Additional Preliminary Comments from Members of the CASAC Sulfur Oxides Panel on EPA's Integrated Science Assessment for Sulfur Oxides – Health Criteria (External Review Draft – November 2015)

Received as of 01-25-16

Mr. George A. Allen 2
Dr. John Balmes 5
Dr. Aaron Cohen 7
Dr. Alison Cullen 11
Dr. Ana Diez Roux 14
Dr. Daniel Jacob 16
Dr. David Peden 18
Dr. Lianne Sheppard 23
Dr. Ron Wyzga 27

Mr. George A. Allen

Executive Summary and Chapter 1

General Comments

Over the last several NAAQS review cycles, the structure of the ISA has become more and more complex, at least in part in response to CASAC review requests. We now have a Preamble (generic, for all ISAs), a Preface, an Executive Summary, and a Summary chapter – all before the actual core ISA chapters. Since to some extent (?) they all need to stand on their own, reading them in sequence is painfully redundant. While I don't have explicit suggestions as to how simplify or combine these documents, this may be worth considering.

HERO continues to be a very useful tool for reviewing these NAAQS process documents, and EPA should be encouraged to maintain it.

The Executive Summary is intended to provide a concise synopsis of the key findings and conclusions of the SOX ISA for a broad range of audiences. Please comment on the clarity with which the Executive Summary communicates the key information from the SOX ISA. Please provide recommendations on information that should be added or information that should be left for discussion in the subsequent chapters of the SOX ISA.

Overall, the Executive Summary clearly communicates the key findings of this ISA. Given the presumably non-technical audience of executives for this section, some of the terms used tend to be fairly technical for a general audience. Sometimes these terms are defined, but sometimes not. One example is on page xli, lines 23-24: "Endogenous sulfite from the catabolism of ingested sulfur-containing amino acids far exceeds exogenous sulfite..." – this may be too technical for this section, and more appropriate for Chapter 1?

Table ES-1 is a concise summary of SO2 exposure and health effects and changes in the causal determination status since the last ISA. Footnote B notes changes to the phrasing of causal determinations. Five of these categories have been moved up one level; are any of these changes in part because of changes in the phrasing?

The "Policy-Relevant Considerations for Health Effects Associated with Sulfur Dioxide Exposure" at the end of the Executive Summary is very well written. This is the level and style that may serve as a model for other sections of this summary.

Specific Comments on the Executive Summary

Page xxxvii: The first page of the Executive Summary is heavily footnoted. Footnote 2, and maybe some others important to understanding the context of this ISA, could be promoted into the text, since it explains what this ISA is actually covering – essentially only SO2 (…"only SO2 is present in the atmosphere at relevant concentrations."). It would help if this could be more clearly explained in the first paragraph – defining the backstory of how we get from SOX (a wide range of oxidized gaseous and particle sulfur species) to SO2 (the NAAQS indicator); some of this is done in the first paragraph of Chapter 1. While the criteria pollutants Pb and CO are unambiguous, others are less so. Where does the term SOX (and NOX) come from in a regulatory sense – the CAA?

As noted previously, the ISA needs to be very consistent throughout in using terms like SOX and SO2, using SOX only where essential – presumably only when setting the ISA stage.

Footnote 4, about blue hyperlinks, seems out of place in this paragraph which has no blue hyperlinks.

Page xxxviii, line 20: "joint exposure to other pollutants" Elsewhere in this section, the term "copollutants" is used for this – it would help to define that here. Do these terms refer only to NAAQS indicators?

Page xxxix, lines 21-23: "Multiple evaluations of AERMOD's performance against field study databases over averaging times from 1 hour to 1 year have indicated that the model is relatively unbiased in estimating upper-percentile 1-hour concentration values." Modeling the 1-h form of the current SO2 NAAQS is much more challenging than modeling the old form of daily or annual SO2 concentrations. From a NAAQS compliance point of view, AERMOD is generally considered to provide a conservative result – e.g., generally over-predicting measured SO2 at the surface, even if this outcome is primarily due to constraints on monitoring locations.

Page xxxix, lines 31-33: central site monitors and "…the relatively high spatial variability in SO2 across an urban area." Since large sources of SO2 in urban areas are now unusual, this wording may need revision. This issue may need to be carried forward elsewhere in the Executive Summary.

Chapter 1 summarizes key information from the Preamble about the process for developing an ISA. Chapter 1 also presents the integrative summary and conclusions from the subsequent detailed chapters of the SOX ISA and characterizes available scientific information on policy-relevant issues.

Please comment on the usefulness and effectiveness of the summary presentation. Please provide recommendations on approaches that may improve the communication of key findings to varied audiences and the synthesis of available information across subject areas. What information should be added or is more appropriate to leave for discussion in the subsequent detailed chapters?

This chapter effectively summarizes the key findings of subsequent chapters, and reads better than the Executive Summary. A few specific comments follow.

Page 1-1, first paragraph: SO2 as the NAAQS indicator for gaseous SOX is just dropped into the narrative. A brief rational and/or background for using SO2 would be helpful.

Page 1-10, lines 27-29: "…SO2 correlations with NO2 and CO were observed to be high, it is possible the data may have been collected before recent rulemaking to reduce sulfur content in diesel fuel…". This fuel cleanup is an important point, and is part of why (along with very few large SO2 point sources) urban SO2 is now usually very low and effectively very homogeneous from an exposure / health effects perspective. Some of these fuel S reductions are still ongoing; New York City started to prohibit 3000 PPM S #6 heating oil only a year ago (#4 is still allowed), and it will be several more years before all heating oil will be less than 30 ppm S.

