**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 December 9, 2016, the United States Environmental Protection Agency (EPA) published a notice in the *Federal Register* (81 FR 89097) that the *Second External Review Draft Integrated Science Assessment for Sulfur Oxides—Health Criteria* (USEPA, 2016) 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 first draft ISA was released for public comment on November 24, 2015 (80 FR 73183). Under a proposed consent decree (82 FR 4866), the EPA will issue a final ISA no later than December 14, 2017, and finalize the review of the primary NAAQS for sulfur oxides no later than January 28, 2019. 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 has done a commendable job of updating certain portions of the second draft ISA with revised causal designations and necessary clarifying text related to error, bias, personal exposure, and controlled human exposure studies.

The Texas Commission on Environmental Quality (TCEQ) appreciates the EPA's efforts to address public comments on the first draft ISA by adjusting causal designations and adding supporting information. The TCEQ agrees with the EPA's consideration of reduced uncertainty when deciding whether to upgrade causal designations. For example, the authors decided to retain the reproductive and developmental causal designations from the last review because studies published since that review have not substantially reduced uncertainties in areas such as mode of action (MOA), exposure measurement error (or exposure error), and copollutant confounding. Further, the TCEQ agrees with the second draft ISA's revised (compared to the first draft ISA) causal determinations for cardiovascular, reproductive, developmental, and cancer effects and total mortality following long-term exposure. The available data are inadequate to infer a relationship between $SO_2$ exposure and these endpoints.

The TCEQ also applauds the EPA on the addition of clarifying text to this second draft. Specifically, the EPA added much-needed discussion on the uncertainties related to the weight of evidence supporting the causal designations in the draft ISA, as well as uncertainties of using modeling as a surrogate for personal exposure, exposure measurement error, and the errors and biases present in ecological epidemiology studies considered in the document. The additional language helps the reader understand the EPA's reasoning behind some of its determinations and the TCEQ encourages the EPA to expand on additional salient points, as described below.

**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.**

Although the second draft ISA expands on exposure measurement error and epidemiology study uncertainty, the TCEQ continues to recommend that the EPA use adjustment factors or another quantitative method in its final analysis to account for these uncertainties. As detailed in the TCEQ's comments on the first draft $SO_2$ ISA, the uncertainties in some studies can be quite severe, even to the point of casting doubt on the usefulness of study conclusions (TCEQ 2016). The EPA should do more than note these uncertainties; the EPA should make an early commitment to account for uncertainties in the analysis itself. Further, the EPA should provide scientific justification for its choice to use effect endpoints that are not statistically significant. Statistical significance, by definition, ensures that the endpoint of concern is unlikely to be due to chance alone. The EPA has provided no scientifically-supported rationale why it would disregard statistical significance to place a greater emphasis on data trends. While evaluating trends could provide meaningful insight into future research, this evaluation has limited value in setting the level of a NAAQS that has far-reaching consequences to the public and economy. The Federal Clean Air Act requires that the EPA Administrator ensure that $SO_2$ exposure (not chance) is causing the noted effects before deriving a health protective standard based on that data.

**Because the goal of the ISA is to provide an assessment of current scientific understanding, the EPA should clearly identify any policy decision or discussion.**

