concerns while still providing some confidence that results are not influenced by chance.

In the IRP for the current evaluation, the EPA asks the questions, "Are the statistical analyses appropriate, properly performed, and properly interpreted? Are likely covariates adequately controlled or taken into account in the study design and statistical analysis?" These questions indicate that statistical significance should have importance when assessing whether a study has found an effect associated with exposure to PM. While a positive, yet not statistically significant finding may indicate an association between an effect and PM exposure, statistically speaking, chance cannot be ruled out. Results that are not statistically significant contribute substantial uncertainty to a science-policy decision without ensuring that the resulting policy would gain some health benefit.

As such, it is imperative that statistical significance be expressly acknowledged in all presentations of results. For example, on page 11-33 of the ISA, the EPA states that "Kim et al. (2015) as part of the DASH study in Denver, CO, examined the $PM_{2.5}$-mortality association at 10 km and 20 km buffers around a single monitor and found no evidence of a difference in the association across buffers." However, the ISA failed to note that this study also found no significant association between $PM_{2.5}$ and total non-accidental mortality. Failure to present this information leaves the reader with the impression that Kim et al. (2015) found a significant association between $PM_{2.5}$ exposure and mortality that did not dissipate over distance, which is entirely false.

The ISA needs to correct its misconception that hazard ratios (HRs) are interchangeable with risk ratios or relative risk. These are different statistical tests with different interpretations.

The EPA should be careful not to conflate HRs and relative risk. For example, the ISA called the estimate from Shi et al. (2015) a relative risk in the text but it is presented in Figure 11-18 as a hazard ratio. Further, the effect estimate from Wang et al. (2017) is referred to as a relative risk for the annual average for $PM_{2.5}$ on line 30 of page 11-70 of the ISA, but the effect estimate for their analysis for exposures less than 12 $\mu g/m^3$ is called a hazard ratio in line 31. It seems unlikely that they would have calculated both, so this oversight should be corrected. According to Sutradhar & Austin (2018), "Although the direction of the HR can be used to explain the direction of the relative risk, the magnitude of the HR alone cannot be used to explain the magnitude of the relative risk. Authors should refrain from using the magnitude of the HR to describe the magnitude of the relative risk." In other words, the two are not interchangeable. A discussion of the difference between the two would increase confidence in the EPA's analysis of reviewed studies.

HRs in the ISA seem to be a single HR averaged over the entire study's follow-up period, though this may not be statistically appropriate.

The ISA frequently presents HRs from various studies in an attempt to show coherence across studies. However, the HRs presented appear to be a single HR averaged over the entire study's follow-up period, which may be statistically inappropriate. According to Sutradhar & Austin (2018), "the common presentation of a single HR averaged over the duration of the study's follow-up may be misleading, particularly when the association is time-varying and period specific. Moreover, the period-specific HRs have a built-in selection bias as they are estimated by conditioning on the absence of the event in the prior time periods." Therefore, the HRs in these figures, which inform the causal determination and ultimately the NAAQS, may not be accurate. The EPA should better consider the statistical appropriateness of the values it uses to conduct its evaluation. Further, the EPA should not only support its use of these values in the ISA, but also discuss the statistical issue in general to stimulate interest and future research to better inform future NAAQS reviews.

The EPA should consider how different monitoring/modeling methods of studies could affect effect estimates.

As detailed above, both monitoring and modeling data are subject to sometimes significant variability and error. The ISA appears to disregard this error in its evaluation of the available literature and, instead, treats exposure estimates as true exposure concentrations. Understanding that no data are perfect, the EPA should still make some attempt at evaluating the uncertainty in exposure estimates and the impact of this uncertainty on effect estimates.

A recent-meta-analysis by Vodonos et al. (2018) showed the following for long-term exposure, which should be discussed in the ISA because it illustrates this issue well: "studies using space time exposure models or fixed monitors at zip-code scale (as compared to land use regression method), or additionally controlling for area level socio-economic status, or with mean exposure less than 10 $\mu g/m^3$ were associated with higher mortality effect estimates." If different monitoring/modeling methods give different effect estimates the choice of key studies used to base risk estimates on becomes even more important. It also means this source of uncertainty needs to be addressed when calculating, using, and comparing HRs from studies using different methods.

The EPA inappropriately presents pooled results from multi-city epidemiology studies, which are likely biased due to well-known regional heterogeneity of risk, concentration, and composition.

Although national estimates from multi-city epidemiology studies of single pollutants generally can be useful for normalizing study results for comparison and evaluating the need for a national standard, this is not the case with PM mass. Unlike single pollutants such as sulfur dioxide or ozone, PM of any size fraction varies substantially in composition between regions and seasons. As such, effect estimates are often highly dependent upon a particular study or study region. For example, Bell et al. (2008) calculated a statistically significant national average increase in respiratory and cardiovascular hospital admission rates (lag 0) with increasing $PM_{2.5}$ exposure. However, it is clear from the presentation of results in that paper that this relationship was driven by effect estimates in the Northeast; estimates in the Southeast, Northwest, and Southwest were not statistically significant. The current ISA acknowledges this dependency, stating that multi-city studies seem to show a regional or even city-specific pattern in associations for both short-term and long-term exposure to $PM_{2.5}$, a statement that is further supported by Zeger et al. (2008) and Baxter et al. (2017). Given this heterogeneity, it is unclear how presenting a national effect estimate would be appropriate. In instances where regional heterogeneity is so significant, the TCEQ recommends that the EPA not use national averages or estimates.

The EPA should also evaluate whether annual estimates are appropriate, given seasonal differences in effect estimates.

The ISA states that examining whether $PM_{2.5}$-mortality associations differ by season can provide a better understanding of the overall relationship between short-term $PM_{2.5}$ exposure and mortality and that, "Across recent multicity studies, there was general agreement that $PM_{2.5}$-mortality associations were larger in magnitude during warmer months." TCEQ concurs with this statement in general because there do seem to be seasonal differences. However, the relevance of seasonal differences need to be discussed in the context of how these differences impact the annual national mortality effect estimates or what these differences mean. This general statement is simplistic because there seem to be regional or inter-city differences that factor into the relationship as well. For example, Zhou et al. (2011) looked at effects in Seattle and Detroit and found that for Seattle there was a stronger association in winter while in Detroit there was a stronger association in summer. Furthermore, although the ISA states that spring generally had the greatest association with mortality, Pascal et al. (2014) did not show spring as having the greatest association with mortality.

Additional studies that were not included in the ISA are pertinent to this topic. Greven et al. (2011) and Pun et al. (2017) both state that the national level association between mortality and long-term $PM_{2.5}$ seems to be confounded while the local estimate is less likely to be so. Whether potential residual confounding may be causing these differences or even driving the associations should be discussed in the ISA. Alessandrini et al. (2016) and Cakamak et al. (2018) also provide useful discussions on differences in effect estimates between cities and certain effect modifiers. In addition, several single city studies (Goldberg et al. 2013, Garrett et al. 2011, and Kim et al. 2015) were not discussed in relation to overall mortality but, taken together, provide additional evidence of heterogeneity.

The relationship with co-pollutants is more complex than is presented in the ISA.