Section 1.4.2 (Assessment of Human Exposure), pages 1-8 to 1-11: This section covers exposure issues in great detail. But even more so than for NO2, the key drivers behind the NAAQS form and level come from controlled human exposure studies as noted in Section 1.8, conclusions (page 1-28). Health outcomes from longer or chronic SO2 exposures come from epidemiological studies, but it is the need to control acute exposures (minutes to 1 hour) that also reduces the more chronic exposures. It may be useful to have a brief discussion of this elsewhere in Chapter 1 since it is prominent in the conclusion.

Table 1-1 (pages 1-21 to 1-23) is an appropriately detailed summary of causal determinations. The different sections of the column on the right listing SO2 concentrations associated with effects can be confusing, and would benefit from additional formatting to separate subsections; see the first part of page 1-21 for an example.

Dr. John Balmes

Comments on Chapter 5

Chapter 5 presents assessments of the health effects associated with short-term and long-term exposure to sulfur oxides. The discussion is organized by health effect category, exposure duration, outcome, and scientific discipline.

a. To what extent does this chapter accurately reflect the body of evidence from previous and recent epidemiologic, controlled human exposure and toxicological studies? What are the views of the panel on the integration of this evidence and the relative emphasis placed on each source of evidence?

In general, the chapter characterizes the body of evidence on SO2 health effects in a fairly accurate way. That said, some of the epidemiological evidence presented in the chapter could be more accurately characterized. I do not think it is appropriate to present associations between SO2 exposure estimates and outcomes per 5 or 10 ppb increase in SO2 when the association is not statistically significant without noting the lack of significance. The sections on cardiovascular outcomes are better at representing nonsignificant associations with wording such as follows: "the 95% CI for the association was wide, indicating an imprecise association." I would prefer that the chapter state something to the effect that "while the analysis between SO2 and asthma incidence suggested an association, the strength of the association did not reach statistical significance. That said, there was an apparent increase in the OR for incident asthma of X% for a 5 ppb increase in SO2."

Overall, the integration of the evidence from controlled human exposure, epidemiological, and toxicological studies is good and the relative evidence placed on each source of evidence is reasonable.

b. Considering the discussion of the strengths and limitations of the evidence in the text and tables within Chapter 5, to what extent is the causal framework appropriately applied to evidence for each of the health effect categories to form causal determinations?

I agree with the chapter's assessment of the strength of the evidence for causality for all outcomes considered.

c. The conclusions in the draft SOX ISA regarding the respiratory effects of SO2 exposure rely heavily on controlled human exposure evidence demonstrating effects of short-term peak exposures. Interpretation of the epidemiologic studies is more complicated due to the longer averaging time used in these studies. Please comment on the extent to which the evidence pertaining to the lowest concentrations associated with effects is appropriately characterized.

I agree with draft ISA's reliance on the experimental human evidence where possible. I also agree that interpretation of the epidemiological evidence is more complicated. Many of the studies that found associations between SO2 and asthma outcomes report mean concentrations and ranges of concentrations that are very low. I find it hard to reconcile the associations reported in these studies with the experimental evidence that indicates lack of bronchoconstriction and respiratory symptoms below 200 ppb and mostly above 400 ppb.

Dr. Aaron Cohen

General Comments on Chapter 5

The authors are to be commended for a clearly written chapter that, for the most part, effectively summarizes and distills a very large literature. Causal determinations have been updated for eight classes of health outcomes, and for five of these the determination has changed since the 2008 ISA, in all cases having been strengthened. For the most part, the rationale for the determinations has been well described.

I have reviewed each section of Chapter 5 below, in each case focusing on the extent to which the authors' have adequately justified the proposed determinations presented in the Executive Summary (Page xliv, Table ES-1).

Section 5.2.1 Respiratory Morbidity Short-Term Exposure

This section is well-written and presents clearly and logically the evolution of the evidence since the 2008 ISA. The determination that the current evidence, based largely on the evidence for exacerbation of asthma from both observational and experimental studies, is consistent with a causal relationship is well-justified.

Page 5-17, lines 18-30: The justification for down-weighting Goodman et al. 2015 seems reasonable.

Page 5-23, lines 14-16: Any idea why effects were seen in just one treatment group? Ages in this small study ranged from 12-65 years. Were treatment groups balanced on age or correlates of disease severity?

Page 5-29, lines 4-8 and Page 5-33, lines 9-11: The exposure-response relationships could be presented more clearly and explicitly. In addition to Table 5.2 a figure(s) might help.

Page 5-35, Table 5-8: In each of the three studies the investigators failed to report key information on either SO_2 exposure (O'Connor et al.; Spira-Cohen et al.) or effect estimates (Dales et al.) did EPA ask the authors to provide these data? If not, could they?

Page 5-36, line 9-10: O'Connor et al. actually reported increased RR for each symptom. The authors have mis-interpreted the evidence because they have used the 95% CI to perform a statistical significance test.

Page -86, line 5: rather than "there was uncertainty," better to say the estimate was very imprecise.

Page 5-108, line 8: better to say "supportive of an inverse association…"

Page 5-134, lines 12-13: the evidence for linearity of the mortality exposure-response function is based on very limited exploration of alternatives and this should be noted.