On many occasions throughout the draft ISA, the EPA appears to rely upon general policy standards, as opposed to scientific data, to generate conclusions. The role of the ISA is to present and evaluate scientific facts that are later used in conjunction with public policy to inform an ambient air quality standard. The EPA should, therefore, clearly delineate scientific evidence from instances when policy standards or guidance are being used to develop or interpret scientific fact. Ambiguity in such presentation of data can mislead or confuse readers. Two examples of potential confusion are the EPA's default assumption of linearity and reliance on epidemiology study conclusions. The EPA has used the assumption that a concentration-response is linear to conservatively account for data uncertainty. This determination is both a policy decision (NAS 2009) and a modeling approach used in instances where the low-end of the concentration-response curve(s) has significant variability and there is a desire to account for interindividual variation via modeling assumptions and selection or elimination of algorithm variables. However, uncertainties in this particular case do not necessarily make a concentration-response linear. In the case of $SO_2$, available low-concentration, controlled exposure data indicate that the concentration-response curve actually has a threshold, as discussed in Section C of these comments. Secondly, epidemiology studies cannot provide information beyond the scope of association, which in many of the studies cited in the draft ISA was rather weak. These studies are confounded by a multitude of uncertainties and inconsistencies, many of which the EPA acknowledges. However, the EPA's policy decision is to continue to rely on epidemiology evidence to inform concentration-response relationships, even when using the linearity assumption may lead to false conclusions that are contradicted by evidence collected in controlled human and animal exposure studies. Clearly identifying these policy decisions would aid in the overall transparency of the NAAQS derivation process.

B. Technical Comments Related to Exposure Measurement Error

**Exposure measurement error is not fully discussed or considered in the second draft $SO_2$ ISA, particularly with respect to inhaled dose, error, and personal exposure.**

The TCEQ appreciates the EPA's additional discussion on the complexities of exposure measurement error, which can lead to bias towards or away from the null (Section 3.4.4). Further, the discussion of strengths and limitations in the summary of exposure methods in Table 3-1 and the expanded discussion of uncertainties of modeling as a surrogate for personal exposure are valuable additions to the current ISA. However, the EPA's discussion of exposure measurement error is still deficient in terms of considering inhaled dose, bias, and personal exposure.

As in the TCEQ's comments on the first draft ISA (TCEQ 2016), the TCEQ strongly encourages the EPA to further consider how inhaled $SO_2$ dose, which includes time-activity patterns and ventilation rate, can bias the exposure metric. The EPA acknowledges the importance of time-activity patterns as a potential source of exposure measurement error (pg. xlv) and has a significant discussion about breathing habit variability in the human population (pg. 4-2). However, the EPA needs to take the next logical step of including these uncertainties in its evaluation and exposure model.

Similarly, the EPA agrees that personal exposure estimates collected from modeling exercises or central site monitors are often poorly or only moderately correlated with ambient conditions; however, the EPA does little to correct for this shortcoming in the draft ISA. Most, if not all, of the epidemiology studies used in Chapter 5 of the draft ISA assume that human exposure is equal to ambient measured concentration; there is no adjustment for the known differences and variability between personal exposure and ambient concentrations. The discussion in the second draft ISA, then, is misleading because the uninformed reader may assume that the studies used calculations to convert ambient concentrations to personal exposures, when they did not. The EPA needs to make it clear in Section 3.2.2, which describes its Conceptual Model of Personal Exposure, what specific exposure measurement was used in the studies and how ambient concentrations could be used to calculate total exposure. In addition, there is no reference for the statement "$C_{a,csm}$ can be an acceptable surrogate [for Ea] if the central site monitor captures the temporal variability of the true air pollutant exposure" (pg. 3-51). As is discussed thoroughly in other parts of Chapter 3, there are many other aspects of exposure, such as spatial variability and time-activity patterns, that go far beyond just temporal variability. As such, assuming that capturing temporal variability will completely account for all variability in personal exposure is flawed.

The EPA also needs to provide greater discussion on direction of bias in epidemiology correlations. Section 3.4.4.1 states that "To the extent that true correlations are less than one, epidemiologic effect estimates based on ambient concentration will be biased toward the null, based on simulations by Zeger et al. (2000)" (pg. 3-54). However, this statement neglects to consider that Zeger's bias towards the null assumes that the differences between personal and ambient exposure are constant. The EPA needs to more fully discuss the intricacies of this error, because it can be so important in interpreting the many time-series epidemiology studies cited in this document.