The EPA does not fully discuss the relationship with co-pollutants. For example, the ISA states that "Across 12 studies that examined potential confounding by gaseous copollutants (Di et al. 2017a, Lee et al. 2015a, Pascal et al. 2014, Samoli et al. 2013), the $PM_{2.5}$-mortality relationship was relatively unchanged." However, this summary is not fully descriptive of relationships in the

cited studies. Samoli et al. (2013) actually showed a numerically decreased effect estimate after gaseous co-pollutants were included with $PM_{2.5}$ in the analysis. In contrast to this, Pascal et al. (2014) only showed a significant association for $PM_{2.5}$ with mortality for the whole year when ozone was added to the analysis. According to the study authors, "risk estimates dramatically decreased for $PM_{2.5}$" when data were evaluated by season (Pascal et al. 2014). Janssen et al. (2013) states that "PM_{10} and $PM_{2.5}$ are too highly correlated to disentangle their independent effects." For long-term mortality, Figure 11-20 of the ISA shows that estimates are at least somewhat inconsistent. In some studies, the estimate increases while in others it decreases after the addition of co-pollutants. For example, Krewski et al. (2000) shows that the effect estimate for $PM_{2.5}$ decreased dramatically after the addition of SO2 into the model. The results presented in Ito et al. (2007) also place great suspicion on the practice of interpreting multi-pollutant models as indicative of the pollutants' relative health effects and throw into question the commonplace practice of using multi-pollutant models in health effects analyses. As such, the EPA should more fully consider the complex relationship with co-pollutants in the ISA and subsequent assessment documents and, at a minimum, provide greater scientific support for their methods and judgement decisions.

The health effect chapters in the ISA appear to disregard important observations related to personal exposure, regional heterogeneity, and dosimetry made in earlier chapters.

Chapters 2-4 of the ISA provided a fairly detailed discussion on exposure, ambient concentrations, and deposition, translocation, clearance, and retention of particles and their components within the body. However, the subsequent health systems evaluations in Chapters 5-12 failed to adequately apply the knowledge from the previous chapters in the interpretation and extrapolation of study findings. None of the health effect chapters consider that concentrations used in epidemiologic associations are at all different than actual personal exposures. The time, space, and compositional heterogeneity known to exist with PM mass is also largely ignored, with greater emphasis being placed on any positive associations with health effects. The application of PM dosimetry knowledge was only evident in very few instances, such as in the interpretation of the study by Ljubimova et al. (2013) on page 8-67. As discussed elsewhere in these comments, issues related to personal exposure, regional heterogeneity, and dosimetry can cause significant biases in the interpretation and integration of results.

Therefore, the EPA should better integrate all available evidence, not just positive associations in health effect studies, in its ISA. This should include some discussion and quantitative accounting of the uncertainty that exposure and measurement error causes to associational evidence and statistical results. The EPA also needs to adopt appropriate methodology incorporating the use of dosimetry analysis (inter- and intraspecies variations in exposure, deposition, translocation, clearance, and retention of particles and their components within the body) in the interpretation and extrapolation of animal toxicological studies to human health outcomes. The EPA should also better represent the heterogeneity of PM mass and determine whether the evidence still suggests a national standard is appropriate.

The ISA does not consistently nor appropriately consider the implications of the extreme heterogeneity of PM mass in its health effect evaluations.

The most obvious consistency in the results from the vast available epidemiological literature is the inconsistency (i.e., incoherence) of those results. For example, while Turner et al. (2011) found that a 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentration was associated with a statistically significant increase (15-27%) in lung-cancer mortality in never smokers, Lepeule et al. (2012) perplexingly found a statistically significant increase in former smokers but not in much larger groups of never or current smokers (Table 2 of the study). Results from the 2010 Risk and Exposure Assessment (USEPA 2010b) also demonstrated heterogeneity and indicated, for

example, that while the current annual NAAQS (12 μg/m³) and 24-hour NAAQS (35 μg/m³) were not predicted to reduce $PM_{2.5}$-associated lung cancer mortality by any margin (0% reduction) in Fresno, CA; Salt Lake City, UT; or Tacoma, WA; the NAAQS were predicted to reduce $PM_{2.5}$-associated lung cancer mortality up to well over 30% in Houston, TX; Birmingham, AL; St. Louis, MO; Atlanta, GA; Baltimore, MD (Tables E-63 and E-72 of USEPA 2010b). If PM mass were truly the toxicologically-relevant pollutant, there would be no reason for this disparity.

More recently, Pun et al. (2017) observed regional heterogeneity in COPD- and lung cancer-associated mortality. They reported that a 10 μg/m³ increase in longer-term $PM_{2.5}$ concentrations was associated with decreased COPD mortality risk in the South in the unadjusted-model, which became statistically significantly *decreased* in the Behavioral Risk Factor Surveillance System (BRFSS)-adjusted model (adjusted for prevalence of nonwhites, current smokers, persons with diabetes and asthma, heavy alcohol drinkers, average median income, body mass index; Table 2 of Pun et al. 2017). Similarly, while statistically increased in other regions, a 10 μg/m³ increase in $PM_{2.5}$ concentration was *not* associated with statistically increased lung cancer mortality risk in the Midwest (Table 2 of the study). Moreover, spatiotemporal analysis in the unadjusted-model showed regional heterogeneity in mortality risk for *all* respiratory endpoints (i.e., all respiratory, COPD, pneumonia, lung cancer) with two regions having negative associations for three of the four mortality endpoints (Web Table 4 of Pun et al. 2017).

Spatiotemporal analyses in the BRFSS-adjusted model reveal stark differences in supposed respiratory mortality risk associated with a 10 μg/m³ increase in $PM_{2.5}$ concentration (i.e., all respiratory, COPD, lung cancer) that appears to be minimized in the ISA. For example, the spatiotemporal analyses indicate several *negative* correlations between increased $PM_{2.5}$ and mortality risk that even achieved statistical significance (i.e., BRFSS-adjusted model: all respiratory mortality in the Midwest, pneumonia mortality in the Midwest and US; unadjusted-model: pneumonia mortality in the northeast; Web Table 4 of the study). Similarly, Pun et al. (2017) demonstrated obvious regional heterogeneity in the spatiotemporal analyses of all cause, all cardiovascular, ischemic heart disease, and congestive heart failure mortality per 10 μg/m³ increase in $PM_{2.5}$ concentration. There were *negative* associations in either the unadjusted- or BRFSS-adjusted model for all cause and all cardiovascular mortality in the South, Northeast, and Midwest; ischemic heart disease mortality in the South and Northeast; and congestive heart failure mortality in the Northeast and Midwest (Web Table 4 of Pun et al. 2017). Moreover, the negative associations were statistically significant for all cardiovascular and ischemic heart disease mortality in the Northeast in both the unadjusted- and BRFSS-adjusted models, ischemic heart disease mortality in the South in the BRFSS-adjusted model, and congestive heart failure in the West for both models (Web Table 4 of the study).

