



**UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D.C. 20460**

OFFICE OF THE ADMINISTRATOR  
SCIENCE ADVISORY BOARD

August 8, 2008

EPA-CASAC-08-017

The Honorable Stephen L. Johnson  
Administrator  
U.S. Environmental Protection Agency  
1200 Pennsylvania Avenue, NW  
Washington, DC 20460

Subject: Clean Air Scientific Advisory Committee's (CASAC) Peer Review of  
EPA's *Integrated Science Assessment (ISA) for Sulfur Oxides – Health  
Criteria* (Second External Review Draft, May 2008)

Dear Administrator Johnson:

The Clean Air Scientific Advisory Committee (CASAC), augmented by subject-matter-experts to form the CASAC Sulfur Oxides Primary NAAQS Review Panel conducted its review of EPA's *Integrated Science Assessment (ISA) for Sulfur Oxides – Health Criteria* (Second External Review Draft, May 2008) on July 30-31, 2008. The first draft ISA was reviewed by CASAC in December of 2007 and subsequently revised in response to CASAC advice transmitted in January 2008. This letter presents CASAC's advice on the second draft ISA issued in May 2008.

The CASAC finds that the second draft ISA is greatly improved and that the Agency has been responsive to the CASAC's earlier review. There are some remaining concerns as described in our answers to the Agency's charge questions in the main body of this letter. Our major concern is the conclusions in the ISA regarding the weight of the evidence for health effects for short-term exposure to low levels of SO<sub>2</sub>. Although the ISA presents evidence from both clinical and epidemiological studies that indicate health effects occur at 0.2 ppm or lower, the final chapter emphasizes health effects at 0.4 ppm and above. As discussed in our responses to Charge Questions 3 and 5, CASAC believes the clinical and epidemiological evidence warrants stronger conclusions in the ISA regarding the available evidence of health effects at 0.2 ppm or lower concentrations of SO<sub>2</sub>. The selection of a lower bound concentration for health effects is very important because the ISA sets the stage for EPA's risk assessment decisions. In its draft *Risk and Exposure Assessment (REA) to Support the Review of the SO<sub>2</sub> Primary National Ambient Air Quality Standards* (July 2008), EPA chose a range of 0.4 ppm – 0.6 ppm SO<sub>2</sub> concentrations for its benchmark analysis. As CASAC will emphasize in a forthcoming letter on the REA, we recommend that a lower bound be set at least as low as 0.2 ppm.

With this and other modifications as recommended below, CASAC finds the scientific quality of the ISA acceptable for rulemaking.

CASAC's response to EPA's charge questions are summarized below. Individual recommendations from Panel members to strengthen the final ISA are appended in Enclosure B.

**Charge Question 1: The framework for causal determination and judging the overall weight of evidence is presented in Chapter 1. Is this the appropriate approach? Is it appropriately applied in the case of SO<sub>x</sub>? How could the framework or its application be refined?**

Chapter 1 has been improved, particularly by drawing on recent reports that offer models of approaches for causal inference and classification schemes for the weight of evidence for inferring causation. The ISA utilizes a five-level hierarchy for causal determination to be consistent with the *Guidelines for Carcinogen Risk Assessment* (EPA, 2005). We concur with using the five levels but recommend that the descriptions be changed to better reflect the level of certainty or confidence in the classification of the level of evidence. The phrasing of the second level is particularly problematic in its addition of the wording "likely causal relationship." The approach to evidence interpretation should avoid using statistical significance as a criterion for evidence interpretation. CASAC recommends that EPA reconsider the language used to describe the weight of evidence, particularly for the first three categories which cover a range of certainty or confidence in causal inference that extends from full certainty to lesser degrees. The language used should be consistent with other such schemes used by EPA.

For the criteria pollutants, the ISA needs to acknowledge that the pollutants exist in complex mixtures and to broadly consider the implications for interpreting the evidence in the ISA. We also specifically recommend improvement in the presentation of the epidemiological concepts of effect modification and confounding that are particularly challenging in the face of multi-pollutant mixtures. Other aspects of the chapter also need greater development including the treatment of uncertainty. The concept of "margin of safety" also needs elaboration. Figure 1 is not effective and unless the text is expanded to explain many of the relationships depicted, it needs to be abandoned or replaced.

Finally, we applaud the specification of questions at the beginning of the first chapter that outline specifically the intent of the ISA, and the integration of the answers to these questions, as obtained from the evidence in the ISA, in the concluding chapter. This structure will provide a clear scientific foundation for the development of the Risk and Exposure Assessment document.

**Charge Question 2: Have these revisions to Chapter 2 improved its assessment of the currently available scientific knowledge on atmospheric sciences and exposure and its relevance to the evaluation of human health effects presented in later chapters?**

Chapter 2 is significantly improved from its earlier version and previous comments from the Panel have been taken into account. There are, however, some points that need to be addressed in greater detail and other points require some clarification. Since the REA will focus on 5-minute averages of SO<sub>2</sub> concentrations, a more comprehensive discussion of the available 5-minute SO<sub>2</sub> concentration data is warranted. For example, a table presenting information similar to that in Table 2-4 would be useful. A better discussion of the distributions and time-trends of 5-minute average concentrations is needed as is greater consideration of which distribution best represents ambient data (normal or log-normal). Further, the analyses should address correlation between the 5-minute and one-hour average concentration distributions. Figure 2-11 needs to be redrafted to provide a better depiction of diurnal SO<sub>2</sub> ambient concentrations. The fact that the trend in SO<sub>2</sub> concentrations is due to changes in SO<sub>2</sub> emissions rather than to changes in measurement technique should be stated more definitively.

The rationale behind the selection of the six states selected for analysis should be better described; some consideration may need to be given to areas where the potential effect of ship emissions on SO<sub>2</sub> could be significant (i.e., major U.S. ports). Analyses (e.g. stratification for source proximity and strength and use of maps) of selected urban areas should be presented to characterize the representativeness of ambient monitors for characterizing population exposure. Since AERMOD is used in the REA, there is a need to describe it in the Annex.

Adsorption of SO<sub>2</sub> onto particles which is discussed in more detail in Chapter 3 needs to be further discussed in Chapter 2. However, this will need to be placed in perspective because concentrations of particulate matter (PM) and SO<sub>2</sub> used in the animal toxicological studies discussed in Section 3.1.5 were several orders of magnitude above typical ambient concentrations. In addition, it should also be noted that atmospheric chemistry studies do not indicate significant amounts of sulfite on atmospheric PM

Chapter 2 correctly points out the difficulties associated with characterizing exposure (e.g., limited information on indoor concentrations, and vertical and horizontal SO<sub>2</sub> concentration gradients). However, the implications for the characterization of health effects could be better described and discussion on the implied uncertainties expanded. More discussion of the effect of exercise on health effects in exposure studies is warranted. In particular, the ISA points out that whether SO<sub>2</sub> is inhaled via nasal vs. oral breathing makes a difference for SO<sub>2</sub> uptake, however, the implications for the analysis of the health effects studies need to be discussed in greater detail.

**Charge Question 3: In the revision, we reduced redundancy, added summary sections and reorganized Chapter 3. In addition, discussions on potential confounding by, and interactions with, co-pollutants have been added. The 2nd draft ISA also includes additional analyses of individual-level data from human clinical studies (Sections 3.1.3. and 4.1.1) that builds upon the analysis included in the 1994 Supplement to the Second Addendum. The toxicology sections were**

**reorganized to focus on studies using more relevant concentrations of SO<sub>2</sub> and sections were added to better discuss mode of action and potential particle-SO<sub>2</sub> interactions. We are requesting CASAC review specifically on these analyses as well as on the integration of the overall evidence from the human clinical, animal toxicological, and epidemiological studies.**

Chapter 3 is vastly improved from the previous draft of the ISA. The new analyses of human clinical studies are helpful. CASAC believes, however, that more emphasis should be placed on effects seen at concentrations lower than 0.4 ppm. The Panel is concerned about the potential underestimation of the proportion of asthmatic persons affected by short-term exposure to SO<sub>2</sub> because only mild and moderate asthmatic adults were recruited to participate in the clinical studies. People with more severe asthma or poor control of their symptoms may be more susceptible and may respond more adversely to SO<sub>2</sub> and discussion of this point should be expanded in the chapter. The potential influence of medication use on asthmatic responses to SO<sub>2</sub> should also be discussed. In general, the evidence from the animal toxicological, controlled human exposure, and epidemiological studies has been satisfactorily integrated. However, the gap between the greater level of SO<sub>2</sub> used in the clinical studies and the relatively lower ambient concentrations associated with respiratory morbidity in the epidemiological studies needs to be clearly acknowledged. The relevance of the higher dose animal studies also needs to be better developed. The results of the studies involving extremely high levels of metal oxide or carbon-SO<sub>2</sub> mixtures suggest that SO<sub>2</sub> effects may be potentiated by co-exposure to particles, but the relevance of these results to ambient exposures is unclear. Section 3.1.5 should be greatly condensed to give a more focused discussion of the mechanistic implications of the mixture studies without presentation of experimental details. While the new summary sections are a welcome addition to the chapter, their quality is uneven. It would be helpful if these sections were written in a style that applied the causal inference approach outlined in Chapter 1 in a consistent manner.

