COMMENTS BY THE TEXAS COMMISSION ON ENVIRONMENTAL QUALITY REGARDING DRAFT INTEGRATED SCIENCE ASSESSMENT FOR SULFUR OXIDES—HEALTH CRITERIA

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I. Summary of Proposed Action

On November 24, 2015, the United States Environmental Protection Agency (EPA) published a notice in the *Federal Register* (80 FR 73183) that the first external Draft Integrated Science Assessment for Sulfur Oxides—Health Criteria (USEPA, 2015a) is available for public review and comment.

The Integrated Science Assessment (ISA) is the first in a series of technical and policy assessments that provide the basis for the sulfur dioxide (SO_2) National Ambient Air Quality Standard (NAAQS). The EPA last revised the primary SO_2 NAAQS based on the available scientific literature supporting that standard in 2010.

II. Comments

A. General Comments

The EPA should more fully consider exposure measurement error and the inherent limitations of epidemiology studies in its evaluation of available literature and causal determinations.

The Texas Commission on Environmental Quality (TCEQ) commends the EPA on its comprehensive evaluation of the strengths and weaknesses of the epidemiological research. The clear discussion of these qualities and EPA's weighting of the various lines of evidence is appreciated. However, the TCEQ highly recommends that the EPA use adjustment factors or another quantitative method in its final analysis to better account for the uncertainties it correctly identified with regard to exposure measurement error and available epidemiology literature. It was unclear from the information presented in the draft ISA if these sometimes quite severe limitations, which are detailed more fully below, would be accounted for in the final analysis or whether the limitations would merely be noted. Exposure measurement error should be better articulated and seriously considered in this document when interpreting results from studies that use ambient concentrations as surrogates for personal exposures. Further, the EPA should more fully weigh uncertainties inherent to epidemiology studies, including inaccuracy in mortality and morbidity risk estimates, the shape of concentration-response curves at environmentally-relevant SO_2 concentrations, and frequent lack of controls for confounders such as co-pollutants. The EPA's reliance on basic assumptions (i.e., surrogates for personal exposure, exposure measurement error bias toward the null, and linear concentration-response) that are unsupported by the scientific literature can inflate both the importance of the study results and causal determinations. Failure to properly account for these issues will result in inappropriate characterization and communication of SO_2-mediated health risks and, ultimately, a flawed standard.

B. Technical Comments Related to Exposure Measurement Error

The EPA's assumption that exposure measurement error biases results toward the null is overly simplistic and biases subsequent conclusions of key epidemiology studies.

Exposure measurement error for air pollution epidemiology studies is a problem that has been discussed for decades, but is still poorly understood. Zeger et al. (Zeger et al., 2000) described three components of exposure measurement error: 1) error in the differences between individual exposures and average personal exposure; 2) error in the differences between average personal exposure and ambient levels; and 3) error in the differences between measured and true ambient concentrations (including instrument error and spatial error). In the draft ISA the EPA notes in multiple locations (pg. xxxix, 1-25, 3-2, 3-41, 3-42, 3-60, 3-61, 3-63, 3-67, 5-28, 5-33, 5-321, 5-322) that exposure measurement error will result in a bias towards the null, or an attenuation of the risk ratio, but does not provide any basis for this assumption. The assumption that exposure measurement error causes bias towards the null was taken a step further in the response to comments document for the 2009 SO_2 final rule, in which the EPA stated that this tendency decreases the likelihood that a statistically-significant association between SO_2 and a health effect is false, and that the real effects are likely to be larger than those that were estimated [pg. 28; (USEPA, 2010)].