Krewski et al. (2009), a key study for long-term $PM_{2.5}$ exposure and mortality in the 2009 ISA, also showed regional heterogeneity. For example, all cause, cardiopulmonary, and lung cancer mortality were *negatively* associated with a 10 μg/m³ increase in $PM_{2.5}$ long-term (3-year) concentration in New York City, which was not the case for Los Angeles (or nationwide) (e.g., Commentary Table 3 and Commentary Figure 4 of Krewski et al. 2009, Table 7-9 of the 2009 ISA/USEPA 2009). Numerous other studies show regional heterogeneity in mortality results as well (e.g., Figure 4 of Cakmak et al. 2018, Table 2 and Figure 4 of Greven et al. 2011, Table 2 of Laden et al. 2006, Pun et al. 2017). In general, there appears to be a lack of increased mortality per 10 μg/m³ increase in $PM_{2.5}$ concentration in the western United States (a relationship that sometimes becomes negative when adjusted for socio-economic status) versus statistically significant increases for the eastern and central United States in Zeger et al. (2008). Figure 21 from Krewski et al. (2000), provided below, is a particularly useful illustration of the significant regional heterogeneity in mortality associations/risk.

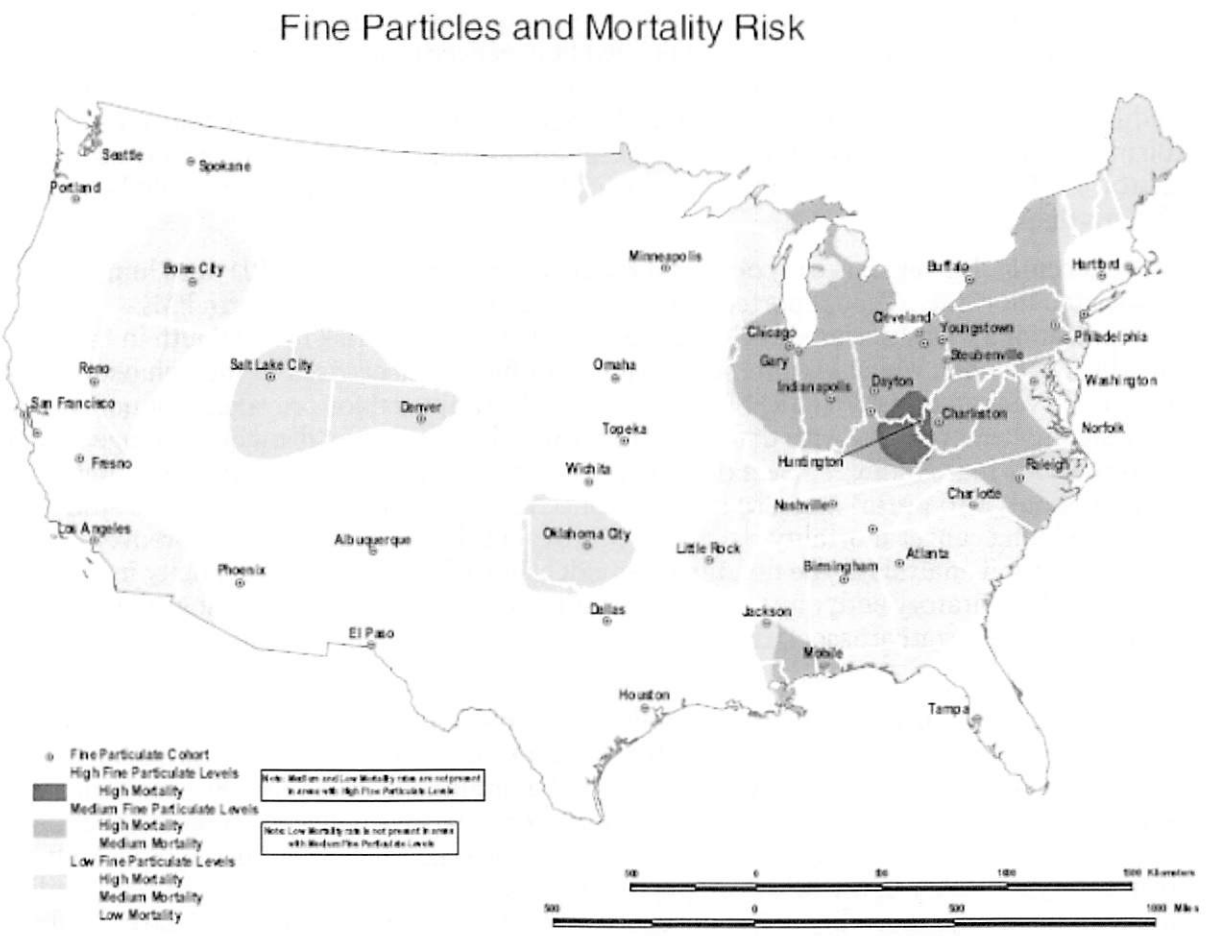

Figure 21. Spatial overlay of fine particle levels and relative risk of mortality. Interval classifications for fine particles (in $\mu g/m^3$): low 8.99–17.03; medium 17.03–25.07; high 25.07–33. Interval classifications for relative risks of mortality: low 0.502–0.711; medium 0.711–0.919; high 0.919–1.128.

As an additional example, Enstrom (2017) reported *no* significant relationships between long-term $PM_{2.5}$ and total mortality in the Cancer Prevention Study II cohort when the best available $PM_{2.5}$ data were used for 85 counties across the US as well as for the Ohio Valley states (12-17 counties) and other states (38-68 counties), including California (see Tables 2, 3 and Appendix Table B-1 of the study). The current ISA only contains a few lines on this study (in Section 11.2.2.1), characterizing it as inconsistent and stating, "Inconsistencies in the results could be due to the use of 85 counties in the ACS analysis by Enstrom (2017) and 50 Metropolitan Statistical Areas in the original ACS analysis." Additionally, You et al. (2018), which was not included in the ISA, showed no statistically significant association between either ozone or $PM_{2.5}$ and acute human mortality in California (see Tables 2-4 of the study) and conclude, "In the absence an association of air quality, as measured by ozone or $PM_{2.5}$, with acute mortality (All Cause, Cardiovascular or Respiratory), there is no evidence supporting current air quality being causal of acute deaths in California." At the same time, the EPA cites Pope et al. (2014) and Turner et al. (2016) in this section as examples of recent studies showing consistency with previous results, seemingly concentrating primarily on results that support previously drawn conclusions. Although subtle, when taken together, the EPA seems to be implying that: (1) negative studies based on certain geographical areas or regional analyses are less important and can be disregarded if inconsistent with available positive studies (even those like Pope et al. (2014) and Turner et al. (2016) that do not evaluate geographical heterogeneity); and (2)

although the NAAQS will apply equally across regions, exposure/effect associations need not be robust geographically/regionally. The TCEQ disagrees with both of these apparent implications.

In terms of key short-term $PM_{2.5}$ exposure studies from the 2009 ISA (USEPA 2009), Zanobetti and Schwartz (2009) results showed regional heterogeneity with an average of 73% of the regional analyses (regions determined by climate type) not having statistically increased mortality for a 10 $\mu g/m^3$ increase in $PM_{2.5}$ for all-cause, cardiovascular disease, myocardial infarction, stroke, and respiratory mortality (Table 4 of study). Zanobetti and Schwartz (2009) also showed seasonal heterogeneity with 1-4 seasons not having statistically increased mortality for all-cause, cardiovascular disease, myocardial infarction, stroke, or respiratory mortality. In fact, there was a *negative* summertime association between a 10 $\mu g/m^3$ increase in $PM_{2.5}$ and both cardiovascular disease and myocardial infarction mortality across 112 cities (Table 1 of study).