**Charge Question 4: The section on concentration-response relationships in Chapter 4 was reorganized and revised to include analysis of individual-level data from the human clinical studies and some additional discussion of the difficulties of discerning a threshold in population-level data. In addition, revisions were made to better characterize groups likely to be susceptible or vulnerable to SO<sub>x</sub> and the potential size of the population at risk for SO<sub>x</sub>-related health effects. Finally, revisions were made to reduce redundancy with material presented in Chapter 3. Have the revisions made to Chapter 4 improved the characterization of the potential public health impact of SO<sub>x</sub> exposure?**

Revisions to Chapter 4 have improved the characterization of potential health impacts of SO<sub>x</sub> exposure, but additional clarification, evaluation, and amplification is needed. The Panel recommends that EPA revisit the definitions of susceptibility and vulnerability. The definition of susceptibility should consider the form of the dose-response relationship and the magnitude of response at a given dose. Greater clarity and specificity is needed in the definition of this concept if it is to be used without ambiguity.

The current definition is limited in concept and inconsistent with toxicological and epidemiological usage. EPA should harmonize the definitions of susceptibility and vulnerability across documents for intra-Agency and inter-pollutant consistency.

Additional analyses of the cited clinical chamber data could be performed to gain insights regarding the population distribution of effects at exposures lower than 0.4 ppm SO<sub>2</sub>; there appears to be an indication of effects below this level when the pooled data are considered. Specific details are provided in individual comments. See comments from Drs. Avol, Hattis, Kinney, Pinkerton, Samet and Sheppard. In addition, the discussion should do a better job of acknowledging that epidemiology studies generally lack power to distinguish between linear and non-linear response forms.

A more complete discussion of potentially at-risk (i.e. susceptible and/or vulnerable) sub-populations is needed. The discussion should emphasize the importance of linking populations at potential risk due to age and disease status with considerations related to exposure and activity distributions in these groups. The joint distribution of all these factors defines the population at risk of adverse health impacts from SO<sub>2</sub> exposures. In addition, discussion of the geographical location of at-risk populations with respect to pollution sources needs to be included and related environmental justice concerns addressed, if appropriate. EPA needs to provide additional justification for its decision to focus on children and older adults with respect to short term respiratory health effects of SO<sub>2</sub>.

**Charge Question 5: Revisions were made to better integrate findings from atmospheric sciences, ambient air data analyses, exposure assessment, dosimetry, and health evidence in Chapter 5. To what extent do these findings support conclusions regarding causality of SO<sub>x</sub> related health effects at relevant exposures?**

The Panel concurs with the conclusion that short term exposures to SO<sub>x</sub> are causally related to changes in respiratory responses, however we do not accept the levels on which the ISA focuses. The clinical and epidemiological studies warrant a stronger conclusion about health effects at lower levels. The range of exposures emphasized in the ISA (0.4 - 0.6 ppm) has clearly carried over to the thinking used in the REA. Adoption of this range might leave substantial numbers of exercising mild asthmatics at considerable risk. Table 5-1 of the ISA presents studies showing that 5 – 20% of mild to moderate asthmatics experience moderate or greater decrements in lung function at SO<sub>2</sub> concentrations as low as 0.2 – 0.3 ppm. For ethical reasons severe asthmatics were not part of these clinical studies, but it is not unreasonable to presume that they would have responded to even a greater degree. In addition, the epidemiological evidence shows emergency room visits and hospitalizations for respiratory illnesses associated with 24-hour SO<sub>2</sub> levels below the current standard (0.14 ppm averaged over at 24-hour period). Collectively, this evidence should lead to a conclusion that 0.2 ppm or even a lower level of short-term exposure is an appropriate lower bound value for EPA's benchmark analysis.

The Panel was impressed by the way the preceding chapters' information was summarized in a series of tables that effectively collated the textual materials, tables, and figures from the preceding chapters as well as the wealth of data contained in the appendices. The conclusions regarding causality with regard to short-term exposures are reasonable. A better discussion is needed on the range of exposures at which effects are observed in the clinical studies and the much lower range at which effects are observed in the epidemiological studies. In addition, the importance of identifying susceptible subgroups of subjects, and estimating the contribution of these groups to population shifts in response characteristics may be a task for the REA, but that document should be informed by a discussion of this issue in the ISA.

The larger question is whether the additional research carried out in the last 10 years has led to a substantial change in the scientific basis for making decisions regarding the basis for setting standards for SO<sub>2</sub>. Although the ISA answers this question affirmatively, the final chapter should be organized to answer all of the policy-relevant framing questions introduced in Chapter 1. The answers to these questions would greatly improve the usefulness of this document as a scientific prelude to the *Risk and Exposure Assessment*.

With respect to the entire ISA, there remains the longstanding issue associated with the Clean Air Act's single pollutant approach to analysis and rulemaking. In the real world, we breathe complex mixtures of multiple pollutants, thus isolating the effects of a single pollutant requires simplifying assumptions that depart from real world phenomena. With SO<sub>2</sub> in particular, the reality of having to adjust for the possible confounding contributions of other pollutants makes definitive determinations of assigned causality a challenge.

In closing, the CASAC is pleased to provide the Agency with advice and recommendations in the development of this ISA for Sulfur Oxides, which is a fundamental part of the new NAAQS review process. We look forward to providing additional advice as the Agency completes the NAAQS review process for sulfur oxides.

Sincerely,

*/Signed/*

Dr. Rogene Henderson  
Chair  
Clean Air Scientific Advisory Committee

Enclosures

**U.S. Environmental Protection Agency  
Clean Air Scientific Advisory Committee (CASAC)  
Sulfur Oxides Primary NAAQS Review Panel**

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\* Did not participate in the July 30-31, 2008 review of the second draft ISA.

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**Individual Comments on the *Integrated Science Assessment for Sulfur Oxides – Health Criteria* (Second External Review Draft, May 2008) from Clean Air Scientific Advisory Committee (CASAC) Sulfur Oxides Primary National Ambient Air Quality Standards (NAAQS) Review Panel**

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**Mr. Ed Avol**

Comments on SOx ISA 2<sup>nd</sup> Draft

Question 1 (a modified Chapter 1 on the framework for causal determination)

The continuing EPA-and-Clean-Air-Act self-imposed restriction to consider individual pollutant effects (in this case, SO<sub>2</sub> from particulate SO<sub>x</sub>) makes the framework for evaluation of the overall weight of evidence a challenging one, due to the common sources of pollutant generation (and virtually no difference in the potential targets of source emission reductions). The reality of having to adjust for the possible confounding contributions of other pollutants makes definitive determinations of assigned causality a messier proposition, since the likely presence of other ambient co-pollutants provides a “smoke-screen” of sorts for the true stimulator (or stimulators) of response and effect.

The framework described in Chapter One, aside from the recurring general concern for an archaic approach that attempts to evaluate health effects on a discrete pollutant-by-pollutant basis in the face of ever-growing information about additive and synergistic physical, chemical, and physiological interactions, seems a reasonable way to proceed.

Question 2 (an expanded Chapter 2 on atmospheric chemistry of SO<sub>2</sub>)

The additional sections about monitoring information are useful in developing an overall appreciation for the historical monitoring network and nationally downward trend in SO<sub>2</sub> exposure. My personal opinion regarding the inclusion of design criteria for station placement is that there is more detail than necessary presented here, and most of it is generic (to any acceptable monitoring site’s placement).

The improved information presented does improve the overall assessment of the currently available knowledge and is relevant to subsequent discussions of human health effects.

Question 3 (a revised Chapter 3 on Integrated Health Effects)

The chapter is still a long compendium of information (over 100 pages), but the summary figures are very helpful in providing a “meta-view” of numerous studies. So much information on such a range of health outcomes is presented that, at chapter’s end, some sort of distillation of what the chapter conclusions were would have been helpful. This might be in the form of a table, listing category (morbidity, mortality, etc), SO<sub>2</sub> exposure (long-term or short-term), health outcome (lung function, symptoms, ED visits, hospitalizations, etc), and judgment (causal, insufficient, etc), which would assist the reader in interpreting the weight of evidence from the 100+ pages of data...which is precisely what appears as Table 5.3 in Chapter 5! Accordingly, it might be worth referring the reader to or providing some linkage to the Chapter 5 summary discussion.

Question 4 (Revisions to Chapter Four, Public Health Impacts)

This revised description of the public health impacts of SO<sub>2</sub> exposure is substantively improved, but could still profit from further clarification, focus, and specificity. The over-arching questions to be addressed include the following: (1) what insights do current data provide regarding the shape of the concentration-response function for SO<sub>2</sub>? (2) Is

there evidence of a threshold of response? (3) Are there populations at risk? (4) If there are populations at risk, who are they? To the credit of the ISA staff, these issues are discussed, but they are not always clearly/succinctly summarized or brought to some final resting point in the document.

For example, the presentation of concentration-response functions and the topic of thresholds of response are understandably linked, but the presentation in the document is inter-twined (in sections 4.1.1 to 4.1.3) and thus more difficult to follow than need be. With regard to the question of concentration-response functions, the presented data from clinical and epidemiological studies suggest there is support for a linear concentration–response function claim (more supportive from the clinical chamber studies, less convincing but somewhat supportive from the epi studies). With regard to a threshold of response, the data are inconclusive. This discussion, particularly in Section 4.1.3, should be separated into two sections (one on the concentration-response function, and the other on threshold response).