However, the statement that exposure measurement error in short-term studies always biases risk estimates to the null is misleading and is an inappropriately simple characterization of the results found in the studies referenced in the draft ISA. Exposure measurement error includes both classical error (affecting bias) and Berkson error [affecting confidence intervals (CIs)]. Classical error can bias effect estimates towards the null and Berkson error can increase CIs in a simple, single pollutant model 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). However, the scientific literature, including many studies cited in the draft ISA, indicates that some or all of these simple assumptions could be false. For example, controlled animal and human exposure studies strongly suggest a threshold of effects (i.e., not a linear response to zero) with SO_2 exposure [section 4.3.2, (Raulf-Heimsoth et al., 2010)]; and, as discussed below, ambient concentrations are likely to be a poor surrogate for personal exposure to SO_2 [section 3.3.2.2; (Sarnat et al., 2005; Sarnat et al., 2000; Sarnat et al., 2001)]. Accepting the potential for bias towards *or away* from the null would also be more consistent with the EPA's assumptions in the ozone ISA [pg. lxii, (USEPA, 2013)]. Further, multiple pollutants are often modeled to consider confounding effects, but classical error using multiple linear regression models can bias towards *or away* from the null (Zeger et al., 2000) because of the interplay between interpollutant correlations and the measurement error for each pollutant (Carrothers and Evans, 2000). At the very least, the EPA should provide a rationale for using this assumption and support it with sufficient scientific references, which are notably absent from the numerous times this assumption is repeated within the draft document.

The EPA should take into account the well-established poor association between personal SO_2 exposures and monitored ambient concentrations in its consideration of epidemiology study results that use central site monitors and averages across monitors to estimate personal exposure.

The assumption that the measured SO_2 concentration is a good surrogate for personal exposure is flawed, as was noted in Section 3.3.2.2 of the draft ISA. In studies that compared pooled 24-hour SO_2 concentrations measured at ambient monitors to pooled 24-hour measurements made by monitors being worn by the study subjects, the correlations between personal and ambient SO_2 concentrations ranged from 0 to 0.43 (Brauer et al., 1989; Sarnat et al., 2006). Put another

way, even the highest correlations indicate that only 43% of the variation in personal concentrations can be predicted by ambient concentrations. Further, median correlations among subjects in longitudinal studies ranged from 0.00 to 0.10 (Sarnat et al., 2005; Sarnat et al., 2000; Sarnat et al., 2001). This poor and inconsistent correlation does not provide confidence that data collected from ambient monitors are adequate surrogates of personal exposures or that differences between these two concentrations are consistent. Similarly, averaging concentrations measured at various monitoring stations across an urban area is likely to bias exposure estimates (i.e., over- or underestimate exposure). Health risk conclusions based on these assumptions, then, are likely to be tenuous.

Although the EPA characterizes differences in monitor placement, particularly as it relates to its effect on pollutants with high spatial and temporal heterogeneity, it does not consider the implications of monitor placement in its review of epidemiology studies.

The draft ISA provides a brief review of current SO_2 monitoring requirements, including requirements for locating monitors in close proximity to stationary point and area sources in order to determine maximum concentrations, as well as locating monitors in neighborhood and urban environments to characterize concentrations to which the public could be exposed. However, none of the EPA's discussion of key epidemiology studies includes an explanation of how these two different monitoring objectives were considered in the study's analysis. Because of the short lifetime of SO_2 in the atmosphere and the well-documented heterogeneity of SO_2 in both space and time, particularly over the 24-hour periods common in epidemiology studies, it is important that analyzer type, monitor placement and objective, and probe height be given close consideration. Source-oriented SO_2 monitors may not be representative of population exposure simply because people may not live in close proximity to a source. Monitors located in neighborhoods better serve the purpose of measuring SO_2 concentrations to which the public could be exposed. Other factors contributing to variance among monitors can also include geographical terrain, meteorological conditions, and analytical uncertainty at ambient SO_2 concentrations near the method detection limit. Therefore, peak SO_2 concentrations very near a source may skew calculated regional 24-hour concentrations, which would in turn, skew concentration-response correlations and conclusions.

Concentration modeling is not an appropriate surrogate for personal exposure.

SO_2 concentrations tend to be highly variable across urban areas. Given the spatial resolution of receptor density in most air dispersion modeling, it is unlikely that AERMOD and similar models would accurately estimate personal exposure due to lack of resolution in the model itself, particularly for a pollutant that is point source specific (Cyrys et al., 2008; Hung et al., 2005; Juneng et al., 2009; Pang et al., 2009; Tayanc, 2000; Wilson et al., 2005; Zou et al., 2011). Furthermore, modeling assumptions are generally conservative and reliant on accurate input of sources, emission rates, duration of emission, terrain, meteorological conditions, atmospheric chemistry, mobile sources, and characterization of area buildings or infrastructure (pg. 2-85). Variations in individual exposures and confounding factors widen CIs around effect estimates, and further obscure the ability of epidemiology studies to be used to evaluate concentration response and subsequent causation (pg. 3-67).