The results of Moolgavkar (2003) corroborate this substantial heterogeneity in their evaluations of associations between components of air pollution (e.g., PM_{10}, CO, SO_2) and nonaccidental and vascular disease mortality *in different locations and from season to season*, with "only weak and inconsistent" associations of mortality with PM_{10} in Los Angeles County and CO and SO_2 being more strongly associated. As with Los Angeles County, Cook County results for cardiovascular mortality showed substantial heterogeneity, with zero to no more than one statistically significant association for PM_{10} across seasons for any given lag (0-5 day lag for four seasons = 5 comparisons per season and 20 comparisons total) and a total of only three statistically significant associations for the 20 comparisons made (Tables 12 and 13 of the study). Furthermore, associations for both Cook County and Los Angeles County paradoxically flip between positive and negative between lags for every season (e.g., positive in the winter for lag 4 but negative for lag 5 for both counties), with the *negative* association between PM_{10} and mortality in the fall being statistically significant for Cook County and the *negative* association in the winter being statistically significant for Los Angeles County (Tables 12 and 13 of the study).

The heterogeneity demonstrated in these key studies from the 2009 ISA (USEPA 2009) is further supported by the more recent Baxter et al. (2018) study, which demonstrated significant heterogeneity ($p<0.0001$) in $PM_{2.5}$-associated mortality estimates across 312 core-based statistical areas around the country (see Figure 1 of the study). Moreover, multivariate regression showed statistically significant *negative* associations of mortality with various factors, such as natural gas for heating (as opposed to a significantly positive association for heating oil) and increased cooling degree days (as opposed to a significantly positive association for heating degree days). Differences in heating fuel has been offered as a potential reason for regional heterogeneity of $PM_{2.5}$-associated mortality estimates in numerous studies. These data add to the considerable database demonstrating significant heterogeneity both regionally and seasonally.

In addition to mortality effects, there is extreme heterogeneity with respect to morbidity effects. Ito et al. (2007) examined the temporal relationships among air pollution and weather variables in the context of air pollution health effects models and showed that pollutant-pollutant and pollutant-weather interactions can vary by season. Further, the authors found that concurvity problems were reduced by separately analyzing the seasons, suggesting the need for season-specific analyses of health effects.

Bell et al. (2008) also noted that respiratory hospital admissions in the winter (0-day lag) were only statistically increased in the Northeast, and on a yearly basis (2-day lag) only statistically increased in the southwest (Table 2 of Bell et al. 2008). Study authors concluded that heterogeneity of $PM_{2.5}$ effects on hospital admissions (respiratory and/or cardiovascular) may reflect seasonal and regional differences in emissions and chemical constituents (e.g., see

Figures 3A and 3B of the study) or differences in exposure patterns by region/season, susceptible subpopulations, composition by region/season, or a varying confounder such as ozone. Further contributing to the heterogeneity within and between epidemiology studies, other studies show no statistically significant relationships between various short-term $PM_{2.5}$ exposure metrics and emergency department visits for respiratory effects (e.g., Table 4 of Tolbert et al. 2007, Table 4 of Salimi et al. 2018).

Limitations of the studies included in the PM ISA need to be explicitly stated.

The EPA should consider the inclusion of limitations stated by authors in the studies cited in the PM ISA. The inclusions can be made within the body of the study discussion and/or in the table of study summaries presented in the document. It is important to highlight the limitations of the studies so that other scientists who wish to review the document or rely on their results are aware of these limitations and can exercise due caution.

For instance, a few toxicological studies have used intra-tracheal or intra-nasal instillation of high doses of collected PM to study toxic effects. There are, however, clear limitations to using intra-tracheal instillation including: bypass of upper respiratory tract, immediate bolus dose exposure, and less homogeneous distribution of the particles in the lung which may result in differences in clearance, doses delivered to certain cells, as well as the extent and site of systemic absorption compared to inhalation studies. Similarly, study design flaws common in epidemiology studies (e.g., the use of fixed-site ambient air monitors; geocoded addresses of study participants; spatial interpolation techniques used to estimate personal breathing space/exposure of participants; participant recruitment, selection, compliance with study protocols, and loss to follow-up) can be an important potential source of bias and must be acknowledged as a limitation where appropriate and accounted for by EPA in the weighing of evidence. In addition, the lack of patient-specific data and/or information on comorbidities may prohibit the proper evaluation of certain patient characteristics such as genetics, obesity, and disease specifics in many studies. Although most study authors do attempt to acknowledge these shortcomings in their publications, the ISA discussion typically does not adequately relay these limitations. The TCEQ strongly encourages the EPA to better communicate study limitations in order to demonstrate a careful, transparent review of the scientific evidence, as well as to encourage future research in areas of the greatest need.

F. General Comments Related to the PM NAAQS

As explained in more detail throughout the rest of these comments, the EPA should determine whether the data justify a national standard.

One of the overall conclusions of the ISA is that "...the evidence does not indicate that any one ... component is more strongly related with health effects than $PM_{2.5}$ mass" (page 1-1). This is an incorrect statement. EPA's own IRIS program has derived different Reference Concentrations (RfCs) for particulate components that range from 30 $\mu g/m^3$ (hexachloroethane) down to 0.002 $\mu g/m^3$ (benzo[a]pyrene). These RfCs are based on specific health effects and demonstrate that based on the IRIS database alone, particulate toxicity varies at least 15,000-fold commensurate with the toxicity of PM chemical constituents. The evidence presented in the ISA also suggests that PM mass is not equally toxic across the country or over time. PM mass may be comprised of constituents such as organic carbon, elemental carbon, nitrate, and sulfate, as well as trace elements such as iron, vanadium, nickel. These chemical constituents emanate from diverse anthropogenic and natural sources like soil or road dust, vehicle exhaust, biomass combustion, sea salt, and forest fires. As such, there may be significant spatiotemporal variations associated with various regional and local sources of PM (Mirowsky et al. 2013). Indeed, multi-city studies of PM reveal that associations between PM exposure and health outcomes (morbidity and mortality) vary across regions (Katsouyanni et al. 2009, Janssen et al. 2002, Zanobetti et al.

2009), with this variation resulting in part due to differences in chemical composition of PM. Therefore, the specific PM components associated with greater public health risk or specific health outcomes remain to be elucidated and appropriately considered for regulation (as opposed to PM mass, which is inappropriately assumed to be equitoxic regardless of source or chemical composition and regulated as such).

Further, there is a high degree of inconsistency in effect estimates in published literature and a paucity of information about mode of action, toxicokinetics, and toxicodynamics. Therefore, there are other logical explanations for noted health effects that should be more fully considered. This suggestion is consistent with previous advice from the Clean Air Scientific Advisory Committee (CASAC) that urged the EPA to investigate new indicators that may be more directly linked to the health and welfare effects (Samet et al. 2010).

III. Specific Technical Comments

A. Technical Comments Related to Respiratory Effects

The relationship between short-term $PM_{2.5}$ (particularly on a mass basis) to respiratory hospital admissions (HAs) and emergency department (ED) visits should not be deemed to be "likely causal" due to significant scientific uncertainties.