Section 5.2.2 Respiratory Morbidity Long-Term Exposure

The determination that the evidence is now "suggestive" of a causal relationship rather than "inadequate," is based on two new studies of asthma incidence in children and one new experiment in rats. This is justifiable given how "suggestive" is defined (Preamble, Table II). However, the results of the longitudinal epidemiologic studies cannot confidently be interpreted as due to SO_2 exposure as opposed to other pollutants and, perhaps, other risk factors.

Section 5.2.2.1 Development of Asthma

It would help to discuss briefly which risk factors in addition to air pollution are most important to assess re. confounding and effect measure modification. When information on a specific covariate (e.g., housing characteristics or smoking) is unavailable to what extent can more readily available data (e.g., SES) serve as a surrogate and how much residual confounding would be expected. This should then be discussed re. studies of Clark et al. and Nishimura et al. which studies include different covariates, as do the cross-sectional studies in Table 5-28.

Is loss to follow-up an issue in either Clark et al. or Nishimura et al.? It is not mentioned.

Section 5.3.1 Cardiovascular Effects Short-Term Exposure

The determination that the evidence is now "suggestive" of a causal relationship rather than "inadequate," is based on new epidemiologic studies, there having been little or no new toxicologic studies. The epidemiologic evidence on MI triggering is given particular weight (Page 5-225, lines 6-10 and Page 5-223, lines 12-14). I find the new determination harder to defend in this case because: 1) the new studies share the main weakness noted for the older studies in the ISA 2008, namely that any observed effects my actually be due to other pollutants; 2) SO_2 effects in studies of MI hospital admissions were substantially reduced or eliminated in two-pollutant models (Page 5-175; lines 18-37; and 3) the only study that precisely characterized exposure at the time of MI onset found no effect (Bhaskaran et al. 2011; Page 5-175; lines 8-10).

Page 5-186, lines 15-29: Are the null studies stronger or weaker methodologically? To say that results are "inconsistent" just states the obvious. Bell et al. (2008) appear to have used considerably more extensive monitoring data than other studies and to have conducted an

assessment of alternative exposure models none of which resulted in increased risk of stroke admission associated with SO_2.

Page 5-194, lines 29-31: this clearly worded description of the evidence for Heart Failure applies with equal force to Venous Thromboembolism (Page 5-194, lines 12-14)

Page 5-200, lines 5-6: what is meant by "clinically relevant?" Is clinical relevance an issue of general concern? If so, there are other places in the chapter, e.g., effects on sub-clinical markers, where this issue should be addressed.

Page 5-209, line 4: typo: should read "…consistent with…"

Page 5-208, lines 9-11 and Page 5-209, lines 7-8: Does this imply that the exposure-response relationship may be nonlinear?

Page 5-213, lines 1-2: the evidence for linearity of the mortality exposure-response function (Chen et al. 2013; Page 5-211, lines 1-6) is based on very limited exploration of alternatives and this should be noted.

Section 5.3.2 Cardiovascular Effects Long-Term Exposure

The determination that the regarding cardiovascular effects of long-term exposure to SO_2 is "inadequate" to make causal determination is well-supported by the evidence reviewed in this section. The authors correctly note the inability to attribute increased rates of cardiovascular disease to SO_2 given high correlations with co-pollutants including $PM_{2.5}$ (Page 5-234, lines 8-11) and the absence of supporting experimental and clinical evidence (Page 5-237, lines 11-14).

Section 5.4 Reproductive and Developmental Effects

The determination that the evidence is now "suggestive" of a causal relationship rather than "inadequate," is based on a growing, largely epidemiologic, literature on adverse birth outcomes that is generally well-summarized in the Chapter. The reasons why the evidence was considered "inadequate" in the 2008 ISA are summarized on Page 5-241, lines 2-6. Although there are now more studies these same reasons: lack of toxicologic support, potential confounding by co-pollutants, and uncertainty regarding exposure, still seem to apply to the current literature as noted by the authors (e.g., Page 5-256, lines 14-17).

Section 5.5 Mortality

Section 5.5.1 Total Mortality Short-term exposure

The determination that the evidence remains "suggestive" of a causal relationship is well-supported by the current review, given that the shortcomings of the literature identified in the 2008 ISA (Page 5-261, lines 7-10) have largely not been addressed in more recent studies. Specifically, the potential for confounding of observed SO_2 effects by co-pollutants remains largely unresolved and, to the extent that confounding by co-pollutants has been assessed, neither $PM_{2.5}$ nor sulfate PM has been included.

Page 5-284, lines 12-16: the evidence for linearity of the mortality exposure-response function is based on very limited exploration of alternatives and this should be noted. That said, to my eye neither Figure 5-22 nor Figure 5-23 strongly support a such a definitive statement on linearity, especially given the uncertainty regarding the role of SO_2 vs. other pollutants that SO_2 may well represent.

Section 5.5.2 Total Mortality Long-term exposure

The determination that the evidence is now "suggestive" of a causal relationship rather than "inadequate," is based on epidemiologic studies reported since the 2008 ISA. However, although the number of studies has increased the authors offer little evidence that the uncertainties identified in the 2008 ISA have been reduced (Page 5-289, lines 1-9), which they appear to acknowledge, at least for European (Page 5-298, lines 10-11) and Asian (Page 5-299, lines 7-9) studies.

The possibility that "sulfate or other particulate SO_x…" might be responsible for increased mortality associated with SO_2 was noted in the 2008 ISA and in the current chapter (Page 5-306; lines 6-9). Absent experimental evidence to the contrary, this remains a tenable explanation for the observed mortality effects of SO_2.