**A more thorough discussion and characterization of known errors (exposure measurement, confounding, concerns about MOA) needs to be included in Chapter 5, and in the integrative considerations of Chapter 1.**

The second draft $SO_2$ ISA appropriately provides more attention and weight to errors and biases that are potentially present in the ecological epidemiology studies considered in this document.

Section 3.5 notes that "The various sources of exposure error and their potential impact are considered in the evaluation of epidemiologic study results in this ISA"(pg. 3-62). While these errors are more thoroughly discussed in Chapter 5 of the second draft ISA than in the first draft, they need to be more consistently discussed in each section of Chapter 5 that has epidemiology evidence. In those sections where they are not discussed (Sections 5.2.1.6, 5.2.1.7, 5.2.1.8, 5.2.2.3, 5.3.1.2, 5.3.1.4, 5.3.1.6, 5.3.1.7, 5.3.1.10, and 5.4.4.1), it is not clear if these errors don't exist, or if they are just not discussed in favor of other, bigger, errors.

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

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

The second draft ISA provided a much better characterization of uncertainties and confounding factors, particularly as they relate to exposure assessment and epidemiology studies. However, the EPA needed to have provided more discussion on the paucity of low-concentration controlled studies and uncertainties associated with interpolating from high-concentration to low-concentration exposures. The adverse effects that occur at high-concentration $SO_2$ exposures are not the same effects that might occur at lower-concentration $SO_2$ exposures, as further detailed below and in the TCEQ's comments on the first draft ISA (TCEQ 2016). Therefore, better effort should be made in characterizing the low end of the concentration-response curve independent from the high end effects that are most likely governed by a different MOA.

**The EPA should restrict its MOA evaluation to ambient-relevant $SO_2$ concentrations of less than 500 parts per billion (ppb).**

The second draft ISA continues to define ambient-relevant $SO_2$ concentrations as less than 2 parts per million (ppm) to "account for differences in dosimetry, toxicokinetics, and biological sensitivity of various species, strains, or potentially at-risk populations" (USEPA 2015). This statement is unsupported by scientific reference. If anything, scientific data would support quite the opposite view; MOA is concentration-dependent and various key events and adverse effects occur at different exposure concentrations (Slikker et al. 2004a and b). The basic $SO_2$ MOA has been evaluated and established in humans and various animal species, particularly in the range of 2000-200 ppb. Specifically, $SO_2$ is a respiratory and ocular irritant at high concentrations (i.e., >2000 ppb). It can even cause bronchitis, bronchopneumonia, fibrosing obliterative bronchiolitis, and death. Generally, these effects have been observed in humans as the result of industrial and mining accidents where concentrations reached well above ambient levels (i.e., >5000 ppb). Moderate concentrations (>500 -750 ppb) may cause prolonged expiratory phase, indicating the induction of pulmonary resistance. These effects are transient, mild, and generally reversible. According to the Committee on Acute Exposure Guideline Levels (AEGLs), "the body of experimental data suggests that 0.25 ppm may be a threshold for bronchoconstriction in asthmatics" (NAS 2010). Furthermore, the NAS (2010) document suggests that "0.2 ppm may be a NOEL [No Observed Effect Level] for bronchoconstriction in exercising asthmatics."

The MOA is unlikely to be consistent over several orders of magnitude, as demonstrated by the evaluation of adverse effect benchmarks in NAS (2010). Further, no new MOA data have been produced by the scientific community since the last $SO_2$ NAAQS review. Thus, there is no evidence suggesting that broadly applying an MOA across the exposure continuum is appropriate, whether the MOA was developed using controlled animal or human studies, or epidemiology studies where exposure is, at best, estimated.