The discussion of susceptible and vulnerable populations (Section 4.2) is also in need of some improved specificity (but is admittedly improved over the previous version). Much of the appropriate information is contained in the discussions, but structurally, the respective sections do not always follow the specified title or deliver on the promised topic. There remains some confusion about definitions of “susceptibility” and “vulnerability”. Reasonable working definitions are provided in the text (at the bottom of p4-9 and top of p4-10), but then these are lumped together into a discussion of “somewhat sensitive subgroups” a few lines later (lines 8-14, p4-10).

A discussion about the potential importance of genetic factors is presented in Section 4.2.2, but much of the two-page discussion is generically about air pollution and not specifically about SO<sub>2</sub>.

Section 4.3 (which needs to be re-titled to “Populations at Adverse Risk” or something, since the current title is the chapter title) is a valuable perspective on how to think about the multiple health outcomes being presented.

Section 4.3.2 (Estimation of Potential Numbers of Persons in At-Risk Susceptible Population Groups in the US) doesn’t quite deliver on its title promise, in that numbers are estimated for only a few of the several susceptible sub-groups identified. Still, the point is made that many people are potential at increased risk for exposure and possible response. The concluding paragraph in the chapter (lines 10 through 18 on p4-23) provides a declarative overview on the issue (in essence, that there are could be a considerable public health impact, because there are large numbers of susceptible sub-groups), but seems to fall short by not saying something about the likelihood of exposure to levels likely to trigger the range of health outcomes identified.

(One final note – is the comment regarding Figure 4.6 “...demonstrating that the SO<sub>2</sub>-related excess risk for asthma is, on average, 50% higher among children when compared

to risk estimates that include all ages...” (lines 7-9, p4-23) over-reaching, given the error bars, available data, and risk range [~RR 1.05-1.1]?)

Question 5 (revised Chapter 5 on Integrated Findings of Causality)

This chapter has a significant task and a large body of multiple outcome data from over 20 years to summarize. The summary Table 5.3 is especially useful, in distilling the current judgments to brief paragraphs of conclusions for endpoints of potential health interest.

The document provides an interesting series of comments regarding “previous conclusions” and “current conclusions” in Table 5.3, but it is not clear to what “previous” review these comments refer. (Presumably, these “previous” comments refer to the 1996 NAAQS SO<sub>2</sub> review, but one could also interpret this as a reference to an earlier version of the ISA). This should be explicitly specified in the document.

The larger question here is the following: have the additional years of data, research, and observations changed our judgment regarding the health effects of SO<sub>2</sub>? The comments in Table 5.3 regarding previous and current conclusions make it difficult to determine, and should be simplified to reflect a clearer conclusion of where we are today.

## **Dr. John Balmes**

### Comments on SOx ISA -- 2<sup>nd</sup> Draft

Charge Question 3: In the revision, we reduced redundancy, added summary sections and reorganized Chapter 3. In addition, discussions on potential confounding by and interactions with copollutants have been added. The 2nd draft ISA also includes additional analyses of individual-level data from human clinical studies (Sections 3.1.3. and 4.1.1) that builds upon the analysis included in the 1994 Supplement to the Second Addendum. The toxicology sections were reorganized to focus on studies using more relevant concentrations of SO<sub>2</sub> and sections were added to better discuss mode of action and potential particle-SO<sub>2</sub> interactions. We are requesting CASAC review specifically on these analyses as well as on the integration of the overall evidence from the human clinical, animal toxicological, and epidemiological studies. To what extent is the discussion and integration of evidence from the animal toxicology and controlled human exposure studies and epidemiologic studies technically sound, appropriately balanced, and clearly communicated?

#### GENERAL COMMENTS

The revised Chapter 3 is much improved by virtue of the reduced redundancy, added summary sections, reorganization, and additional discussions involving co-pollutants. The new analyses of human clinical studies in Sections 3.1.3 and 4.1.1 are helpful. In general, the discussion of the results of the animal toxicological, controlled human exposure, and epidemiological studies that have been reviewed is technically sound. The major exception to this comment is the discussion of the effect of SO<sub>2</sub> on lung function responses to inhaled house dust mite allergen in asthmatic adults with pre-existing sensitization to this allergen on page 3-31. As written, the draft indicates that SO<sub>2</sub> “enhanced sensitization to house dust mite”. This is incorrect. In fact, it would be unethical to induce or enhance sensitization to a common aeroallergen in human subjects.

The integration of the animal toxicological, controlled human exposure, and epidemiological studies that have been reviewed is also technically sound, balanced, and clearly communicated with several exceptions on page 3-91. The summary statements about the evidence in Sections 3.4.2.2 and 3.4.2.3 are too strong as worded. I have suggested revised wording (see below in Specific Comments).

Perhaps my biggest concern about the current draft of Chapter 3 involves the references. Many papers cited in the text are simply not listed in the References, and some citations are obviously wrong (see some examples below in Specific Comments).

#### SPECIFIC COMMENTS

p. 3-13, line 28        The word “allergic” should be deleted from this sentence. SO<sub>2</sub> is too small of a molecule to elicit an allergic response on its own. The presence of

eosinophils in bronchoalveolar lavage fluid does not mean that SO<sub>2</sub> induced an allergic response. In addition, the Gong et al. (2001) study is not listed in the References.

p. 3-30, line 11        The Gong et al. (2001) study is both not listed in the References and is not a sheep study.

p. 3-31, lines 8-14    The two studies cited in this paragraph did not show that SO<sub>2</sub> “enhanced sensitization to the allergen in asthmatic individuals.” Rather, these two studies showed enhanced airway responses to inhaled allergen in asthmatic individual with preexisting sensitization to house dust mite.

p. 3-31, line 7        The word “preexisting” should be deleted from this sentence. Increased morbidity with infection does not necessarily mean that there was preexisting disease.

p. 3-32, lines 24-25   For clarity, the sentence should read “...and was also higher in the winter months (mean 25.7 ppb [SD 15.8]) than in the summer months (mean 10.6 ppb [SD 15.1].”

p. 3-39, line 11        The Ito et al. (2003) study is not listed in the References.

p. 3-39, line 13        This sentence should be revised as follows: “A study conducted in New York City...” In addition, this study is not listed in the References.

p. 3-42, line 25        For clarity, this sentence should be revised as follows: “In summary, only a few studies provide results for respiratory health outcomes other than asthma and COPD, and these results are mixed.”

p. 3-45, lines 14-15   I would delete “and to a more limited extent the human clinical studies” from this sentence.

p. 3-46, lines 24-26   This sentence should be revised as follows: “These findings of increased airway resistance are in concordance with the limited epidemiological study results of Taggart et al. (1996) that showed SO<sub>2</sub>-induced increases in AHR among asthmatic adults.

p. 3-46, line 31        I would add “non-elderly” before adults in this sentence.

p. 3-48, line 4        “bronchial responsiveness” should be changed to lung function responses. A decrease in FEV<sub>1</sub> is not necessarily a bronchial response.

p. 3-49, lines 1-3     The dog study discussed in the 1982 AQCD should be cited.

p. 3-51, line 25 and p. 3-52, line 1   For clarity, this statement should be split into two sentences as follows: “...of sulfite. Dose-dependent decreases... and above were also observed.”

- p. 3-53, line 8           The Peters et al. (1996) paper cited appears to be the wrong reference for the Hong Kong study.
- p. 3-58, line 4           The Routledge et al. (2006) study cited is not listed in the References
- p. 3-59, line 3           The Gold et al. studies cited are not listed in the References.
- p. 3-61, line 4           The Peters et al. (2000) study cited is not listed in the References.
- p. 3-61, line 15          The Dockery et al. (2005) study cited is not listed in the References.
- p. 3-64, line 1           The Liao et al. (2005) study cited is not listed in the References.
- p. 3-67, line 1           The Ballester et al. 2001 study cited is not listed in the References.
- p. 3-75, line 4           “...the association between air pollutants and mortality was examined...”
- p. 3-76, line 2           The Le Tertre et al (2002) and Ballester et al. (2002) studies cited are not listed in the References.
- p. 3-77, line 26 and p. 3-78, line 1   For clarity, I would revise these two sentences into one as follows: “..health effects studies in Asia that summarized the results from mortality and hospital admission studies published in the peer-reviewed scientific literature from 1980 through 2003.”
- p. 3-91, line 2           I would revise this statement as follows: “...studies do not provide sufficient evidence to infer that long-term exposure to ambient SO2 has a detrimental effect on lung function.”
- p. 3-91, lines 18-19      Similarly, I would revise this statement as follows: “...studies do not provide sufficient evidence to infer that long-term exposure to ambient SO2 causes prolonged effects on lung morphology.
- p. 3-94, line 11          I would add “ambient” before SO2 in this sentence.
- p. 3-97, line 28          “Furthermore, the epidemiological studies do not provide...”
- p. 3-102, line 19         The Liu et al. (2003) study cited is not listed in the References.
- p. 3-102, lines 26-27     For clarity, I would revise this sentence as follows: “The most robust association with intrauterine mortality was observed for an index of three gaseous pollutants NO2, SO2, CO).”

p. 3-105, line 2  
should be cited.