The EPA should more fully describe and evaluate the effects of physical activity on an individual's inhaled dose of SO_2 when assessing both exposure measurement error and reported associations with health outcomes.

In the SO_2 literature it is clear that exercise affects an individual's response to SO_2 [(Gong et al., 1995), Section 5.2.1.2], yet this hasn't been considered in any model, or even in the discussion of how error could affect risk estimates. In the draft ISA it is noted that, "Time-location-activity

patterns have a substantial influence on exposure and dose by determining an individual's extent and duration of exposure. Omission of this information can lead to exposure error" (pg. 3-37). Despite this statement, there is no evidence that this important concept is even considered, let alone modeled, in the SO_2 epidemiology studies considered in this analysis.

The EPA should clarify the number of person-days included in the Consolidated Human Activity Database (CHAD).

In Chapter 3 there is a discussion of the use of the CHAD diaries to model time-activity patterns. The text states that the CHAD diaries have 33,000 person-days collected between 1982-1998 (pg. 3-41). However, in the most recent review of the ozone NAAQS, the CHAD diaries were stated to contain 53,000 person-days collected between 1982 and 2010 [(USEPA, 2014), pg. 5-12]. A reason for this discrepancy in person-days and years of collected data should be included in the SO_2 draft ISA, or the number should be corrected.

The EPA should quantitatively consider exposure measurement error in its interpretation of epidemiology study results because of the considerable effect this type of error could have on causal designations.

The draft ISA contains considerable discussion of SO_2 exposure and modeling as well as potential errors and concerns. These are very important points, and the EPA did well to discuss them to such an extent. However, it is not clear how this information was utilized in the interpretation of epidemiology literature in Chapters 5 and 6. Although the EPA questioned the conclusions of two studies due to concerns about exposure measurement error [(Miller et al., 2007), pg. 5-229; (Atkinson et al., 2013), pg. 5-233], the same discussion was not provided for studies that the EPA considered to be of higher quality and that were cited often (Atkinson et al., 2013; Chen et al., 2010; Chen et al., 2013; Chen et al., 2012; Jalaludin et al., 2008; Kan et al., 2010; Katsouyanni et al., 1997; Li et al., 2011; Lipfert et al., 2006a; Lipfert et al., 2006b; Lipfert et al., 2009; Meng et al., 2013; Son et al., 2013; Strickland et al., 2010). Our evaluation of these key and oft-cited studies indicates that most (12/14) only used ambient air concentrations without any considerations of SO_2 concentration heterogeneity. Two of the 14 studies did some air modeling, although the modeling was either used to assess a single city in a county and then to assign that concentration to the entire county (Lipfert et al., 2009), or the authors found that the air dispersion model correlated poorly with actual measured concentrations (Atkinson et al., 2013). While many of these studies (10/14) discussed the problems of exposure measurement error, *none* attempted to quantify it or calculate how it affected their results. Several noted the simplistic conclusion that exposure measurement error biases towards the null. Although the EPA discusses the exposure measurement error in these time-series epidemiologic studies in the draft ISA (e.g. pg. 5-28), the EPA also relies on the same misleading statement about this error attenuating the health estimate.

The draft ISA notes one study, Strickland et al. (2011), that tested various exposure metrics, including central monitor estimates, unweighted averages, and population-weighted averages. This study concluded that there was a statistically significant association between SO_2 and pediatric asthma emergency department (ED) visits in Atlanta using any of their exposure metrics. From this, the conclusion in the draft ISA was that "the different approaches used to assign exposure across the studies evaluated may alter the magnitude, not direction, of the associations observed" (pg. 5-56). This is, again, an over-simplification of the problem. The stated considerations, although a good start, still don't adequately address several aspects of exposure measurement error (Zeger et al., 2000), nor do they consider this statistically in their models.

C. Technical Comments Related to Dosimetry and Mode of Action (MOA)

The EPA should provide justification for its use of effects observed in high-concentration animal studies to inform MOA at the low-concentration exposures.