Additionally, as indicated in the TCEQ's comments on the first draft ISA, ambient-relevant $SO_2$ concentrations are significantly lower than 2 ppm (TCEQ 2016). Worst-case ambient

concentrations appear to have reached levels as high as 387.5 ppb outside of the United States (Zhao et al., 2008). Although similarly high $SO_2$ concentrations have been evaluated 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), none of these studies provide much information about the effect of current ambient $SO_2$ exposure levels in typical United States populations. In fact, mean annual 99$^{th}$ percentile daily maximum 1-hour ambient $SO_2$ concentrations in the United States have remained below 350 ppb since 1980 and have remained below 140 ppb in the last 10 years. Therefore, the EPA could conservatively restrict its assessment to health effects that are informed by an MOA that occurs at more ambient-relevant concentrations less than 500 ppb.

**The EPA should rely more heavily on conclusions from controlled experiments to inform the shape of the concentration-response curve.**

Although the EPA has softened the language regarding the low end of the concentration-response curve and expanded the discussion of uncertainties, the current ISA insists that the concentration-response relationship between $SO_2$ and various adverse effects is linear based upon evidence collected in epidemiology studies (p.1ii, lines 10-12; p. 1-26 to 1-27 lines 25 and 1-2; p. 1-27, lines 8-10; p. 5-65, lines 16-19; p. 5-71, lines 34-35; p. 5-136, lines 9-15; p. 5-199, lines 4-10; p. 5-271, lines 24-26, p. 5-274, lines 7-11 and 15-19; p. 5-277, lines 35-38). This conclusion appears to be unsupported by controlled human and animal studies. More details are provided in the TCEQ's comments on the first draft ISA (TCEQ 2016), and those comments are incorporated into these comments by reference to this document. Despite the EPA's effort to discuss the details of certain animal studies, including the exposure levels used in those studies, a proper link between many of these high-concentration MOAs and an MOA that would be relevant for ambient conditions and still explain a linear concentration-response relationship was not apparent. Instead, the EPA's conclusion of linearity appears primarily based on modeling exercises evaluating human epidemiological data at the low end of the concentration-response curve, which is highly variable and more uncertain. To further complicate the analysis, the EPA assumed that the relationship stayed the same across the concentration-response continuum, which ignores the probable MOA transitions that occur across these concentrations. The EPA should re-evaluate the shape of the concentration-response curve at ambient-relevant concentrations, taking into better account the strength of the data.

**The EPA should clarify the intent of the expanded respiratory physiology section in the draft ISA.**

The second draft ISA includes a good discussion of respiratory physiology and breathing rate variability in human populations. This discussion is significant, as varied breathing habits would affect the inhaled $SO_2$ dose. Inhaled dose is also correctly linked to obesity, where obese adults and children may experience increased nasal resistance and an increased oral fraction of breathing relative to children of normal weight. This discussion appears to be used to inform uncertainty at the low-dose end of the dose-response curve in human populations, particularly in the sensitive sub-population of obese children. It would be helpful to the reader for the EPA to clarify if this uncertainty is intended to help justify the EPA's conclusion that it is unable to discern an $SO_2$ threshold for adverse respiratory effects in human populations.

**The EPA should report exposure concentrations consistently throughout the draft ISA.**

$SO_2$ concentrations in animal, human, or epidemiology studies were not consistently reported throughout the draft ISA. It would be of great value to the reader to see exposure concentration data, as well as exposure-response estimates, written clearly and consistently in the text. Further, where possible, a figure illustrating dose/concentration-dependent transitions in the

MOA may prove helpful in characterizing the actual nature of various $SO_2$ dose-responses (i.e., respiratory, cardiovascular, mortality, etc.).

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 TCEQ again encourages the EPA to use epidemiology studies for their scientific purpose: to inform scientists of correlations that warrant more in-depth research. Epidemiology studies are not capable of providing evidence of actual exposure or harm due to a level of exposure. In addition to the numerous overall inconsistencies and weaknesses in the epidemiology studies noted by the EPA in the second draft ISA, controlled studies do not corroborate correlations noted in the cited epidemiology studies. This indicates that the correlations noted in the epidemiology studies likely have no relation to a causation concerning $SO_2$ exposure. The EPA should rely on conclusions from controlled studies with study designs that allow the assessment of causality, rather than epidemiology studies that lack the study design and statistical power to make such conclusions.