The Japanese study discussed in the 1986 Secondary Addendum

## **Dr. Doug Crawford-Brown**

### Comments on SOx ISA – 2<sup>nd</sup> Draft

My comments here focus largely on Chapters 4 and 5, although it was necessary to review the earlier chapters as well because Chapter 5 especially draws on materials from those earlier chapters. It is clear to me that the EPA is getting better at this process of creating an ISA. The document is well organized; it is easy to follow the reasoning used by the authors; and they appear to me to have reached the appropriate summary conclusions on the ability of SOx to produce effects even at levels below the current NAAQS, at least for short-term exposures. The document overall provides an adequate basis “to provide support for future risk, exposure and policy assessments”, in the sense that it establishes the existence of effects in policy-relevant ranges of exposure, identifies issues associated with exposure, and identifies sensitive subpopulations. It would not be possible to use the document alone as the basis for performing an actual risk assessment because there is inadequate assessment of exposures nationally or in specific subpopulations. But I presume such a formal, quantitative risk assessment would be the task of the Exposure and Risk Assessment document. Still, I continue to have trouble understanding the role of the ISAs in meeting the needs of risk assessment. This document continues the pattern of being an inadequate basis for such a quantitative approach, even if it does systematically review the evidence on which such a quantitative assessment might ultimately be based.

My specific comments are:

1. I like the formulation of the questions on page 1-2. They seem to be a refinement of these questions in previous ISA documents, recognizing the need not to just consider new information but to integrate new information into past assessments.
2. On page 1-5, the authors note that associations are not sufficient for proof of a causal relationship. Later they mention that epidemiological studies provide evidence of an association. Still later in the document, they use the epidemiological evidence as a basis for concluding that there is a causal relationship. This is not consistent, although I think the inconsistency begins with the first claim: that associations do not prove causality sufficiently. This needs some nuance, as associations ARE an important component of causal reasoning, even if not fully compelling. I disagree with views that associations are not relevant in claims of causality – they can in fact be compelling, rational evidence if sufficiently well established and reliable.
3. In the figure on page 1-6, I note that some aspects of the bottom half of the figure, such as lifestyle, CAN be influenced by community norms, and so are not strictly individual-level factors.
4. The topic of multifactorial causation on page 1-9 is interesting. But there are real questions as to whether policy can deal with such complex mixtures, leading perhaps to

different standards in different regions where the mix differs. The common basis could be overall risk, not the allowed concentration of any one contaminant, but there will still be significant issues of equitable treatment of the class of emitters in different regions if the mix differs between those regions (which in turn would require different levels of control on the same class of emitters in different regions).

5. On page 2-39, the authors state that exposure misclassification may result if total human exposure is not disaggregated. I am not sure WHICH exposure is then misclassified. Is it the exposure to ambient levels? If one is using total exposure to SO<sub>x</sub>, perhaps through personal monitors, in epidemiological studies, there is no exposure misclassification due to a lack of disaggregation. There WOULD be misclassification if one is trying to get at the effect of ambient, policy-relevant exposures alone. I assume they don't mean misclassification of total exposure.

6. Table 2-9 presents a number of studies, and then the authors appear to settle on 0.13 as the slope. This value is the highest one in the table by a factor of 2 to 3, and I don't feel the authors have explained adequately why they chose this particular result from amongst those in the table. I'm sure there is a rationale, but it doesn't come across in the writing and so there will be suspicion that the choice was based on conservatism rather than this being the best study.

7. The discussion of Berkson type errors on page 2-53 is correct, although I don't see where the authors eventually conclude whether the errors in the specific studies used here are or are not Berkson type. I presume they assume the errors will lead to misclassification and bias towards the null, but I can't see this stated clearly. If there IS bias towards the null, they should state this as a final conclusion, which then has implications for application of any slope factors and the degree to which a standard is health protective with a margin of safety.

8. On page 2-54, the authors have not noted that the slope factor can be incorrectly increased if location near a source is correlated with sensitivity. For example, if poverty causes sensitivity due to poor nutrition, and land prices decline the closer one gets to a major source, then exposure and sensitivity are correlated and beta will be increased above that found when this correlation is not present.

9. In the section on Dosimetry, the authors have summarized the studies adequately. However, there remains the problem of how SO<sub>x</sub> gets into the deep lung given the rapid absorption in the nasal passages, or how its movement into the surface of hygroscopic particles might affect this penetration. I came away from the chapter not quite clear whether the authors were saying penetration to the deep lung is insignificant, significant only for mouth breathing, or unknown quantitatively.

10. On page 2-61, the middle paragraph seems inconsistent. How can uptake in a 3 year old be slightly higher than for an adult but uptake per unit surface area be the same, given the smaller surface area in a 3 year old? It seems to me a higher uptake in a 3 year old

would produce an even larger difference in uptake per unit surface area. Or could the authors be in some sense conflating uptake fraction and total uptake?

11. The figures in Chapter 3 are good and useful. It is especially good that they are in a consistent format. The authors could improve the text by describing how the studies could be combined quantitatively or at least qualitatively. Otherwise, the reader is left with just “eye-balling” the graphs for a mean value - or choosing a single study - IF quantitative analysis is needed. Is meta-analysis not appropriate, and if not, why not? But perhaps the figures are there only to suggest a robust claim of an association. Still, the authors should state that if it is the case. The reader also needs to be told whether the studies in the figures represent a full sampling of such studies, or have been selected from a larger set to form a subset – this subset would then need to be defined.

The following questions are related to Charge Question 4:

12. In Chapter 4, I continue to have a problem with the ISAs separating exposure levels and sensitivity in determining the public health impact. The authors do a good job of describing the sensitive subpopulation, and then of estimating the size. It is evident that there are a significant number of people who fall into this category. But having sensitive people present does not equate to a public health impact unless exposures are sufficient, and this chapter makes no attempt to quantify the exposures to these people. So I am not convinced that tables such as 4-2 provide a quantitative measure of public health impact.

13. On page 4-1, there is mention of a population-response threshold. I don't know what this term means. Populations don't have thresholds, individuals do and these thresholds are distributed. There are several places in this chapter where the authors make it sound as if there are population characteristics such as thresholds that can be found in studies, and I don't believe there are. The belief in population thresholds also is inconsistent with earlier claims in the chapter that intersubject variability is one of the causes of linearity of population response at low exposures.

14. I don't understand why the exposure-response section is not placed into Chapter 3. Surely this is both important information for that chapter, and is in fact the MOST important information for understanding the effect of any lowering of the NAAQS.

15. It is unfortunate that the clinical E-R curves do not extend down into the region of policy interest. Figures 4-2 and 4-3 suggest there may be some leveling of the curves in the lower region of exposure, which has significant implications for the incremental or marginal effectiveness of policies that push exposures below these levels.

16. It would be useful to show the existing NAAQS level on these E-R curves, so the reader can see where extrapolation is needed. This is particularly important because the units of the X axis change between several of the figures.

17. The complexity of the curve in Figure 4-5 is intriguing, as we find the same thing in radiation dose-response curves. It usually occurs when there are competing beneficial and detrimental effects at low exposures, due to compensatory mechanisms kicking in.

18. On pages 4-9 and 4-10, a susceptible subpopulation is defined as one that might show effects below concentrations needed in the general population. This is much too vague of a statement, as it applies to any individual whose individual threshold is below the population median (50% of the population therefore being susceptible). And again, there IS no general population response, only the aggregate response of individuals with a distribution of thresholds. Better definitions of susceptible and sensitive are needed, ones related in some way to percentiles of the intersubject variability distributions and some notion of bimodality of these distributions.

Based on Comments 12-18, I judge that Chapter 4 is better overall than the previous draft, and is nicely organized for the kinds of information presented. But I continue to have problems with the way in which public health impact is quantified. I don't believe this chapter provides quantitative information on actual impacts, but rather the POTENTIAL for impacts if exposures are sufficient.

19. Figure 4-6 suffers from having a wide range of ages in the young group (0-14 years). Is there no way to narrow in on the much younger ages where sensitivity seems especially pronounced?

The following comments apply to Charge Question 5:

20. Chapter 5 continues the pattern of having little formal framework for integrating information. The EPA seems to cite a different source for frameworks in each ISA (here it is the NAS Institute of Medicine Report). I don't have an alternative to offer, so just believe it would be best if the authors just state the principles they are using directly and not rely on a particular source (requiring the reader to go back to those sources for clarification).

21. On page 5-2, line 20, a causal relationship is inferred (reasonably), but needs to be accompanied by a statement of the levels of exposure at which the relationship applies. The existing statement is too broad. There are causal relationships between exposure and adverse effect for all things in the world, at some level of exposure.

22. The discussion of uncertainty throughout is inadequate. It could be lifted out of here and placed down into any of NAAQS ISAs, it is so generic. There needs to be a better summary of the uncertainty and its implications for specific judgments that might be required in exposure and risk assessments.