The authors' conclusion re. the epidemiologic evidence (Page 5-306, lines 9-18) seems inconsistent with the change in determination from "inadequate" to "suggestive."

Section 5.6 Cancer - Long-term exposure

It is not entirely clear to me why the determination has changed from the 2008 ISA wherein the evidence was considered "inconclusive." Given the evidence reviewed in the chapter that still seems the best description. Notably the two of the three largest studies reviewed (Krewski et al. 2009 and Brunekreef et al. 2009) report null results for lung cancer. Studies of lung and other cancers are more numerous but largely share the same limitations as earlier ones with regard to whether other pollutants are responsible for observed effects.

A summary Table and/or forest plot would be helpful in presenting the epidemiologic studies.

Dr. Alison Cullen

Comments on Chapter 3

In considering subsequent charge questions and recognizing an overall goal of producing a clear and concise document, are there topics that should be added or receive additional discussion? Similarly, are there topics for which discussion should be shortened or removed? Does the Panel have opinions on how the document can be shortened without eliminating important and necessary content?

Chapter 3 describes scientific information on exposure to ambient SO2 and implications for epidemiologic studies.

a. To what extent is the discussion on methodological considerations for exposure measurement and modeling clearly and accurately conveyed, appropriately characterized, and relevant to the review of the SO2 NAAQS?

b. Please comment on the accuracy, level of detail, and clarity of the discussion regarding exposure assessment and the influence of exposure error on effect estimates in epidemiologic studies of the health effects of SO2.

In light of the charge questions the most important overall need for the exposure related portions of the ISA is to improve clarity, reduce redundancy and emphasize new information as well as the science that drives policy. Substantial rewriting is warranted. Thus is difficult to separate responses to the two questions at this stage. However, below I include my preliminary comments.

The 2015 Draft ISA serves as a review of the policy relevant science and an update to the 2008 ISA, with a particular emphasis on new information available between January 2008 and April 2015. The most relevant studies from previous assessments are also carried forward. In the 2015 Draft, studies from previous assessments and those available since 2008 are presented together in tables (e.g., Tables 3-3 and 3-4) using alphabetical ordering by author. A temporal ordering would be useful as updates in the language regarding causal determination for relationships between sulfur dioxide and health effects has been strengthened (e.g., from "inadequate to infer" to "suggestive") presumably based on the newly available studies.

Confusion in the use of basic terms leads to a lack of clarify in places. For example exposure and exposure concentration are sometimes used interchangeably. The definition of exposure as related to conditions at the human boundary, in contrast to the movement of pollutants across the human boundary (as implied by the inclusion of Table 3-6 with ventilation rates), remains an

important distinction. Specific passages and segment edit suggestions will be included in the next set of comments.

In Section 3.2.2.1 there is a muddled discussion of comparisons of measurements and model results, as well as intercomparison of models. Clarify that the SPM and EWPM were both compared to AERMOD, and also one or several sets of model results were compared to measurements from 3 monitoring sites.

In the discussion of land use regression models the distinction between spatial variability and inter-individual variability gets lost.

The discussion of "exposure error" and "bias" is quite difficult to follow as written and would benefit from a more systematic layout. Reference to spatial and temporal variability, and its interaction with the relationship between site monitoring versus personal monitoring, in particular needs more clarity beyond the blanket reference to wider confidence intervals around exposure and health effect estimates. The layout in the figures of Section 3.3.3.2 is valuable.

Eliminate and tighten up repetitive language. For example, language introducing Section 3.3.3.4 appears in exact duplicate twice.

Edit presentations related to correlation (person-ambient relationships). These currently incorporate measures below the detection limit, as well as measures above, and then report the inevitable impact of the proportion of below DL measures on the correlation or R^2. This information appears in multiple sections and could be consolidated. The representation of measures below the DL needs clarification. It may help to include a parallel presentation focused on the measures above DL alone. However, overall, the conclusion at the top of page 3-35 (and bottom of 3-48) is correct, thus there is a real question regarding how much analysis in this area is warranted.

The document should focus on information specific to sulfur oxides which forms the basis for the conclusions presented. Within Section 3.2.1 there is a tremendous amount of excellent background material on monitoring, the instruments and methods that are used and the development of the field over time. Much of this is generic. There is also a substantial discussion of emerging technology for sulfur dioxide monitoring, that is currently in the early stages and not yet commercially available. Some of this text could be removed and the content simply referenced, to increase clarity of the presentation, and to sharpen the focus.

Similarly, the background information related to modeling (e.g., time activity, microenvironmental exposure, total personal exposure, etc.) does not always focus on considerations related to sulfur dioxide. Background is important, but the balance of strictly background text, versus that which is necessary for a discussion of sulfur dioxide, is skewed to the former. This document could rely more extensively on the 2008 ISA and referencing.

The use of tabular formats for bias information (e.g., in Table 3-2) is an efficient use of space and should reduce the need for extensive discussion in the individual sections.

Table 3-9 includes substantial detail associated with studies of reproductive timing and effects however this content is not clearly explained. The duration is sometimes expressed in terms of trimesters of pregnancy or months prior to conception. In short, the level of detail in Table 3-9 is inconsistent with the discussion provided.

In Table 3-10 and the text directly above there is confusion between the terms “true value” and modeled estimate.

Dr. Ana Diez Roux

Comments on Chapter 6

Charge Question: To what extent has the available scientific evidence from epidemiologic, controlled human exposure, and toxicological studies been integrated to inform conclusions on at-risk populations and/or lifestages? Is there information available on other key at-risk factors that is not included in the draft SOX ISA and should be added?