The available animal model data indicate that exposure to high concentrations of SO_2 exacerbates inflammatory and allergic responses and alters lung function in animals exposed via inhalation. The EPA reports that there is only one study, conducted in guinea pigs, that observed increased pulmonary resistance at an SO_2 concentration of 0.16 ppm (USEPA, 1982). However, neither the primary reference nor the time or method of exposure for this study was provided. is the study results are also inconsistent with data from other studies discussed in the draft ISA where exposures as high as 1 ppm have failed to increase airway responsiveness in naïve animals (pg. 5-114). It is defensible that exposure to high SO_2 concentrations would increase respiratory inflammation, allergic responses, and airway resistance; however, data collected in animal studies and controlled human exposure studies indicate that these effects may not occur at ambient SO_2 concentrations. Thus, interpolation of these MOAs broadly across the concentration-response continuum is likely to be inappropriate.

It would be of value for EPA to describe how high-dose animal exposure studies provide a pathophysiologic basis for the development of respiratory effects at much lower concentrations in humans. This data gap produces significant uncertainty that weakens the hypothesis that SO_2 has a linear, non-threshold concentration-response in humans.

The EPA's review of additional MOA data as part of the NAAQS review cycle should be restricted to ambient-relevant SO_2 concentrations of less than 500 ppb and should include necessary context specifically related to concentration and adversity of observed health effects. MOA is dose-dependent with various mechanisms existing at different doses (Slikker et al., 2004). Thus, it is critical to address potential health effects that could occur at ambient-relevant concentrations. Health effects potentially induced by exposures well over these concentrations are not relevant for evaluating the national *ambient* air quality standard. According to the EPA's sulfur trend analysis, SO_2 levels have been steadily decreasing from a mean of 67.7 ppb in 2004 to a mean of 28.9 ppb in 2014. Figure 1 below displays the annual 99th percentile of daily maximum 1-hour averages from nationwide ambient air monitors.