The evidence provided in the ISA and in the available scientific literature is not sufficient to determine that $PM_{2.5}$ likely causes respiratory HAs and ED visits. The EPA's framework states that to reach this causal determination, the pollutant must be shown to "result in health effects in studies where results are not explained by chance, confounding, and other biases" (EPA 2015). According to the available evidence, however, confounding and bias *cannot* be ruled out. The EPA's causal determination is based on epidemiological studies that are of insufficient quality to be able to rule out any number of sources of confounding and bias. Further, there is little evidence that PM mass is independently and consistently capable of inducing even subclinical respiratory effects, much less respiratory HAs and ED visits, which the EPA claims have the strongest evidence. The significant heterogeneity (e.g., region, season, lag) in these respiratory HA and ED visit results suggests that PM mass may not actually be the causative pollutant. As such, the relationship of $PM_{2.5}$ mass to these effects should not be deemed to be "likely causal."

The findings cited by EPA do not provide evidence for reasoned biological plausibility for an independent effect of short-term $PM_{2.5}$ exposure on the exacerbation of chronic obstructive pulmonary disease (COPD).

While the ISA indicates that recent studies generally support an association between short-term increases in $PM_{2.5}$ concentration and exacerbation of COPD, the ISA fails to provide evidence that the effects were related to $PM_{2.5}$ mass or to provide adequate justification for the extrapolation of effects from high exposure concentrations to environmentally-relevant concentrations. In Section 5.1.4.4, the EPA actually admits that copollutant confounding was not adequately examined overall, making it unclear the extent to which the results can be attributed specifically to $PM_{2.5}$ exposure as opposed to other ambient pollutants. Further, although the EPA states that experimental studies support an independent effect of short-term $PM_{2.5}$ exposure on exacerbation of COPD, Section 5.1.4.4.2 is essentially devoid of relevant evidence from controlled human exposure studies.

The ISA also fails to acknowledge the uncertainty in extrapolating results from high exposures to environmentally-relevant concentrations. Section 5.1.4.4.3, related to high dose animal studies, does not discuss the clear lack of dose-response concordance between epidemiology associations at low concentrations and high-dose toxicity study phenomena. The section in general also does not discuss the dose-response concordance between epidemiological study results and

experimental results when exposure concentrations in the controlled human exposure studies were almost 6 times the level of the current short-term NAAQS (i.e., humans exposed to 200 $\mu g/m^3$ CAP; Gong et al. 2004, 2005) and were 5-21 times higher than the level of the short-term NAAQS in the cited animal studies (Saldiva et al. 2002, Clarke et al. 1999, Kodavanti et al. 2000) (Table 7-4 of USEPA 2004),

Consistent with standard risk assessment process, the 2018 ISA needs to cite study exposure levels in its summaries and use those to evaluate dose-response concordance, especially when considering the biological plausibility of epidemiology results at much lower levels. As written, available study findings do not provide evidence for reasoned biological plausibility for $PM_{2.5}$-induced exacerbation of COPD.

The most relevant data to biological plausibility in the inarguably most relevant species and subpopulation (controlled human exposure study data in asthmatics) support the lack of biological plausibility for $PM_{2.5}$-induced lung function decrements in populations with asthma, especially at environmentally-relevant concentrations.

The EPA admits that exposure studies in humans, inarguably *the* most relevant species for evaluating the biological plausibility of similar effects in the United States population, have failed to observe lung function decrements in adults with asthma following short-term $PM_{2.5}$ exposure. Human controlled exposure study data should provide much more weight in a weight-of-evidence of the plausibility of effects in humans than animal studies, which according to Section 5.1.2.3.2 are lacking in this case. Therefore, it is noteworthy that a recent controlled human exposure study (Urch et al. 2010) that included asthmatics found no effects on any measurement of lung function, breathing parameters, or airway responsiveness even at concentrations up to 4-fold higher than the current short-term NAAQS value (Table 5-4 of the 2018 ISA). This overall lack of effect of $PM_{2.5}$ exposure on lung function has also been shown in a study investigating the exposure of individuals with asthma to $PM_{2.5}$ CAPs (Gong et al. 2003) and is consistent with the lack of effect in previous controlled human exposure studies (Section 5.1.2.3.1). The available controlled exposure study evidence in humans and asthmatics does not support the proposed biological plausibility discussion (especially at environmentally-relevant concentrations; see Figure ES-2 of the 2018 ISA) or the causality determination in the ISA.

There is a lack of sufficient evidence and dubious biological plausibility evidence for short- and long-term $PM_{2.5}$ causing respiratory effects in healthy humans (or even in sensitive subpopulations).

The ISA indicates that short- and long-term $PM_{2.5}$ exposures are inconsistently related to respiratory effects in healthy adults, evidence is limited for any given endpoint, confounding by copollutants is inadequately examined where supporting evidence does exist, and uncertainties remain as to whether $PM_{2.5}$ leads to overt respiratory effects in healthy populations. That "uncertainty remains" appears to be a gross understatement given the lack of sufficient evidence and dubious biological plausibility even in sensitive subpopulations (i.e., asthma and COPD exacerbation and lung function effects in asthmatics, as detailed elsewhere in these comments). While the ISA makes allowances for why controlled human exposure and animal toxicological studies do not provide good, consistent supporting data (e.g., time points for assessing effects, doses and particle composition, model sensitivity), the fact remains that evidence from controlled exposure studies in humans have failed to observe any sufficiently supporting results. Section 5.1.7.2 admits that there is little evidence that exposure results in pulmonary function decrements or subclinical inflammatory effects in healthy adult populations. In fact, there were no changes in lung function measures or sensitive BALF cellular and biomarker constituents (e.g., LDH, IL-6, IL-8, α1-antitrypsin) in healthy subjects exposed to 2.6-7 times the current short-term NAAQS value (Petrovic et al. 2000, Ghio et al. 2000, Behbod et al. 2013, Huang et al.

2012, Gong et al. 2000, Gong et al. 2003). These negative human controlled exposure study findings for sensitive effects in the most relevant species are telling as to the lack of biological plausibility of similar effects in the United States population, especially since the exposure concentrations are still several times higher than the level of the current short-term NAAQS.

Animal toxicology studies should not be misconstrued to outweigh reliable controlled human exposure data. First, animal studies are conducted in much less relevant, non-target laboratory animal species as opposed to the highly relevant human in controlled human exposure studies. Additionally, animal studies have reported mixed results (Section 5.1.7.3) and many have been conducted at environmentally-irrelevant high concentrations (see Table 5-13 and Figure ES-2 of the 2018 ISA). Unfortunately, there is a noticeable lack of discussion in Section 5.1.7.3 about the dose-response disconcordance between concentrations known to produce effects in high dose animal studies versus lower epidemiology study concentration results. In fact, Section 5.1.7.3 is devoid of any discussion of the animal exposure concentrations producing the toxicity study effects that EPA is trying to use to support the biological plausibility of effects in humans at lower epidemiology study concentrations. Dose-response concordance must be thoroughly analyzed and discussed by EPA for the sake of making any scientifically credible assertions about the relevance of high dose animal toxicity data to the biological plausibility of epidemiology study results.

The relationship between short-term $PM_{2.5}$ (particularly on a mass basis) to respiratory and respiratory cause-specific mortality and long-term $PM_{2.5}$ exposure to respiratory effects should not be deemed to be "likely causal" due to significant scientific uncertainties.