Overall, Chapter 5 provides a good compendium of information that should prove useful for the exposure and risk assessment stages. It adequately summarizes causal claims, although I don't believe it properly places caveats with respect to the exposure levels at which these causal claims are strong.

## **Dr. Terry Gordon**

### Comments on SO<sub>x</sub> 2<sup>nd</sup> Draft ISA

#### General Comments:

This is an excellent draft ISA and for the most part is clear and logical. The authors have made logical connections between the epidemiology, clinical, and animal studies and arrived at fair conclusions regarding the adverse health effects associated with ambient exposure to SO<sub>2</sub>. Also, the order of the sections in each Chapter is very good. Perhaps, NCEA should formalize the order and format of sections so that future ISA's follow this order (to avoid everyone's suggestion to change the order to their individual preferences).

Charge Question 3: "In the revision, we reduced redundancy, added summary sections and reorganized Chapter 3. In addition, discussions on potential confounding by and interactions with copollutants have been added. The 2nd draft ISA also includes additional analyses of individual-level data from human clinical studies (Sections 3.1.3. and 4.1.1) that builds upon the analysis included in the 1994 Supplement to the Second Addendum. The toxicology sections were reorganized to focus on studies using more relevant concentrations of SO<sub>2</sub> and sections were added to better discuss mode of action and potential particle-SO<sub>2</sub> interactions. We are requesting CASAC review specifically on these analyses as well as on the integration of the overall evidence from the human clinical, animal toxicological, and epidemiological studies."

The reduction in redundancy and the addition of summary sections has aided in making this Chapter clear and concise. The authors have reduced the animal studies so that a true picture (of their contribution to understanding the biologic plausibility of the adverse effects of SO<sub>2</sub>) is now presented. The addition of the toxicology section that discusses potential particle-gas interactions and enhanced responses in exposed animals is very appropriate in the level of detail and its relevance to the ISA.

Charge Questions 4 & 5: The revisions are excellent and made the chapters very readable with minimal overlap with Chapter 3 and each other. The dose-response evaluations are appropriate, but the final conclusions in Chapter 5 might be worded more strongly so that the REA working group has more guidance as to which health endpoints and data sets (epidemiology and/or clinical) are appropriate for risk evaluations.

#### Detailed Comments:

Page 1-1, line 13 – While this statement is probably true for sulfite, given the added section(s) on particle-sulfur dioxide interactions, it seems premature to conclude on the first page of the ISA that sulfuric acid (potentially layered on particles) are present in insignificant concentrations in the ambient environment.

Page 1-5, line 11 – typo: data complement

Page 2-44, line 11 – Chao ref is missing here (2001 ref?).

Page 2-52, lines 5-16 – This section is a bit redundant with similar discussions on page 2-47 lines 7 & 8, page 2-48 lines 1-5, and page 2-42 lines 19-28. Possibly combine in one place?

Page 3-6, lines 3 and on – Should a brief discussion of sulfuric acid be added to the discussion of sulfite chemistry/interactions/metabolism?

Page 3-7, line 9 – Because line 5 mentions ‘cholinergic’ pathways, saying that acetylcholine is ‘also thought to be involved....’ is incorrect.

Page 3-12, figure 3-1 – Add ‘provocative’ to the definition of PC(SO<sub>2</sub>).

Page 3-14, lines 19-30 (and onto the next page) – This section should be condensed to a couple sentences or cut because of the questionable relevance of 100-2000 ppm sulfur dioxide even if the dosing was brief or in vitro.

Page 3-27, line 8 – Please add refs for the ‘several other studies....’.

Page 3-31, line 5 – Insert ‘pseudo-’ before ‘measure of airway obstruction’

Page 3-37, Figures 3-6 & 3-7 – Would a meta-analysis be appropriate for these studies? Also, The visual separation of the ED visits and the Admissions studies should be more distinctly labeled.

Page 3-39, line 13 – ‘study conducted in ??’ Where?

Page 3-40, line 13 – A positive association for the Lee, 2002 study is not presented in Figure 3-7. The only Lee study in the figure has a negative association (2006). Typos?

Page 3-50, line 15 – Chen, 1992?

Page 3-55, line 22 – Is this statement true regarding adults? Page 3-25 says inconclusive evidence. Should the text read ‘older adults’?

Page 3-57, line 1 – Should the word ‘peak’ be inserted before ‘ambient’?

Page 3-57, line 18 – What are ‘consequent cardiac deaths’?

Page 3-83, line 13 – ‘and/or’ is unclear

Page 3-85, lines 4-10 -  $\mu\text{g}/\text{m}^3$  should be converted to ppm for ease of reading.

Page 3-92, line 10 – This statement about 3 other recent studies should be deleted or expanded/referenced.

Page 3-99 – This section is nicely written and clearly hits the right level of discussion of high dose studies and their quasi-relevance.

Page 4-3, figure 4-1 – Inclusion of 0.10 and 0.50 in the bar graph implies that zero percentage changes occurred vs. the actual absence of data at those exposure concentrations.

Page 4-6, line 8 – This sentence is not consistent with figure 4-5 which shows no real change at 10 ppb.

Page 5-2, line 1 – Is this sentence accurate? ‘west to east’ implies a gradient from the west coast to the east coast.

Page 5-10, 5-11 – A nicely written evaluation.

Page R-24 – Zeger ref has a typo on the pages.

**Dr. Dale Hattis**

Comments on SO<sub>x</sub> ISA – 2<sup>nd</sup> Draft

Response to question 4 and to some extent question 3 on the analysis of individual-level clinical concentration-response data for the short term bronchoconstriction response to SO<sub>2</sub>.

I was encouraged that the ISA authors included empirical information from three papers by Linn et al. (1987, 1988, and 1990) that are similar to the Horstman et al. individual data for these responses that I analyzed in my comments to the earlier draft of the ISA. Unfortunately there does not seem to have been any effort to compare the risk assessment implications of the Linn et al. data with those of the Horstman data, let alone put them in to a combined analysis for derivation of an overall estimate of the concentration-response function for asthmatics. The concentration-response section of the REA also lists several other sources of individual data on similar responses that have not been summarized or analyzed as of yet.

Three types of information can readily be extracted from the existing body of clinical observations: The ED<sub>50</sub> for particular responses, the breadth of the population distribution of thresholds, and the form of the distribution (i.e. does it appear to be lognormal, or some more complex shape?)

For reference, the Horstman et al. paper gave individual SO<sub>2</sub> threshold concentrations for 27 asthmatics for a doubling of specific airway resistance. These data are reasonably, but not perfectly compatible with a lognormal distribution (Figure 1). (In this figure, the straight line represents a fitted lognormal distribution for the data. The slight departures of the data above the line on both the low and higher-concentration ends of the distribution may suggest some tendency toward bimodality in the underlying distribution of individual thresholds, but these data are not sufficient to make a firm conclusion on that point). By averaging the logarithms of the individual thresholds for this effect we find an ED<sub>50</sub> (geometric mean dose expected to produce the response in 50% of an exposed asthmatic concentration) of 1,040 ppb, with 90% confidence limits of 739-1475 ppb. From the standard deviation of the logarithms of the individual values we find a geometric standard deviation for interindividual variability in the thresholds of 2.38—meaning that based on these data, 90% of the individual thresholds in a similar population of asthmatics should be expected to be between 250 and 4340 ppb.

The newly presented information from the Linn et al papers for the same response are unfortunately not given as individual values, but essentially in histogram form—the number of asthmatics studied who respond at a few discrete dose levels. I have analyzed these assuming a lognormal distribution of individual thresholds using an Excel program adapted from Haas (1994) and used extensively in my prior work on human interindividual variability in susceptibility (Hattis et al. 2001). The data provided from the Linn et al. papers suggest an ED<sub>50</sub> for the doubling of specific airway resistance in exercising asthmatics of about 580 ppb—a little lower, but probably not significantly lower than the range indicated by the Horstman et al. data. (I did not assess the

confidence limits for the ED50 in this case) The Linn et al. data also indicate a slightly greater amount of interindividual variability than those of Horstman—a geometric standard deviation of 2.85 with 90% confidence limits of 2.10-5.75. Together, if we assume a lognormal distribution of individual thresholds as before, the central estimate of interindividual variability and the central estimate of the ED50 from the Linn et al data would indicate that 95% of exercising asthmatics should have this response at between 104 and 3250 ppb. Unfortunately, there is reason to doubt that the distribution is perfectly lognormal—a goodness of fit test indicates a barely statistically significant departure of the data from expectations from a lognormal model at  $P < .05$ .

There are a couple of ways to combine these data for an aggregate analysis. One simple way that I did was to add the Horstman observations where they would fall in the histogram-like data from the Linn et al. papers. When this is done, the ED50 indicated by the combined data is just under 700 ppb and the geometric standard deviation for interindividual variability is 2.52 with 90% confidence limits of 2.01-3.83. The revised central estimate ED50, combined with the central estimate of the geometric standard deviation would indicate that 90% of exercising asthmatics should respond between 150 and 320 ppb. Again, however, the combined data depart from expectations of a lognormal distribution model at a P level of slightly less than 0.02. In further exploration of the combined data (including experiments of other research groups) I would recommend an attempt to fit a mixture of two lognormal distributions. I could not attempt this in this analysis, however because a mixture of two lognormals involves estimation of 5 parameters (two means, two standard deviations and a parameter to measure the fraction of the population that belongs to each component distribution) and the Linn et al. data are aggregated only into 4 ranges. There is likely to be an infinite number of perfect-fit solutions when one uses only 4 data points to estimate 5 parameters.