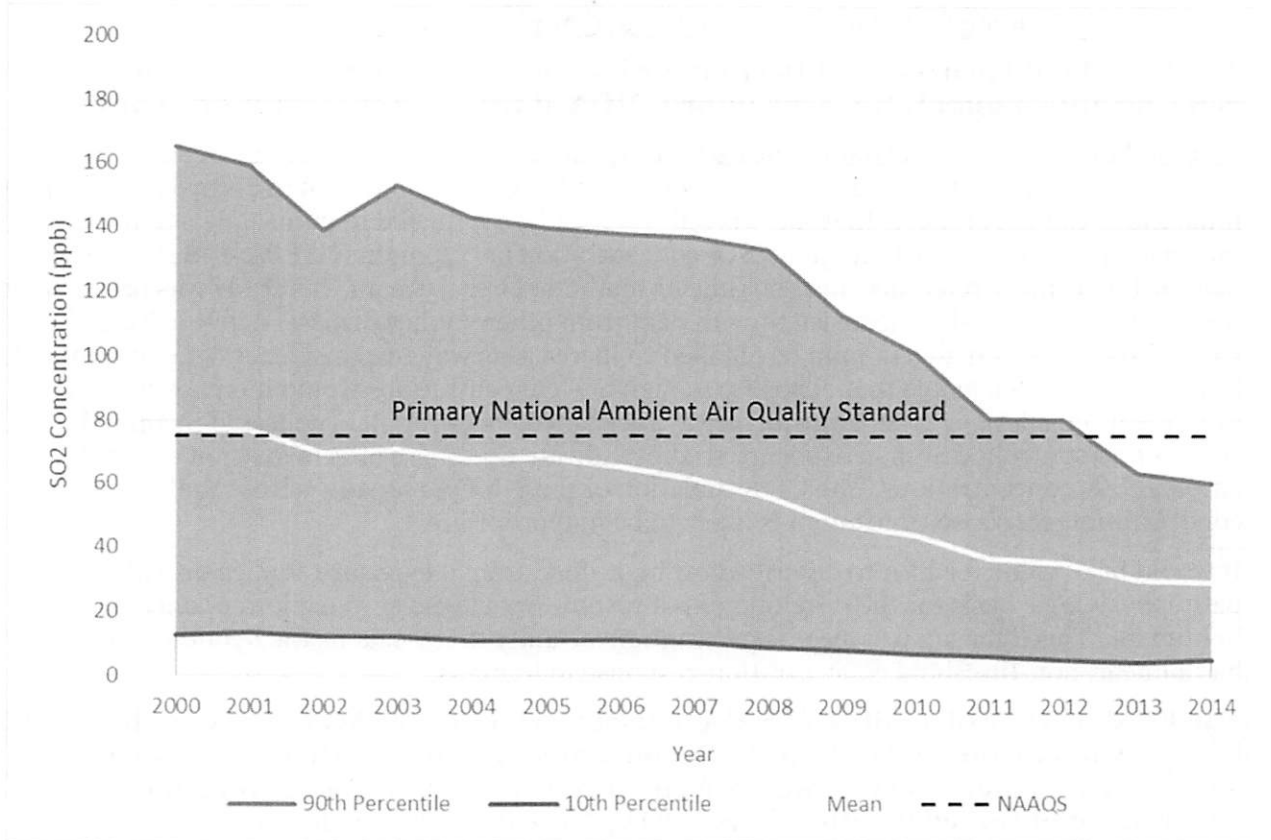

Figure 1. Mean annual 99th percentile daily maximum 1-hour ambient SO_2 concentrations have decreased 62% from 2000 to 2014 nationwide (recreated from http://www3.epa.gov/airtrends/sulfur.html).

Regardless of this data, the EPA defines ambient-relevant concentrations as concentrations within one to two orders of magnitude of current conditions, or up to an extremely rare 2000 ppb SO_2 [executive summary, Section 2.5, Preamble [(USEPA, 2015b), Section 5c]. Epidemiology studies presented in the draft ISA present maximum 24-hour ambient SO_2 concentrations of 65 ppb or less with averages generally less than 20 ppb (Chapter 5, Section 5.2), which are more in line with concentrations measured at ambient monitors nationwide. One study presented 1- hour SO_2 concentrations measured near an active volcanic island ranging from 0 to 3500 ppb with maximum values ranging from 3790 to 10,320 ppb, representing environmental conditions that would indeed be quite rare (Ishigami et al., 2008). Aside from SO_2 concentrations measured near naturally-occurring volcanic activities, even worst-case scenario exposures located outside of the United States indicate maximum weekly SO_2 concentrations have reached levels of 387.5 ppb [(Zhao et al., 2008), Table 5-24]. Such levels may be directly relevant to concentrations tested in controlled human studies cited in the draft ISA (Andersen et al. 1974; Gong et al. 2001; Linn et al. 1984; Raulf-Hemisoth et al. 2010; Tunnicliffe et al. 2003; van Thriel et al. 2010).

Therefore, in reality it is not reasonable to expect that the population would be chronically exposed to 2 ppm, nor does the scientific literature indicate that chronic animal doses at 2 ppm would be relevant to chronic human exposures of less than 100 ppb. Even EPA's justification for using this elevated upper exposure concentration [to "account for differences in dosimetry, toxicokinetics, and biological sensitivity of various species, strains, or potentially at-risk

populations" (draft ISA preamble)] is not properly supported by a scientific reference. Because the basic SO_2 mechanism of action has been established and species differences spanning several orders of magnitude are unlikely, a better division of expected mechanisms between higher exposures (> 1 ppm) and ambient concentrations (< 500 ppb) should be provided in the draft ISA.

If a thorough analysis of effects at higher concentrations is deemed important, the EPA should provide more consistent discussion of concentrations in the draft ISA and include a summary that separates mechanisms that occur at higher concentrations from those known to occur at lower concentrations. There are numerous examples of discussions of study results (e.g., all but two of the studies referenced in section 4.3.1) where conclusions are drawn without providing the reader with information about whether the effects are relevant to high or ambient concentrations. Further, section 4.3 of the draft ISA mixes discussion of MOAs at multiple concentration ranges, which can confuse and distract the reader. For example, in section 4.3.6, it is noted that sulfite in the blood in extrapulmonary tissues is highly reactive and could be responsible for oxidative stress in the circulation and in extrapulmonary tissues. This is followed by the statement: "However, this is likely to occur only at very high concentrations or during prolonged exposures because circulating sulfite is efficiently metabolized to sulfate in a reaction catalyzed by hepatic sulfite oxidase." These types of conclusions about MOA should be clearly marked and separated from those that discuss MOA that is plausible at ambient concentrations and using realistic exposure scenarios. Similarly, the statement "Thus, the potential exists for prolonged exposure to high concentrations of inhaled ambient SO_2 to result in extrapulmonary effects due to circulating sulfite" should be separated and clearly marked as a conclusion that is highly unlikely to be relevant to ambient exposures. There are also some conclusions drawn where the necessity of a high concentration for the response is not made clear in the text. For example: "The initiating event in the development of respiratory effects due to long-term SO_2 exposure is the recurrent or prolonged redox stress due to the formation of reactive products in the ELF." (pg. 4-26). By itself this seems reasonable. However it was noted in section 4.3.2 that "There is little evidence of injury or inflammation in response to acute exposures to concentrations of 2 ppm SO_2 or less in human subjects." This suggests that inflammation or injury is unlikely to occur at ambient concentrations (more than an order of magnitude below 2 ppm), and therefore there would be little expectation that the long-term SO_2 toxicity pathway would even be initiated.