Despite confusing terminology used in the literature, I think it would be helpful for EPA to be clearer and more succinct in what it means by "populations-at-risk". On one hand a population subgroup may be at higher risk simply because *they are more exposed* (e.g. they spend more time outdoors or tend to live closer to sources). A second way in which a population subgroup may be at higher risk is because *the adverse health effect of the pollutant is greater* (this is usually referred to as effect modification in epidemiologic studies or sometimes statistical interact). This may occur for example in the presence of a genetic predisposition. In the case of SO2 asthmatics may experience greater adverse effects of exposure because of existing alterations of the respiratory tract related to their underlying asthmatic disease. The introduction could be clearer on this distinction and indicate that the main focus of this chapter is effect modification.

Overall I very much appreciate the careful and systematic review of the effect modification studies and the way results are presented in tables (as opposed to simply narrated in the text). A bit more clarification of the up and down arrows (see comments below) would be helpful. It is also important to indicate whether all the studies reported actually found that the effect modification was statistically significant.

<u>Specific comments</u>

Pg 6-2 lines 17-19. Do you mean "stratified analyses to compare magnitude of effects in different groups"?

Table 6-3. Does the down arrow for HRV on page 6-7 mean a weaker adverse effect? This is confusing because less HRV is often considered more adverse. Table 6-6 says Decrements in HRV which is a bit clearer. If the association of SO2 with less HRV is stronger in asthmatics or in diabetics than in individuals without the condition then the arrow should be an up arrow indicating a stronger effect in the disease group. A clarifying footnote would help (0ne is included in table 6-7 but not the others where HRV is included).

Table 6-6. The footnote explaining the up arrow is confusing. An up arrow means that the effect was *reduced*?

Pg 6-32 lines 7-9. I would just say that SES can be indexed using measures such as income, education, or occupation. Since you show results for a deprivation index as well might be worth mentioning this measure.

Pg 6-32 lines 9-12. SES may modify the effect of SO2 primarily due to the presence of diseases (such as asthma) or possibly other co –occurring exposures. I am not sure there is evidence to argue that nutrition or access to health care modify effects.

Pg 6-34 lines 13-14. I suggest avoiding the intrinsic and extrinsic mechanism terminology unless you define it somewhere (I find it confusing generally).

Dr. Daniel Jacob

Comments on Chapter 2

Chapter 2 describes scientific information on sources, atmospheric chemistry, and measurement and modeling of ambient concentrations of gaseous sulfur oxides. I found it to be overall well-informed and informative. With regard to the charge questions,

a. To what extent is the information presented regarding sources, chemistry, and measurement and modeling of ambient concentrations accurate, complete, and relevant to the review of the SO2 NAAQS?

I think it's good but I have a lot of minor comments, listed below.

b. Please comment on the extent to which available information on the spatial and temporal trends of ambient SO2 concentrations at various scales has been adequately and accurately described. In particular, what is the extent to which the analyses of recently available 5-min SO2 concentration data are informative in considering relationships between 5-min and 1-hr SO2 concentrations?

I think that this is done very well and that the correlations between 5-min and 1-h concentrations provide the information needed to model 5-min exposure on the basis of 1-h concentrations.

c. *How informative is the analysis of correlations between SO2 and co-occurring pollutant concentrations for interpretation of epidemiologic studies?*

I think it's good enough – correlations are weak, as one would expect.

Below are specific comments related to charge question a). (Page, line)

1. (2.1, 14) Smelters are also important.
2. (2.9) Figure 2.5 has strange left and right y-axes title/labels (which is correct?). I don't understand the green line labeled as "fuel comb. Industrial" – it doesn't fit with any of the other information and why would it be as large as the EGUs? That's not consistent with Table 2.1. A general problem with the different source type attribution estimates presented in figures and tables in this section is that they are not internally consistent because they come from different sources – this needs to be either fixed or acknowledged.
3. (2.10, 5). Hydrogen disulfide is not atmospherically relevant. Dimethylsulfide is and would be worth mentioning.

4. (2.11) Figure 2.6: CS_2, not CS. DMS source is inconsistent with other numbers given in tables and text. Volcanoes also emit H_2S. Not sure that it's worth mentioning primary sea salt and dust sulfate sources – they can't make SO_x. And I would put a number on the volcano source because it's no more uncertain than DMS. It's variable year-to-year but that's a different matter.
5. (2.12, 5) They're not difficult to estimate, they're just variable year to year.
6. (2.15, 6) These may be modeling studies but their specification of volcanic emissions is not based on their model.
7. (2.16, 5) Volcanoes release H_2S in larger amounts than COS or CS_2.
8. (2.18, 14) COS loss is mainly by OH, see Table 4b of Chin and Davis (JGR 1993).
9. (2.19, 1-2) Awkward, suggests that NO3 is dominant sink for DMS.
10. (2.20, 10) Radical, not ion
11. (2.21, 1-3) Real issue with Criegees as SO2 oxidants is their hydrolysis; see Kim et al., ACP 2015. http://acmg.seas.harvard.edu/publications/2015/kim2015_seac4rs.pdf
12. (2.21) Equation 2.4 should be written as 3-body reaction.
13. (2.21, 14-15). Major sulfur species in cloud would be sulfate. Also, "acid dissociation" is better terminology than "react with water".
14. (2.28, 26) To say that satellites don't measure SO2 directly is gratuitous. The same could be said for other methods, in particular DOAS.
15. (2.28, 30) Real problem with SO2 sensitivity is air scattering, not ozone column.
16. (2.28, 36) Probably should mention detection of emissions from oil sands in western Canada (McLinden C A, Fioletov V, Boersma K F, Krotkov N, Sioris C E, Veefkind J P and Yang K 2012 Air quality over the Canadian oil sands: A first assessment using satellite observations Geophys. Res. Lett. 39 L04804)
17. (2.29, 1-3) Throwaway statement. Cut.