As discussed in other sections of these comments, there is still "limited coherence across epidemiologic and controlled human exposure studies" (p. 5-108), which complicates the interpretation of the associations observed for short-term $PM_{2.5}$ exposure and respiratory mortality. Substantial uncertainty remains in both short- and long-term exposure studies regarding regional heterogeneity, seasonal heterogeneity, and exposure and measurement error, as well as inconsistency between studies, all of which limits any ability to draw defensible conclusions. Additionally, the lack of biological plausibility and dose-response concordance preclude a "likely to be causal" determination for long-term $PM_{2.5}$ exposure on a national, mass basis (e.g., ignoring composition/source and regional/seasonal differences) and respiratory effects as well as a scientifically credible nationwide, one-size fits all NAAQS. Even assuming that $PM_{2.5}$ from certain sources is capable of causing increased mortality at environmentally-relevant concentrations, the inability to identify the causative $PM_{2.5}$ constituent(s) for any particular endpoint precludes identifying $PM_{2.5}$ mass as "likely causally related" to these effects. The EPA has acknowledged that these $PM_{2.5}$ constituent differences contribute to the heterogeneity observed in study results, which support that all $PM_{2.5}$ is not created equal in terms of toxic characteristics/properties or potency, and by corollary that all $PM_{2.5}$ (i.e., simply on a mass basis) should not in fact be assumed to be causally related to a particular effect either across regions or seasons. As such, the relationship of $PM_{2.5}$ mass to these effects should not be deemed to be "likely causal."

B. Technical Comments Related to Cardiovascular Effects

The assessment method and level of evidence the EPA accepts in determining that an association is due to exposure instead of chance alone is too weak.

As detailed elsewhere in these comments, the application of the causal framework and the method used to evaluate the weight of evidence for health effects, and in particular cardiovascular effects, contains numerous shortcomings for which the EPA fails to account. In addition to exposure and measurement error issues, there are issues related to the reporting of effects.

If the EPA is to rely on changes in a health endpoint, a discussion of the accuracy of the method used to measure that endpoint and the diagnostic accuracy of that endpoint to predict an eventual health condition should be provided.

Measurement error in evaluation of health endpoints should also be considered in the EPA's analysis. For example, the EPA determined that there is some evidence that short-term $PM_{2.5}$ exposure can result in blood pressure changes. Of the seven controlled human exposure studies reviewed by EPA, the amount of change in BP was only provided for two studies—Brook et al. (2009) with a maximum increase of 2.9 mm Hg and Tong et al. (2015) with a maximum increase of 2.1 mm Hg. The EPA neglected to note that most sphygmomanometers used in medical care have an accuracy of 3 mm Hg (A'Court et al. 2011). Further, the EPA provides little discussion as to the clinical relevance of these changes in blood pressure. The suggestion that any change in blood pressure, particularly at levels below those that can accurately be measured by an instrument, are potentially hazardous or lethal is without merit. The human body is well equipped to deal with minor fluctuations in blood pressure, which normally occur constantly throughout the day.

The relationship between short-term $PM_{2.5}$ (particularly on a mass basis) and cardiovascular effects should not be deemed to be "causal."

As with the respiratory effects discussion above, the ISA fails to provide the level of scientific evidence necessary to determine that $PM_{2.5}$ causes cardiovascular effects. The EPA's framework states that to reach this causal determination, the pollutant must be shown to "result in health effects in studies in which chance, confounding, and other biases could be ruled out with reasonable confidence" (USEPA 2015). The epidemiological evidence underpinning this determination can, in fact, be explained by plausible alternatives or even chance alone, particularly due to the extreme inconsistency in study results and uncertainty (especially with respect to exposure and measurement error). Additionally, there is a lack of biological plausibility. According to the EPA's own discussion on biological plausibility, short-term PM-induced health effects occur either through upregulation of the renin-angiotensin system or through inflammation or activation of nerves in the respiratory tract. The only evidence of an upregulation of the renin-angiotensin system is from two studies in rats. The proposed subsequent effect of this upregulation is increased blood pressure, for which the EPA states there is only limited evidence (page 6-50). Clearly this pathway is not plausible. The second proposed pathway (i.e., inflammation or activation of the respiratory tract) is commonly known to be a threshold response. Neither individual scientific studies nor the EPA have first determined that PM exposure at environmentally-relevant concentrations overwhelms the body's natural compensatory mechanisms in order to cause inflammation or nerve activation.

C. Technical Comments Related to Central Nervous System Effects

The "Nervous System Effects" chapter should be re-named the "Central Nervous System Effects" chapter.

As in the 2009 PM ISA, the present ISA should appropriately caption the chapter on PM nervous system effects as "Central Nervous System effects" of PM. All of the apical events of PM exposure in the biological plausibility discussion are central nervous system (CNS) effects. The CNS comprises the brain and spinal cord, while the peripheral nervous system consists of the Somatic Nervous System and the Autonomic Nervous system. The Somatic Nervous system works during voluntary activities to relay information to and from the skin and skeletal muscles. The Autonomic Nervous System (ANS) on the other hand, works during involuntary activities to relay information to all the internal organs in the human body. The ANS is further divided into the Sympathetic Nervous System (which controls body organs in times of stress) and the Parasympathetic Nervous System (which controls body organs when the body is at rest).

Aside from a mere mention of the activation of the Sympathetic Nervous System (SNS) and the Hypothalamus-Pituitary- Adrenal (HPA) stress axis, the entire health endpoints/outcomes reviewed in this section of the ISA were centered on the CNS, not the whole human nervous system.

The ISA fails to provide adequate justification for the causal determination that CNS effects are likely caused by $PM_{2.5}$ exposure.

The ISA notes that the strongest evidence for the causal determinations for short-term ("suggestive of, but not sufficient to infer") and long-term ("likely to be causal") exposure to $PM_{2.5}$ and CNS effects was provided by animal toxicological studies showing effects on the brain. However, flaws in the EPA's evaluation indicate that the available scientific evidence is not strong enough for either of these causal determinations.

First, the EPA failed to employ appropriate methodologies incorporating the use of dosimetry analysis (inter-and intraspecies variations in exposure, deposition, translocation, clearance, and retention of particles and their components within the body) in its interpretation and extrapolation of the results from animal toxicological studies. As discussed elsewhere in these comments, there are many reasons that such an analysis is necessary and regarded as standard practice in risk assessment. Instead, the EPA relied on animal toxicological results on face value to create proposed, and otherwise hypothetical, pathways that justify its causal determinations for adverse impacts on the human nervous system.

In addition, the EPA failed to establish a biologically plausible pathway for the effects to occur. The ISA proposed that particulate matter (soluble components of $PM_{2.5}$ and poorly soluble particles that are part of the $PM_{2.5}$ fraction and smaller than approximately 200 nm) may translocate into the systemic circulation and contribute to inflammatory or other processes in extrapulmonary compartments and/or be transported via the olfactory nerve to the olfactory bulb of the brain. The ISA, however, acknowledged that the extent to which translocation into the systemic circulation or transport to the olfactory bulb occurs is currently uncertain and, therefore, hypothetical. In a study by Bos et al. (2012), which examined two groups of C57BL/6 mice placed in a highway tunnel for five days in cages with and without particle filters, found no evidence of pulmonary or systemic inflammation. It is unclear, then, how $PM_{2.5}$ exposures could "likely" cause CNS effects when inhaled particles may not even reach the system.