Finally, it would the helpful to the reader if the EPA would include information about the adversity of observed effects. For example, it is noted that in two controlled human exposure studies the subjects were exposed to 0.2 ppm SO_2 and changes in heart rate variability were observed in healthy adults and asthmatics (Section 4.3.4). The clinical significance of these findings and their relationship with overt toxicity (i.e., relationship between heart rate variability and heart attacks) are necessary for interpretation of the significance of this result.

The EPA's improper assumption that SO_2 exhibits a linear dose-response does not appear to be based on the available scientific literature. This assumption biases EPA's conclusions and obscures true understanding of SO_2-mediated health risks.

Chapter 4 of the draft ISA presents compelling evidence that the SO_2 MOA exhibits a threshold of response. For example, in human subjects there is little evidence of injury after acute exposure to 2 ppm or less of SO_2 (pg. 4-17). However, even with the wealth of scientific evidence presented by the EPA in this chapter, the EPA relies on default assumptions of linearity in epidemiology studies for its determinations of causality.

Seemingly linear concentration-responses can occur due to inadequate understanding and consideration of exposure measurement error. Yoshimura (1990) noted that the presence of exposure measurement error can mask the presence of a threshold in the response, which can,

in turn, mask evidence that supports a threshold. This casts fundamental doubt on epidemiology studies that find that a linear regression is the best fit for their data without thorough evaluation of the exposure measurement error and other causality considerations. In addition to the problematic exposure measurement error assumptions noted above, there are other modeling choices that can affect how exposure measurement error biases effect estimates, including the choice of how monitoring data is combined (population-weighted averages versus area-weighted averages, Goldman 2012), or of how the risk is estimated (using a set range, such as change of 10 ppb SO_2 versus interquartile range, Goldman 2011).

The EPA should include information on bias, errors, and statistical significance in its presentation of epidemiology results.

The Chapter 6 MOA discussion adequately assesses the biological plausibility of a particular at-risk population's sensitivity to SO_2. However, it is very important, particularly when discussing the results from epidemiology studies, to include considerations of bias and errors, particularly exposure measurement errors, in the conclusions drawn by those studies. It is also critically important to include the *statistical significance* of differences between populations when presenting each study's results. This information should be added to the summary tables included in this chapter (Tables 6-3 to 6-15).

D. Technical Comments Related to Epidemiology Studies

The numerous limitations and biases of epidemiology studies preclude their ability to be used in establishing concentration-response relationships.

The EPA repeatedly indicates that data from epidemiology studies do not collectively provide evidence of a threshold; however, use of these studies to assess this endpoint is wholly inappropriate. When personal exposure is unknown (as is the case with the ISA-referenced epidemiology studies due to the personal exposure issues noted above) the shape of a concentration-response curve cannot be known. Thus, attributing a linear, no threshold concentration-response to SO_2 exposure and various morbidity (ED visits, seasonal patterns, etc.) and mortality endpoints is inappropriate. Available data do not indicate that "even the lowest measured ambient SO_2 concentrations" have the potential to cause harm (pg. 1-24). Instead, available epidemiology studies do not provide adequate data to estimate the shape of the concentration-response curve. It is well appreciated that the noise within the low end of population-based concentration response curves is so great that it masks the shape of the concentration-response relationship. Thus, the "best fit" for the concentration-response curve may appear linear even though the available biological data (e.g., controlled human studies and toxicology studies) indicate a threshold is likely to exist (Rhomberg et al. 2011). Despite this compelling evidence, the EPA erroneously concludes that "there is no reason to conclude a deviation from linearity or the appearance of a population-level threshold" (pg. 1-25).