**The EPA should provide standard criteria for assessing copollutant confounding.**

The TCEQ agrees that it is important to consider copollutant confounding if there is a correlation between the pollutants. However, there does not appear to be a clear distinction of at what correlation pollutants can be considered to be confounding (e.g., 0.2, 0.4, etc.). It would be useful to the reader, as well as those conducting those studies, to have some standard guidance, supported by scientific study findings.

E. Technical Comments Related to Causality

**The causal associations between $SO_2$ and all respiratory effects is not clear in the summary portions of the draft ISA.**

In the sections of the draft ISA responsible for discussion of the overall causal conclusions (i.e., the Executive Summary and Chapter 1), it is not clear what aspects of "respiratory effects" are being causally related to $SO_2$ exposure. While it is clear that asthma exacerbations are considered to be strongly associated, these sections do not appropriately communicate that the other respiratory effects (i.e., allergy exacerbation, chronic obstructive pulmonary disease (COPD) exacerbation, and respiratory infections) in fact have little evidence linking them with $SO_2$ exposure. It should be clearer in these synthesis sections of the ISA those effects that have scientific evidence and those that do not.

In addition, the EPA should clarify the discussion in Section 5.2.1.9 relating to the summary and causal conclusions of short-term $SO_2$ exposure and respiratory effects. Specifically, the draft ISA states that "[t]he limited and inconsistent evidence for these non-asthma-related respiratory effects does not contribute heavily to the causal determination." It is not clear to the reader what this statement means. Does this mean that the EPA is choosing not to weigh the limited and inconsistent evidence very heavily in their causal determinations; or, that non-asthma-related effects are not important for a causal conclusion about total respiratory effects? This statement should be clarified, and the EPA should better explain how a causal designation is decided for a broad category of effects (e.g., respiratory effects), when a few effects (e.g., asthma exacerbations) show convincing associations and MOA, while many effects (e.g., COPD exacerbation, allergy exacerbation, and respiratory infections) do not. The same argument can be made for long-term respiratory effects, where the EPA only considers asthma development as a potential causative link, but not other effects such as lung function and development of allergies.

**The EPA should provide adequate justification for using a "suggestive" causal designation for long-term $SO_2$ exposure and respiratory effects.**

In the second draft ISA, the causal determination between respiratory effects and long-term $SO_2$ exposure is "suggestive," which was upgraded from "inadequate" in the 2008 ISA. In other sections of the second draft ISA, it is noted that the causal designations are not changing from the last ISA because, although there is new evidence, it does not substantially reduce the uncertainties present in the last review. In Section 5.2.2, the authors note that in the 2008 review, for the relationship between respiratory effects and long-term $SO_2$ exposure there were "[u]ncertainties related to assessing the consistency of findings across a diverse set of respiratory outcomes, the potential for exposure measurement error to influence results, and the lack of information available to assess the impact of copollutant confounding..." (Section 5.2.2, pg. 5-143). It seems that there are still inconsistent findings between a diverse set of respiratory outcomes, with the only potentially convincing respiratory effect in this section being the development of asthma, with little evidence coming from severity of asthma, lung function, development of allergies, respiratory infections, other respiratory diseases, or respiratory mortality. In addition, as noted in Section 3.4.4.2, none of the epidemiology studies in this chapter had conducted bias analysis to determine the effects of exposure measurement error on their findings. As also noted in that section, this error in long-term studies can bias the effect estimate either towards or away from the null, calling into question the results from these types of studies. Lastly, it is noted in Section 5.2.2.7 that there is no evidence in the new studies to address the impact of copollutant confounding. Therefore, it is not clear to the readers why this causal designation was upgraded, when there was no significant progress made in reducing the uncertainties present in the last review of the $SO_2$ NAAQS.

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