Dr. David Peden

Comments on Chapter 4

Chapter 4 characterizes scientific evidence on the dosimetry and modes of action for SO2. Dosimetry and modes of action are bridged by the absorption and reaction of SO2 in the epithelial lining fluid to form SO2-derived products (e.g., sulfite and/or S-sulfonates) that are widely distributed throughout the body.

a. *To what extent is the discussion of the chemistry of inhaled SO2 and the processes of absorption, distribution, metabolism, and elimination accurate, complete, and relevant to the review of the SO2 NAAQS?*

It is likely that decreased upper airway airflow in children and obesity (in all ages) will modify deposition of SO2 or H_2SO_4 in the airway. This may be covered in section 5 (though I did not find it). Using radiolabeled particle uptake data assessment of deposited marker particles, children had decreased nasal contribution to breathing and increased deposition to the lower airway (1). In a comparable study, it was found that children with increased BMI also had increased central airway deposition of inhaled agents (2). There is a gap in the literature for this as well regarding SO2. However, the data in these reports l demonstrate changes in airflow associated with nasal and orophergygeal breathing in children (though there are data derived from labeled particles), which may be germane for SO_2 exposure in the form of H_2SO_4. It seems likely that these factors may be as much of a physiological parameter as asthma in directing deposition of SO2 onto specific airway sites.

Extrapolating the robust literature on obesity and obstructive sleep apnea, it is very likely that functional nasal obstruction, with increased oropharyngeal breathing will occur in obese and overweight individuals of all ages. This will likely be true for breathing at rest (see note above). Thus the lower airway distribution/deposition of SO_2 (or any pollutant) will likely be greater in obese individuals. Given the rate of obesity/overweight in the US, this is an important consideration, especially as much of the data on radiolabelled SO2 uptake is fairly dated (when obesity was a much less prevalent issue) (refs 3-12).

b. *Please comment on the discussion comparing endogenously generated and ingested sulfite with that derived from ambient inhalation.*

I have nothing of substance to add here

c. *To what extent are the discussion and integration of the potential modes of action underlying the health effects of exposure to sulfur oxides presented accurately and in sufficient detail?*

Are there additional modes of action that should be included in order to fully characterize the underlying mechanisms of sulfur oxides?

One area that may need better definition is the impact of genetic factors on response to SO2. A cursory search identifies a study in which persons with the AA genotype for the -308 TNF promoter region have increased airway response to SO_2 (13). As increasing data are accumulated showing the effect of SO2 on signaling and inflammatory mechanisms, there is an increased likelihood of identifying genetic factors in response to SO2 (14,15).

There has been an association with decreased death due to emphysema and decreased SO2 exposure, suggesting SO2 may impact structural integrity of the lung parenchyma (16)

There are a number of studies that suggest that So2 contributes to airway infections (17-19) and there are other several studies (some relatively dated) that indicate an impact of SO2 on mucociliary clearance, and subsequent effect of this on infections, including otitis media and bronchitis (20-22). The study by Carson et al demonstrates the structural effect of SO2 on cilia (23).

Systemic effects do occur with SO2 (15). SO2 has effects on psychosis, cardiovascular effects and risks of respiratory effects. While the gender and age specific aspects of the effect of SO2 vary by endpoint, there are certainly data showing gender and age based differences impact susceptibility to SO2, with women having more effect of SO2 on CVD and age being a determinant of asthma effects of SO2 (24-26). These suggest specific mechanistic considerations as well.

References

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Dr. Lianne Sheppard

Comments on Chapter 3

From my perspective the primary purpose of this chapter is to allow readers to understand human exposure to SO2, as well as how it is measured and modeled, in order to appropriately interpret the epidemiologic study results in Chapter 5. Is this EPA's intent? Assuming it is, then I believe the primary objective has not been met. Overall I judge that this chapter needs considerable reorganization and revision. I find it less clear than other similar sections/chapters from previous ISAs. In numerous places the wording is confusing or misleading, making it difficult to grasp the key messages the chapter should convey.

I think an important objective of the chapter is to give readers an understanding of SO2 as a pollutant (in the context of human exposure) and the implications of this understanding for how well various epidemiological study designs will perform under different exposure metrics (focusing only on the ones relevant to the discussion in Chapter 5). It should clearly distinguish between the understanding of exposure that is generally applicable to any ambient air pollutant from insights that are specific to SO2. In addition this chapter should clearly covey new understanding since 2008 and distinguish this from the material discussed in the 2008 document.

I'm having some difficulty distinguishing between how to divide my responses to the two charge questions for this chapter. I interpret that the first one is focusing on exposure measurement and modeling, while the second on exposure assessment and measurement error in epidemiological studies. (Are these intended to address sections 3.2 (Methodological considerations for use of exposure data) and 3.3 (Exposure assessment and epidemiologic inference), respectively?) I would not separate exposure modeling from exposure assessment and measurement error. EPA's definition of exposure assessment (in Guidelines for Exposure Assessment, EPA/600/Z-92/001 May 1992) is "The determination or estimation (qualitative or quantitative) of the magnitude, frequency, duration, and route of exposure." This clearly includes exposure measurement and modeling. Thus I find it difficult to understand how EPA staff want us to approach these two questions. For the moment I have not attempted to separate my comments by charge question.