If it is of interest to EPA staff, I will provide the Excel spreadsheet showing these calculations.

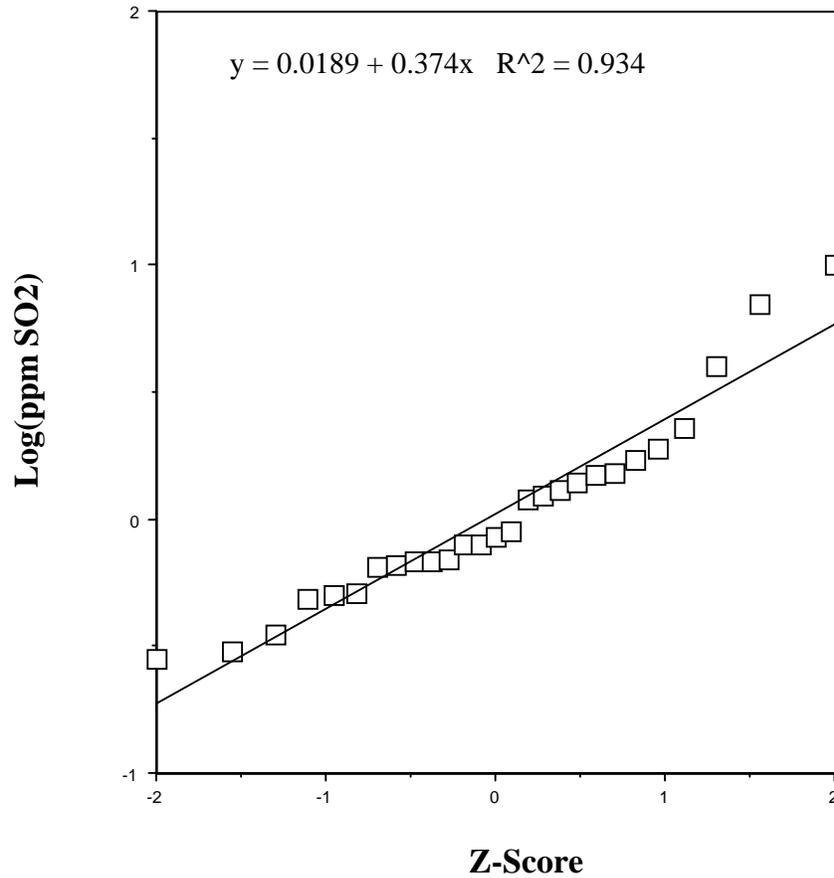
## References

Haas, C. N. "Dose Response Analysis Using Spreadsheets" *Risk Analysis* 14:1097-1100 (1994).

Hattis, D., Russ, A., Goble, R., Banati, P., and Chu, M. "Human Interindividual Variability in Susceptibility to Airborne Particles," *Risk Analysis*, Vol. 21(4), pp. 585-599 (2001).

Figure 1

**Lognormal Plot of the Distribution of Individual Sensitivities  
(SO<sub>2</sub> Concentrations Needed to Double Specific Airway  
Resistance) For 27 Exercising Asthmatics (Horstman et al. 1986)**



**Dr. Donna Kenski**

Comments on SOx ISA – 2nd Draft

General comments: The revisions to Chapter 2 have improved it substantially. In particular, Sections 2.5.3 and 2.5.4 on exposure measurement errors were improved and clarified. The added tables and discussion were helpful. The added information on 5-minute averages was a good start, but lacked enough detail to form adequate basis for decision-making. The dismissal of these data because of the voluntary nature of the reporting and their variability over time and space is troubling. In light of the number of health studies showing effects at 5- to 15-minute exposure times, the importance of the information for the Risk and Exposure Assessment, and given EPA's request that the states collect this data, it seems unreasonable to dismiss it in this document without even a rudimentary summary of the data. The REA goes on to glean important information from the relationship of the 5-minute peaks to hourly means, so the very limited discussion in this document is surprising. This particular shortcoming was not apparent in the previous version of the ISA, before the REA had been drafted. The removal of the NOx information from Annex B was a good decision; it makes it much easier to find the relevant data for SO2. Some specific comments follow:

2-1 line 13 The initial phrase, "Industrial emissions..." is somewhat mischaracterized; perhaps the authors meant anthropogenic emissions? Utility emissions are usually regarded separately from industrial emissions.

2-2 1<sup>st</sup> paragraph. This section still needs a simple sentence quantifying biogenic or natural sources. It is unacceptable to spend 2 paragraphs describing natural sources and still not quantify them except as 'small', which could be 10% or 1% or 0.01%. Even Table B-3 doesn't do so; the reader is left to infer that such emissions are less than 0.00 Tg/yr.

2.2. Line 12 Refers to Table B-6, which does not exist. It doesn't look like this data is available in the revised Annex.

2.3 line 14 Reference to Annex B.5 should be B.6

2.8 Sec. 2.4.1 The addition of the monitor siting criteria was helpful. The open-path information is probably unnecessary, however. The sampling and analysis discussion didn't describe any open path instruments for SO2 and since these are a tiny fraction of the reporting network, if there are any at all, it could be deleted without harm to the rest of the discussion.

2.11 The new figures 2.1-2.6 are a useful addition. However, the rationale for choosing these 6 areas for focus needs to be clearly stated. Was it because they have the most monitors, or the highest concentrations, or the most spatial heterogeneity or homogeneity?

- 2-11 line 16 ...as well as the subset of *monitors* in Cuyahoga County.
- 2-19 line 9 'Overrepresentation' sounds judgmental. 'Predominance' might be a better word choice
- 2-23 Fig. 2-11 At the risk of sounding like a broken record, I will point out again that this figure is a poor depiction of diurnal cycles. If the point is to show diel variation, as the text says, then the variation in the median (or some higher percentile, if all the medians are zero) is of much more interest than the outliers, which is all one can see on this plot. Plot the medians on a scale that can be read, as in Figs. 2-12 – 2-15, rather than emphasizing the meaningless noise in the outliers. Maybe a log scale would work better. The plot is not useful as currently configured. Also, it's not clear what the caption means by 'all cities *in focus*.' It seems to imply that these are the cities included in the Figs. 2.1-2.6, but the text says it summarizes all the data in AQS, so that should be clarified.
- 2-26 The description of the 5-minute sample data is still lacking. The text and Tables 2-6 and 2-7 don't agree. For example, Table 2-6 has 80 monitors reporting 5-min averages and Table 2-7 lists 16 monitors reporting all 12 5-minute values. The text reports that 108 monitors reported 5-min averages and 15 monitors reported all 12 values. These need to be reconciled.
- 2-34 line 6 Annex Section B-6 should be B-3
- 2-46 line 27 A monitoring site at an elevation of 250 *m* above street level? Is this correct?
- 2-47 line 1 ...should 'outdoor' be 'personal' instead? Ambient concentrations *are* outdoor concentrations.
- 2-56 line 19 or -> for
- 2-63 line 5 delete 'of'
- 5-2 lines 5-6 Transport of SO<sub>2</sub> plumes from Asia and Europe really wasn't discussed in the previous sections, so this statement doesn't belong in the conclusions unless it is supported by the earlier text.
- 5-2 lines 15-18 Here's another dismissal of the 5-min data as unimportant for determining concentrations and exposures at short time durations. This just doesn't make sense. Perhaps the data are insufficient to make sweeping generalizations about national exposure, but they certainly are useful and valid, and their temporal variability is exactly what makes them valuable and why we collected them in the first place. A more reasonable statement here would be that the existing 5-minute data are not adequate to assess exposure on a national scale – but then, neither are the hourly data.
- 5-2 line 24 remove the 7 after exposures

5-3 lines 8-11 This statement is correct, but would be much stronger if the 5-minute SO<sub>2</sub> concentrations had actually been summarized in this document.