The EPA should rely more heavily on conclusions from controlled experiments, rather than the inadequate data provided by epidemiology studies.

Due to the uncertainties in the epidemiology studies (particularly due to limitations in quantifying personal exposure and adequate experimental controls), and those associated with confounders (e.g., actual exposure and co-pollutants), the most informative data comes from controlled human studies and toxicology studies conducted in animals. The EPA should place greater emphasis on MOA and dose-response relationship findings from these controlled environments. The controlled human studies consistently indicate that SO_2 concentrations of 400 ppb and above decrease lung function and increase respiratory symptoms in exercising asthmatics (pg. 5-135). They further indicate that SO_2 concentrations of 200 ppb may cause symptoms such as cough, chest tightness, or throat irritation in some exercising asthmatics (pg. 5-29). Notably, 200 ppb was the lowest concentration where lung function decrements were

reported in some asthmatics exposed to SO_2 for 5-10 minutes during exercise. The TCEQ agrees that these respiratory endpoints are the most appropriate and encourages the EPA to use these findings as the basis for its risk characterization.

The TCEQ encourages the EPA to use epidemiology studies for their scientific purpose: to inform scientists of correlations that warrant more in-depth research. The collective body of evidence regarding SO_2-mediated impacts on human health is, admittedly, complicated and challenging to interpret. However, epidemiology study results showing associations between short-term and long-term SO_2 exposure and increases in respiratory morbidity and mortality are suggestive, at best. In general, odds ratios, risk ratios, and correlation coefficients across studies identified in the draft ISA were only moderate to weak in their magnitude. Likewise our interpretation of the weight of the evidence presented in Chapter 5 indicates that ambient SO_2 levels are *not* associated with various respiratory effects, including asthma development, exacerbation of allergies, chronic obstructive pulmonary disease (COPD), infections, increased hospitalizations, and increased ED visits. The lack of controlled human exposures and animal studies demonstrating effects of SO_2 at typical ambient concentrations (e.g., 0.6 to 70 ppb) casts further doubt on the findings of the epidemiology studies cited in the draft ISA.

The TCEQ agrees that short term SO_2 exposure can cause respiratory effects potentially at concentrations above 200 ppb in exercising individuals that are more susceptible to respiratory irritants. The TCEQ also agrees that, at *high enough concentrations* and ventilation rates, available data provides evidence that is suggestive to infer a causal relationship between long-term exposure to SO_2 and respiratory effects such as asthma exacerbation. However, the lower concentration(s) at which those effects may occur appears to be unknown, as they cannot be identified via epidemiology studies (pg. 1-21, and as discussed above) and have not been identified in controlled human exposure scenarios. Thus, while the TCEQ agrees with the EPA's evaluation and synthesis of the effects of SO_2 on lung function across animal and human studies, there is a clear lack of evidence that these MOAs continue to be relevant across all SO_2 exposure levels, particularly ambient concentrations.

The EPA should more consistently consider the potential confounding of the results by other pollutants or mixtures of pollutants when interpreting the results of epidemiology studies.

The majority of epidemiology studies presented in the draft ISA do not address co-pollutant confounding. Inconsistencies in dose-response, coherence with MOA, and the conclusions drawn by different studies are apparent across all epidemiology studies regardless of whether or not co-pollutants were considered. This lack of consensus across studies permeates both short-term and long-term exposure scenarios. For these reasons, the TCEQ interprets the available evidence to be subsequently limited.

The EPA clearly states that uncertainties in the epidemiologic evidence are reduced by the biological plausibility provided from experimental studies. However, animal studies and controlled human studies do not provide evidence that ambient SO_2 concentrations cause allergic sensitization, airway remodeling, or airway hyperresponsiveness. Instead, available data indicate that these effects occur at higher exposure concentrations and that there is a paucity of data, either animal or human, indicating that these effects are occurring at typical ambient SO_2 concentrations.

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