Charge question draft responses

CQ1: *To what extent is the discussion on methodological considerations for* ***exposure measurement and modeling*** *clearly and accurately conveyed, appropriately characterized, and relevant to the review of the SO2 NAAQS?*

CQ2: *Please comment on the accuracy, level of detail, and clarity of the discussion regarding* ***exposure assessment and the influence of exposure error*** *on effect estimates in epidemiologic studies of the health effects of SO2.*

The level of detail seems uneven. I think the total length of the chapter is reasonable in principle as 70 pages is sufficiently long to delve into important topics while not so long as to put off readers. However, as currently written, the chapter should be shortened to eliminate unnecessary content and redundancies.

The clarity and accuracy of the discussion are insufficient. There are many statements in the chapter that are inaccurate or unclear. There are a number of broad issues:

- There are topics covered that are not relevant to interpretation of epidemiologic studies, specifically several pages devoted to probabilistic exposure modeling. While some of this discussion is specifically noted as relevant for the risk and exposure assessment, and thus could be retained for that purpose, not all of the discussion of this topic is so carefully delineated. (e.g. p 3-41)
- There is confusion between 1) exposure measurement error that comes from the uncertainty of the exposure metric being used relative to an uncertain version of that metric, and 2) a different target parameter of interest in the epidemiologic study than one might prefer. The latter comes from the distinction between the exposure metric selected vs the exposure of interest (e.g. the most common case is that the exposure metric selected is ambient concentration while the exposure of interest is personal exposure to ambient SO2). The entire discussion needs to be revised with this distinction in mind.
- There is discussion of dose (by bringing in the topic of ventilation) that is not clearly distinguished from exposure. Using EPA's own definition (in Guidelines for Exposure Assessment, EPA/600/Z-92/001 May 1992), exposure is "The condition of a chemical contacting the outer boundary of a human is exposure." In my opinion, ventilation is not at the outer boundary of a human. Thus most of Section 3.3.3.1 could be eliminated.
- In discussions of the impacts of mismeasured exposures it is not clearly articulated what is meant. For instance, when a mismeasured exposure "widens the confidence intervals", is this relative to using the true (albeit unknown) exposure? And how does this statement relate to understanding of the correct (i.e. nominal) coverage of the confidence intervals? Related to this point, it should be clearly stated what happens when measurement error is ignored in the analysis vs. what happens when it is corrected for. (Specifically, what happens to the effect estimates, standard errors, and coverage of confidence intervals when measurement error is corrected? What are the implications for interpretation of studies that do not correct for measurement error?)
- Some of the studies are not clearly identified as simulation studies. The assumptions of the studies are treated as data and thus the reader can easily incorrectly infer that these assumptions are properties of SO2. (see e.g. p 3-49, paragraph starting on line 3)
- There are broad-brush statements made that may not be adequately worded or valid. Often they should be backed up with references to the literature or other sections of the document. Consider for instance the sentence on p 3-37 lines 6-8: "The use of SO2 measurements from central ambient monitoring sites is the most common method for assigning exposures in epidemiologic studies." How does EPA equate using measurements from central site monitors to a method for assigning exposure? Does this pertain to all epi study designs?

The organization of the chapter should be revisited. I think it is important to convey 1) a general understanding of exposure to ambient air pollutants along with 2) an appreciation for the specific characteristics of SO2 that relate to this understanding. These specific characteristics have implications for measurement and modeling of SO2 as well as for accurate inference about SO2 health effects in epidemiological studies. Similarly, there are general approaches to measuring criteria air pollutants (e.g. ambient concentrations at fixed locations, indoor-outdoor measurements at homes and other subject locations, and personal measurements) and specific technologies to measure SO2. These specific features of measuring SO2 further inform our understanding of epidemiologic studies and the SO2 exposure studies. I expect 70% or more of this chapter should consist of material that could appear in any ISA exposure chapter while the remainder of the text would be specific to SO2.

More specific comments: (I am skipping many details to concentrate on larger issues.)

- Section 3.2.2 needs to be completely revised. Its organization and grouping of models are problematic. There is a strange mixing of methods and results in this section. It is written with insufficient clarity making it difficult for a reader to make much sense of the literature or understand the key points.
    - What is the point of the discussion of time-activity models (Section 3.2.2.2)? What epi studies take these into account?
    - Why is Section 3.2.2.3 on models of air exchange rates and microenvironmental models needed?
- Table 3-2: While the intent of this table is helpful, only methods that have at least one epidemiological study of SO2 discussed in Chapter 5 should be listed. Furthermore, the list should be comprehensive for the important epidemiological studies and overlap with the models described in Table 3-3.
- Table 3-4: It is unclear why a table of this length is needed since 10 of 12 cited studies were available for the 2008 ISA. Furthermore, the table mixes reporting of ratios and slopes. These are not the same and it makes it difficult for readers to distill key points from the information presented.
- I found Section 3.3.3 (the opening paragraph) to be very broad-brush and speculative.
- The introduction of new rules for ultra-low sulfur diesel was brought up as potentially important factor in interpretation of reported correlations between pollutants (p 3-50 line 30). However, the subsequent discussion did not appear to take the timing of these studies into account.
- Important terms have not been clearly defined. Examples include the specific R2's reported in the text in Section 3.2.2.1 and in some entries of Table 3-3, and the definitions or data used to compute the correlations in Table 3-9 and the text discussing it. (For instance, for the copollutant correlations in long-term epi studies, are the correlations based on purely space or space and time? Also, are they based on predictions or measurements?)