## Dr. Patrick Kinney

### Comments on SOx ISA – 2nd Draft

One general concern I have relates to the way the ISA interprets the public health relevance of concentrations below those studied in the human clinical studies, i.e., 0.2-0.4 ppm. As noted in the ISA, these studies look at effects in groups of people who do not represent the full range of susceptibilities present in the general population. In addition, clinical studies study very small numbers of subjects as compared with the population exposed to ambient concentrations. These two issues limit the power of clinical studies to quantify exposure-response relationships at ambient-relevant concentrations. Given this, it is incorrect to assume, as EPA seems to do in the current ISA, that the lowest-observed effect concentration represents a threshold below which no effects occur. After all, we are concerned with protecting the US population, which contains over six orders of magnitude more people than have been studied in a typical clinical study. A better way to interpret the exposure-response results from clinical studies is that they provide points on a exposure-response function that extends down to zero ppb. This concept should be discussed in the ISA, providing a better foundation for its application in the health risk assessment in the REA. It also would help to bridge the large gap that currently exists between the exposure levels at which responses/associations are observed in clinical/epidemiologic studies.

p. 1-7, line 12: change “occur” to “exist”

p. 1-7, line 24: change “with” to “with respect to”

p. 1-8, line 2: it should be noted as well that control for confounders, whether by adjustment or stratification, is only successful when the confounder is well measured. This point is often overlooked.

p. 1-8, first full paragraph: Needs to be reworked. It's not clear whether you're talking about confounders, the exposure of interest, or both. It seems to change from one sentence to the next.

p. 1-8, second full paragraph: To the lay reader, it may be unclear what you mean by covariates as opposed to confounders here. Also, this section on confounders would benefit from a clear definition of confounding at the outset.

p. 1-13, line 13, insert “controlled human exposure studies,” before “epidemiological”

p. 1-14, box on causality categories, in the row labeled “inadequate to infer the presence...”, insert “quantity,” before “quality”

p. 2-8, section 2.4. This section should start off with an intro paragraph stating purpose and approach of the section. The very technical minutia of the initial text is off-putting as written.

p. 2-8, line 17: need to insert definitions of the three geographic scales in terms of kilometer ranges or such.

p. 2-9 through 2-11, line 2: this whole section reads like a guidance manual for setting up a monitoring station. I don't think we need that here. Can't we assume that existing monitors satisfy these criteria, and move on? One sentence would be enough to say that.

p. 2-9, line 3: define “monitoring path”, or better yet, delete this whole discussion.

p. 2-10, line 6: I don't think the "open path" analyzer was defined or described earlier. Please add that. How relevant is this? Is this an EPA equivalent method? If not, why discuss?

p. 2-11, section 2.4.2: It would be better to start off by presenting descriptive information and summary statistics on the national data (e.g., table 2-4) rather than focusing on six particular states. Rationale for these six states is not sufficiently clear. Please expand.

p. 2-21, Figure 2-10: a similar map showing emissions at US ports would be a very useful addition.

p. 2-21, line 10: what is "diel"?

p. 2-22, Table 2-4: This table should be referred to repeatedly throughout subsequent sections, especially chapter 4.

p. 2-23, figure 2-11: not clear what is meant by "cities in focus"

p. 2-32 and vicinity: I was surprised not to see any data from the 5-min so2 results. Why mention it here if no data are to be shown? Must explain why data are not shown.

p. 2-38 and later in Section 2.5: The uncertainties are discussed extensively, but are never summarized quantitatively in any way.

p. 2-57, line 9 and elsewhere: should be beta hat, not beta.

p. 2-57, line 19: add text on effect of measurement error on SE(beta hat)

p. 2-58, line 5: spelling of physicochemical

p. 3-25, line 15: please provide a quantitative measure of how prevalent these observations are. e.g., what fraction of 10 min avgs are above 0.4? the term "sometimes" could be mis-interpreted as something like 10-20%. Reality is probably many orders of magnitude lower than that.

p. 3-39, line 13, sentence starting "a study conducted" needs grammar fix.

p. 3-43, line 4: state range of ppb for which excess risk is calculated here, and put this range into the context of SD of ambient 24-hour averages.

p. 3-44, figure 3-8 and following text: I'm troubled that there are no studies reported here that included PM2.5 as a co-pollutant. This omission is an important caveat that should constrain any conclusions regarding robustness. Especially so given the dismissal of the long-term mortality results for SO2 on the basis of concerns over sulfate PM2.5 confounding.

p. 3-45, lines 13-18: This seems too glib. I don't agree that coherence and biological plausibility are satisfied when comparing chamber results at 200-600 ppb and epi results are for ambient levels two orders of magnitude lower. Need to include this caveat.

p. 3-55, lines 16 to 25: This section needs to acknowledge the exposure levels observed on average in epi studies, in metrics equivalent to those used in chamber studies, e.g., 1-hr averages – noting means, sds, 95th percentiles etc. This is done for the chamber results but for some reason is ignored when describing the epi findings. Table 2-4 is the relevant reference.

p. 4-1, sentence on lines 20-23. This sentence is false. It is not true that most epi studies evaluate whether there is a threshold. Few if any epi studies evaluate that question directly. Please edit.

p. 4-3, Figure 4-1: indicate in footnote which of these results are statistically significant.

p. 4-4, section 4.1.2: in linking the chamber findings with the epi findings, it is important to compare the dosimetry in at least a semi-quantitative way, taking into account the differences in exposure concentrations and activity levels.

- p. 4-4, line 10: change “was” to “could not be distinguished from” The key point is that there is very limited power to formally test whether something is linear or not. Failure to reject linearity isn’t equivalent to “observing that the relationship was linear”
- p. 4-5, lines 8-10: this is a good example of the kind of concentration cross-referencing that I was looking for earlier.
- p. 4-6, Figure 4-4: tell us which of these results are statistically significant, or better yet, provide confidence intervals at each point on the curve. OK to limit to one lag to simplify display since they all say roughly same thing.
- p. 4-9, line 4: insert quantitative LOD (e.g., 3 ppb) in parenthesis after “detection”
- p. 4-9, lines 13-14: again the issue of “observing that the relationship was linear”
- p. 4-17, Figure 4-6: throughout the document, EPA concludes that ED visits and hospitalizations are associated with SO<sub>2</sub> for children and older adults. This doesn’t come through very clearly from this figure. Can the results for younger adults be added? Can histograms be created of the RRs within each age range? This would provide stronger backup for EPA’s conclusions about age-related effect modification.
- p. 4-19, line 19: Edit grammar. As stated, it suggests that most studies examine effect modification by SES, which is clearly untrue.
- p. 4-22, lines 19-27: need to include the fact that these findings are observed only with heavy exercise. Then later you need to estimate fraction of asthmatics who spend time at those exertion levels, and also the fraction of time that people are exposed to these ambient levels. Both are needed for risk assessment discussions that follow.
- p. 4-23, line 9: this is obvious place to insert 1-2 paragraphs discussing the fraction of relevant exposure levels and exertion levels experienced by sensitive subgroups.
- p. 4-23, line 16: risk only occurs with exposure, so need to discuss exposures here too.

**Dr. Steven Kleeberger**

Comments on SO<sub>x</sub> 2<sup>nd</sup> Draft ISA

3. In the revision, we reduced redundancy, added summary sections and reorganized Chapter 3. In addition, discussions on potential confounding by and interactions with copollutants have been added. The 2nd draft ISA also includes additional analyses of individual-level data from human clinical studies (Sections 3.1.3. and 4.1.1) that builds upon the analysis included in the 1994 Supplement to the Second Addendum. The toxicology sections were reorganized to focus on studies using more relevant concentrations of SO<sub>2</sub> and sections were added to better discuss mode of action and potential particle-SO<sub>2</sub> interactions. We are requesting CASAC review specifically on these analyses as well as on the integration of the overall evidence from the human clinical, animal toxicological, and epidemiological studies.

Overall, the reorganized Chapter 3 is greatly improved over the previous version. In particular, the following aspects of the Chapter were useful:

- Summary of findings from the previous review – these provide much needed and useful reference points to enable evaluation of the more current investigations.
- Redundancy was largely eliminated, though some repetition remains that could be edited or removed.
- Additional individual-level data (i.e. specific numbers of individuals in response groups) enabled better evaluation of between-individual variation and the impact on interpretation of results.
- Removal of animal studies that used SO<sub>2</sub> concentrations that had questionable environmental relevance was appropriate, though some remain that likely could also be removed.
- The end-section summaries were very useful and largely presented a reasonable evaluation of the literature with respect to weight of evidence for causal determination.
- Incorporation of the effects of SO<sub>x</sub> intervention and subsequent change in health outcomes into evaluation of causality was appropriate and useful.

Additional Comments:

While it may be argued that SO<sub>2</sub>/particle interactions should be included in the ISA document, the case was made in the REA that the current review of the SO<sub>2</sub> NAAQS would focus on gaseous species of sulfur oxides and not consider health effects directly associated with particulate sulfur oxide species. These species and their health effects instead will be reviewed in the PM document. However, one of the sections in the

SO2 document (3.1.5) includes effects of SO2 layered on particles and sulfite aerosols. I did not find the section fit particularly well with the rest of the document and raised additional questions that could not be answered, or may have been answered in the PM document. My recommendation would be to eliminate this section.

The REA clearly differentiates between long-term exposure (months to years), short-term exposures (hours to days), and short-term peak exposures (5-10 minutes) throughout the document, especially beginning with the Health Effects chapter (part 4). The ISA differentiates primarily between long-term exposure and short-term exposures, with the short-term peak exposures embedded in the latter (e.g. section 3.1.3). An introductory statement or small paragraph placed at the beginning of the major sections of Chapter 3 (e.g. 3.1) which define the distinction may help the reader to place the studies in the intended perspective.

#### Minor

P 3-4, line 5: delete “a” from “presenting a more details”?

P 3-13, lines 26 and 28: is it correct to suggest that SO2 may elicit an allergic inflammatory response? SO2 is not an allergen.

P 3-17, lines 9-21. I am not sure that this section really provides “biological plausibility for the effects of SO2 on respiratory symptoms in humans”. The relevance of MUC5AC expression induced by SO2 using in vitro models and in rats exposed repeatedly to 2 ppm SO2 to respiratory symptoms in humans is questionable, and presenting these preliminary studies is not necessary.