Further, the EPA does not show coherence among the available evidence in the ISA. Although some toxicological studies did demonstrate changes in neurotransmitters in the hypothalamus and upregulation of inflammation-related genes indicative of brain inflammation, several epidemiological and controlled human exposure studies did not find similar effects. These inconsistent study findings cast doubt on the relevance of animal effects with respect to predicting responses in humans.

The EPA should have placed a greater emphasis on human studies, which do have greater coherence. For example, a large U.S. study of Medicare enrollees reported a small increase in hospital admissions for Parkinson disease but not dementia or Alzheimer's disease following short-term exposure to $PM_{2.5}$ (Zanobetti et al. 2014). This result agrees with the study by Linares et al. (2017) in Madrid, Spain, which found no association of short-term $PM_{2.5}$ exposure with dementia-related hospital admissions. Additionally, a Canadian study (Szyszkowicz 2007) found no overall increase in hospital admissions for depressive symptoms following short-term exposure to $PM_{2.5}$. Finally, the only controlled human experiment cited in the ISA examined the effects of a 130-minute exposure to 238.4 ± 62.0 $\mu g/m^3$ $PM_{2.5}$ CAPs in Toronto on urinary and blood biomarkers and found no SNS or HPA stress axis-related biomarkers (Liu et al. 2017). These studies of short-term $PM_{2.5}$ exposure and nervous system effects indicate that there is no

consistent evidence suggesting a causal relationship between short-term-exposure to $PM_{2.5}$ and nervous system health outcomes.

Long-term $PM_{2.5}$ exposure studies have found some positive associational results, but also have important inconsistencies that the EPA should further evaluate. Loop et al. (2013) conducted a cross-sectional analysis of incident cognitive impairment using data from a large U.S. cohort designed to study stroke (REGARDS) and observed that $PM_{2.5}$ exposure was not associated with cognitive impairment, defined as a score of ≤4 on a telephone administered Six-Item Screener (SIS), after full adjustment for potential confounders including demographic factors and incident stroke. In another cohort study, Schikowski et al. (2015) examined the association of $PM_{2.5}$ exposure with several domain-specific tests of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery, which includes the Mini Mental State Examination (MMSE). Although associations with a figure copying subtest measuring constructional praxis was reported, no association of $PM_{2.5}$ with global cognition was observed. In a study of rural populations in North Carolina and Iowa, an imprecise, positive association between 4-year average $PM_{2.5}$ concentration and Parkinson disease among farmers in North Carolina (4-year average concentration of 17.7 $\mu g/m^3$) was found, but no association was observed among farmers in Iowa where exposures were lower (4-year average concentration of 11.5 $\mu g/m^3$; Kirrane et al. 2015). Finally, Jung et al. (2014) found no significant evidence of an association between annual average $PM_{2.5}$ exposure at baseline (mean = 34.32 $\mu g/m^3$) and development of Alzheimer's disease in Taiwan[2].

Additional concern has been raised about prenatal and early childhood exposures to $PM_{2.5}$ and CNS effects. Several studies evaluating $PM_{2.5}$ exposure during pregnancy or other childhood stages with cognitive or motor development in children have generally found little evidence of association with cognitive development (Harris et al. 2015, Lertxundi et al. 2015, Porta et al. 2015, Guxens et al. 2014). Where decrements on tests of cognition were observed, confidence intervals were wide. For example, Harris et al. (2015) reported only weakly positive and negative associations between long-term $PM_{2.5}$ exposure during pregnancy and from birth through 6 years of age and cognitive assessment scores in children enrolled in Project Viva. Also, Guxens et al. (2014) reported no decrease in general cognition score in association with $PM_{2.5}$ exposure, although a decrease in psychomotor development was observed. Similarly, Guxens et al. (2015) observed no associations between $PM_{2.5}$ during pregnancy and either borderline clinical or clinical autistic traits using information from cohort studies across four European countries.

Considering the relatively high PM exposure doses, lack of a biologically plausible mechanism, inconsistencies in results reported from animal toxicological studies, insufficient human controlled experimental and epidemiological studies, the EPA should revise its causal determinations for potential adverse effects of PM exposure on the nervous system.

D. Technical Comments Related to All-Cause Mortality

The EPA does not always fully or accurately represent the results of critical studies used in the mortality section.

The way that the EPA summarizes study results often leaves out key information in favor of only reporting data that suggests an effect of PM. For example, the ISA discusses the effect estimates of $PM_{2.5}$ mass from Beelen et al. (2015), but fails to mention that the $PM_{2.5}$ mass effect estimate was reduced to the point of no longer being statistically significant when it was adjusted for sulfur particulate. Wang et al. (2017b) was only discussed with respect to $PM_{2.5}$ mass, but also explored effect modification by various chemical components of $PM_{2.5}$. The authors determined

[2] Jung et al. (2014) studied a cohort in Taiwan, but the ISA references this study population as being in China.

that the risk associated with $PM_{2.5}$ increased relative to the concentration of elemental carbon, vanadium, copper, calcium, and iron and decreased with nitrate, organic carbon, and sulfate. Interestingly, the ISA reports findings from the same study differently. Significant associations between short-term exposure to $PM_{2.5}$ and mortality found in Janssen et al. (2013) were reported as strong evidence, but non-significant associations for $PM_{10-2.5}$ were blamed on the study's short-time series design. The authors of the paper said it may be due to low variability and low concentrations for $PM_{10-2.5}$, which is inconsistent.

Furthermore, the EPA needs to correct the following inaccuracies in Chapter 11.

- Zhou et al. (2011) is mentioned in Table 11-3 but is not included in Figure 11-13. This seems to be a mistake as the other studies in this table are in the figure.
- Figure 11-24 shows that long-term exposure to $PM_{2.5}$ mass has a statistically significant relationship with total (nonaccidental) mortality in Ostro et al. (2015), but the supplement to that paper identifies the HR as 1.01 (0.98, 1.05) for total mortality. The statistically significant HR is for ischemic heart disease, not total mortality.
- Figure 11-24 is also missing at least two components: sulfur from Beelen et al. (2015) and sodium from Chung et al. (2015).
- Page 11-70, lines 7-16 of the ISA makes it seem as if Shi et al. (2015) "applied the refined spatial resolution (i.e., 1 × 1 km grid cells) to all Medicare beneficiaries in the continental U.S. between 2000 and 2012" when it was in fact a different paper, Di et al. (2017b).
- Baxter et al. (2017) stated that "Significant heterogeneity was observed among city-specific effect estimates (Q-statistic P = 0.1)." This is not mentioned in the ISA when EPA discussed this study but could be useful for the discussion of regional heterogeneity.
- The ISA also cites Lepeule et al. (2012) as evidence for the relationship between $PM_{2.5}$ and mortality but in this paper, when the authors stratified the analysis by follow up period, this study was only significant for the period of 1983–1991 for all-cause mortality.
- The results for rural areas for all studies mentioned in Section 11.1.7.2 should be presented.
- The component results for Wang et al. (2017b) should be presented in Section 11.2.6 Associations between $PM_{2.5}$ Sources and Components and Mortality.