Throughout this chapter there are many sentences with poor wording. Experts other than the primary author(s) of this section should review the chapter and help improve the wording. To support this effort, I will provide some suggested text rewording for paragraphs that discuss my work or work of my UW colleagues.

New Reference:

Bergen S, Szpiro AA: Mitigating the impact of measurement error when using penalized regression to model exposure in two-stage air pollution epidemiology studies. Environmental and Ecological Statistics. 2015, 22:601-631.

Dr. Ron Wyzga

Comments on Chapter 5

p. 5-61, ll 14-31.: Exposure error could also be due to differences in time averaging. The human clinical studies find responses occurring after exposures as brief as 5 minutes. Most acute epidemiological studies consider a 24 hour average. If the 24 hour period includes short exposure windows of 5 minutes or so with higher SO2 levels, these could be masked in a 24-hour average; hence the 24-hour average contains considerable measurement error in estimating the relevant short (5-10 minute) exposures that could be responsible for any health response.

p. 5-62, ll. 17-20: Measurement error can also distort the estimated shape of the dose-response function and mask the existence of any threshold.

p. 5-77, ll. 1-13: In consideration of the correct co-pollutants, there may be guidance in terms of looking at the relevant sources of SO2. For example, it is diesel emissions, there is a greater need to consider pollutants such as EC or OC. If it is power plants, these co-pollutants are less important.

p. 5-99, ll 17-20: It could be misleading to generalize from this one study.

p. 5-103: This section could also include Klemm, R. J.; Lipfert, F. W.; Wyzga, R. E.; Gust, C., Daily mortality and air pollution in Atlanta: Two years of data from ARIES. Inhalation Toxicology 2004, 16, 131-141.

p. 5-141, l. 1: Is).95 and OR or RR?

p. 5-143, Table 5-28: is that a minus sign in from 1.47?

p. 5-144, Table 5-28: For Nishimura et al., are we uniformly talking about ORs?

p. 5-175, l. 6: Can you be more explicit about what is meant by “some”?

p. 5-179, Table 5-33: Is the risk or odds ratio for Ballester et al, for a single pollutant model or after adjustment? Similar question for Cheng et al.

p. 5-191 Szyszkowicz et al, were any organics considered in multi-pollutant models?

p. 5-208, ll. 12-29: See comments for p. 5-77.
l. 25: please give confidence interval.
l. 28: please give confidence interval.

p. 5-219, Table 5-40: do we have results for other lags for Dubowsky et al.?

Section 5.5.1. you may want to add the following reference to the studies considered:
Klemm, R. J.; Lipfert, F. W.; Wyzga, R. E.; Gust, C., Daily mortality and air pollution in Atlanta: Two years of data from ARIES. Inhalation Toxicology 2004, 16, 131-141.

p. 5-315: l. 1: It is often difficult to distinguish between "suggestive" evidence and "inadequate" evidence. I struggle with the choice between these two for the cancer endpoint. There are a couple of studies (imperfect) that suggest a possible relationship between SO2 exposure and cancer; on the other hand, the available information is limited and frankly inadequate to make any judgment. More guidance on the distinction between these two categories would be helpful.

Comments on Chapter 6

Charge Question: To what extent has the available scientific evidence from epidemiologic, controlled human exposure, and toxicological studies been integrated to inform conclusions on at-risk populations and/or lifestages? Is there information available on other key at-risk factors that is not included in the draft SOX ISA and should be added?

<u>Overall comments</u>

By and large this chapter utilizes the information from Chapter 5 to identify populations and lifestages potentially at risk. I have three major comments on this chapter. First of all the chapter largely ignores the fact that indoor SO2 levels are largely very low; hence populations who spend more time outdoors have greater potential to be exposed to higher levels of SO2. Secondly behavioral factors can add to this potential; for example, asthmatics appear to be more sensitive while exercising and there is some evidence that asthmatic medication can be protective of response. These issues should be mentioned here and to some extent they may explain while children could be more responsive as they exercise more frequently and probably spend more time outdoors as well. The last issue concerns the definitions of the "Direction of Effect" symbols in the tables. They need better definition and perhaps they should be expanded to be more informative. For example, I doubt the "-" symbol really means "no difference" in the absolute sense; for example, Table 6-4 presents a "-" for the study by Amadeo et al.. If we go back to Chapter 5 (Table 5-21) we note that there are non-zero differences between exposed and non-exposed subjects, but these differences are far from being statistically significant. My question is what is the dividing line between a "-" and an up or down arrow? Is it statistical

significance or some other measure? I also wonder if it would more informative to have additional symbols, such as a double arrow when the difference is very large (to be defined). The various tables or text could also indicate which direction of effect is considered adverse. For example, in Table 6-8 we see contrasting directions.

Chapter 5 gives different weightings to North American studies and those undertaken overseas. This chapter does not do likewise. If such a distinction is made, it could change some of the inferences. For example, Table 6-11, looks at the older adult lifestage; of the 17 studies considered, only 3 are from North America, and two of the 3 show no difference in direction of effect. The third study finds no difference for those 65-74, but it does for those >74 years.