The EPA failed to adequately support its claim that short-term exposure to $PM_{2.5}$ can cause both minor, subclinical effects and mortality at the same concentrations.

The ISA discussion on short-term $PM_{2.5}$ exposure and mortality fails to fully meet the biological plausibility consideration of the Bradford Hill criteria. As further described in comments above, the causal pathways for various health effects, such as cardiovascular effects from short-term exposure to $PM_{2.5}$, are incomplete, with toxicological studies offering limited and inconsistent evidence. The EPA has not provided any scientific or biological evidence for the ISA determination that $PM_{2.5}$ can cause both minor, subclinical changes in biomarkers and major health effects, such as mortality, at similar concentrations.

The choice of the shape of the C-R function is not fully supported in Section 11.1.10 of the ISA.

The results for the main studies mentioned for short-term exposure to $PM_{2.5}$ differ, with one showing the same results at lower concentrations (Shi et al. 2015) and the other two showing a greater effect (Di et al. 2017a, Lee et al. 2015b). However, these studies used different cut point concentrations, which makes it difficult to compare them. They also don't look at multiple points but, rather, limited their analyses to either above or below a certain concentration. Using more points would result in a more thorough C-R assessment.

IV. Recommended Methodological Improvements

The NAAQS review process is inarguably one of the most important and impactful processes conducted by the EPA. Therefore, it is important that the review be thorough and correct. As detailed in the comments above, the TCEQ suggests making the following refinements to the ISA method to increase transparency and scientific rigor in the development of the PM NAAQS. A stronger science assessment would ensure that the greatest progress is made toward our two agencies' mutual goals of more meaningful policies for reducing toxic ambient concentrations and greater public health benefits.

- The EPA should adopt a more transparent systematic review-type assessment style. Study quality review should be conducted before studies are used in the causal determination analysis.
- As with other NAAQS developments, the EPA should focus on controlled human exposure studies whenever possible and use epidemiologic and animal toxicology studies as support.
- The use of studies and the presentation of results throughout the ISA should be more consistent.
- The ISA summaries should provide crucial context to effect estimates, including the presentation of confidence intervals and discussion of statistical and clinical significance.
- The EPA should create a more scientifically defensible threshold for causal determinations.
- The EPA should attempt to quantitatively account for uncertainty instead of disregarding it in the final analysis. Qualitatively discussing or considering uncertainty is wholly insufficient in this analysis in particular due to available quantitative uncertainty analysis methods, the wealth of data available on this topic that is directly relevant to PM, and the importance of this standard.
- The EPA should re-evaluate whether the available scientific evidence justifies a national standard.

V. Additional References for the EPA's Consideration

The TCEQ encourages the EPA to consider reviewing and including the following papers in its subsequent draft of the ISA.

- Alessandrini et al. (2016),
- Garrett et al. (2011),
- Goldberg et al. (2013),
- Greven et al. (2011),
- Cakmak et al. (2018),
- Pun et al. (2017),
- Salimi et al. (2018),
- You et al. (2018).

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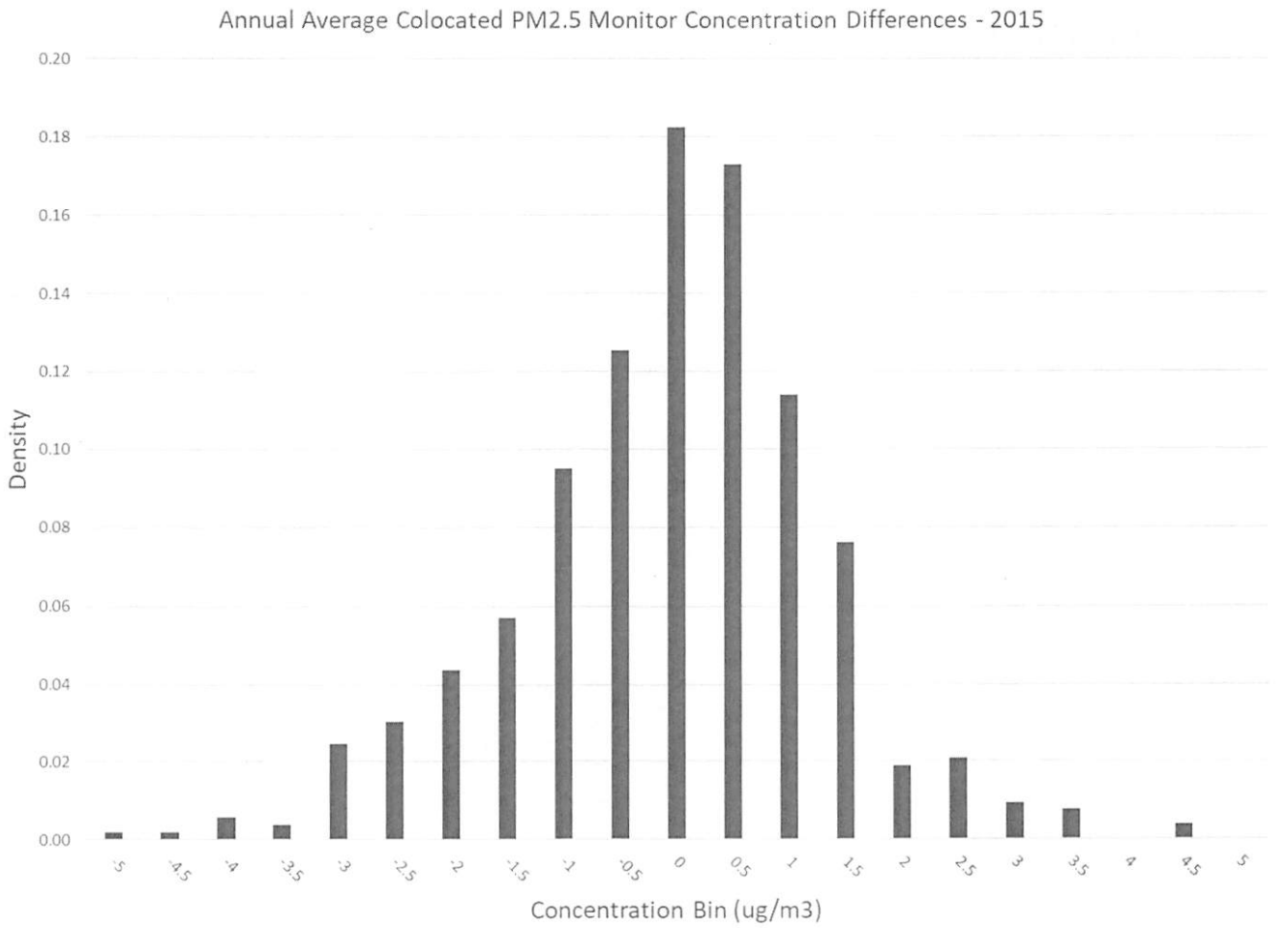
Attachment A

Distribution of 2015 annual average concentrations from FRM monitors in the EPA's Air Quality System



Attachment B

NERA Economic Consulting

Summary of Work Accomplished Under TCEQ Work Order 10

Simulation of Prospective Cohort Data