P 3-103, line 10. “is” should be “are”?

**Dr. Timothy Larson**

Comments on SOx ISA 2<sup>nd</sup> Draft

*Chapter 2:*

Section 2.4 is reorganized and shortened with a more appropriate focus on interurban variability. Tables 2-4 and 2-5 are particularly useful in this regard. The information on correlations with other pollutants is obviously limited by the lack of co-located monitors. The discussion of the available 5-minute data is an important addition to the chapter, but it is very brief, given the importance of this data in the REA. We are left with a statement that these data are “very difficult to use precisely”, without knowing exactly what that means. Do the authors mean the measurements are difficult to use because they are inaccurate or that they are accurate but are highly variable across time and space?

Based on my prior review comments, I note that on page 2-52 the statement is still made that “when personal exposure concentrations are above detection limits, a reasonably strong association is observed between personal exposures and ambient concentrations”. This statement is based primarily on the results of one study done in one city over two seasons. In addition, there are no studies that have assessed the relationship between community exposures and central site concentrations of SO<sub>2</sub>. Appropriately, the summary chapter has been changed to place the significance of these results (or lack thereof) in the context of epidemiological study design and now avoids repeating the statement on page 2-52.

*Other comments:*

On page 3-52 the statement is made that “aerosol particles act as carriers and deliver SO<sub>2</sub> to the lower respiratory tract”. The evidence supporting this is based primarily on studies done on rats exposed to relatively high levels (1 to 10 milligrams per cubic meter) of freshly generated zinc, copper or carbon black particles in combination with SO<sub>2</sub>. These studies report a synergistic effect of SO<sub>2</sub> in combination with the particles and measure sulfate and/or sulfuric acid coatings on the particles exposed to SO<sub>2</sub> as a possible explanation for the interaction. There is one study listed on page E-17 by Clarke et al (2000- it is not in the reference list but I assume it is the one in *Inhalation Toxicology* v12, pp169-186) that is summarized as seeing synergistic effects at more realistic levels of sulfate particles (~20 micrograms per cubic meter). However, to produce these particles in the lab required 1 milligram per cubic meter of carbon black particles and 1 ppm SO<sub>2</sub> at 85% RH. In summary, the studies listed in support of the statement on page 3-52 were done at very high levels relative to contemporary atmospheric SO<sub>2</sub> levels (effects in the Clark et al study were seen after 5 to 6 days of exposure to 1 to 10 ppm whereas the ISA summary of typical SO<sub>2</sub> levels over this averaging period are typically below 0.01 ppm; similarly, the PM levels were 1 -10 mg/m<sup>3</sup> whereas typical PM levels of fine carbon are 1-10 ug/m<sup>3</sup>). Although these studies do support the notion of an increased response to sulfate-coated particles, they do not support the summary statement on page 5-11 that “the synergism observed with combined exposure to SO<sub>2</sub> and PM in

the animal toxicological studies provides supportive evidence for the SO<sub>2</sub>-related respiratory effects observed under ambient conditions in the epidemiological studies”. In fairness, this is presented in the document as an interpretation rather than a conclusion. Given the unrealistically high SO<sub>2</sub> and PM levels used in the animal studies (factor of 100 to 1000 relative to realistic ambient levels) , its hard to claim that these studies provide supportive evidence for the relevant epidemiological studies.

## Dr. Ted Russell

### Comments on SO<sub>x</sub> ISA -- 2<sup>nd</sup> Draft

The 2<sup>nd</sup> Draft ISA is an improvement over the first, though could still benefit from some pointed analyses, particularly in light of the direction of the associated RWA. In particular, the REA deals predominately with assessing the exposure and risks associated with 5-minute average SO<sub>2</sub> concentrations, and how such concentrations are associated with 1-hr average levels. Thus, this section of the ISA could be improved. In particular, added analysis of the structures of 5-minute and 1-hr average concentrations, and how the two correlate. In particular, the concentrations that lead to the 5-minute maximum and 1-hr levels are from the same distributions, and thus are strongly linked. Having the correlation structure would be useful to the staff developing the REA. Indeed, such information could help streamline their chapter on air quality data. At present, the ISA has little analysis of the five-minute results. It is interesting to note that the current ISA says that it is “very difficult to use (these data) precisely”, yet the REA does significant analysis of the data (and I am not sure what they mean by “precisely”).

I would think that SO<sub>2</sub> concentrations being observed at a monitor will tend to follow a log-normal distribution, whether one considers five-minute or one-hour average values, and that the two distributions would have a similar mean, but that the GSD would differ. (The geometric means of the two would not necessarily be the same, given that the one-hour average is an arithmetic average). Thus, this section should consider presenting concentration statistics in terms of the geometric averages and standard deviations (GSD) (they will need to address how the below detection limit values are treated). From this, one could assess how the GSD's of the five-minute and one-hour levels correlate, as well as how the five-minute and one-hour maximums correlate. One might think that the five-minute maximum can be well approximated as a function of the one-hour maximum and associated GSD.

Page 1-1, line 12: monomeric, gaseous, sulfur species.

Page 1-9, line 18: The science is not uncertain... the results contain uncertainty.

Page 2-3, line 13: The sulfuric acid will move to a condensed, not necessarily aqueous, phase. Further, it is not removed.

Page 2-3, line 18: What about sulfate?

Page 2-4, lines 20 on. This section is a bit confusing. They state that most of the oxidation is via aqueous phase chemistry, then use the gas-phase lifetime to calculate an overall lifetime. Again, it would be best if they used results from a US-based set of simulations to address the formation, fate and lifetime.

Section 2-3: Again, provide a straightforward answer to the question as to whether sampler issues impact the issues under consideration here, and I suspect the answer is no.

Table 2-4: Define units, make the caption more complete.

Page 2-25, line 9: I still think you mean three summer months, not seasons.

Figure 2-11: This figure is still of limited utility. It is impossible to see the frequency of observations at the low end. Provide a plot that actually provides such information. All this figure does, really, is indicate an average (which is too low to discern) and the

maximums. Use a log scale. Better yet, give a table of arithmetic mean, geometric mean, maximum, minimum and geometric standard deviation. If you want, you can add a traditional SD, though I would state this is less helpful.

I was pleased to see Sections 3.1.5.2.1-3.1.5.2.5 dealing with SO<sub>2</sub>-particle interactions, though none of these dealt with the dynamics of SO<sub>2</sub> uptake, and evaded the question of how likely such mechanisms may be in the atmosphere. Uptake of SO<sub>2</sub> on atmospheric particles is likely very slow, as is seen by the ability for SO<sub>2</sub> and particles to coexist in the atmosphere for long amounts of time. Further, the studies' use rather artificial surfaces that would be considered much more reactive and potentially absorbing than atmospheric aerosols. A further limitation to how the results in these sections may be applied in this assessment is that the products of the interaction between SO<sub>2</sub> and the particles would be monitored as part of the PM matrix, and be regulated as PM. While there is a significant amount of sulfate in PM, which can be explained by gas and aqueous phase oxidation of SO<sub>2</sub>, there is rather little sulfite, suggesting that particles would provide little avenue as a mechanism to transport significant quantities of SO<sub>2</sub> deeper in to the lung. SO<sub>2</sub> has a low Henry's law constant, so little will be stored as sulfite in the aqueous phase in a naturally occurring aerosol. This section should be more critical in its assessment of the importance of such processes. At present, there is no indication from observation of atmospheric aerosols that the studies discussed are relevant, and, conversely, there is ample evidence to suggest what is found is limited to laboratory generated aerosols that are then exposed to extremely high levels of SO<sub>2</sub>.

Summary and Conclusions:

Page 5-1, line 25: I would add "... facilities, though emissions from tall stacks may have a lesser impact on high concentrations at ground level due to diffusion."

5-11, line 2: Here, it says that effect estimates were found to be robust when using 2-pollutant models, but in Chapter 3, Fig 3-8, suggest that the significance of the SO<sub>2</sub> effect decreases when including PM<sub>10</sub>, sometimes leading to its being insignificantly different from zero? I probably also take exception to the conclusions in Chapter 3 dealing with their interpretation of the multi-pollutant assessment.

In response to the Charge Questions:

*1. The framework for causal determination and judging the overall weight of evidence, is presented in Chapter 1. Is this the appropriate approach? Is it appropriately applied in the case of SO<sub>x</sub>? How could the framework or its application be refined?*

The current version is improved. I will leave the adequacy issue to those with a more appropriate expertise.

*2. The discussion of the atmospheric chemistry of SO<sub>x</sub> has been expanded to provide a better characterization of the spatial heterogeneity of urban SO<sub>2</sub> concentrations and correlations of SO<sub>2</sub> with other pollutants. We also included new sections describing the regulatory network and siting criteria with maps of SO<sub>2</sub> and other monitors. A*

*brief section describing the available 5-minute SO<sub>2</sub> data was also included. In addition, the relationships between outdoor, indoor, and personal exposure to SO<sub>2</sub> were clarified with additional details on sources of exposure error. Have these revisions to Chapter 2 improved its assessment of the currently available scientific knowledge on atmospheric sciences and exposure and its relevance to the evaluation of human health effects presented in later chapters?*

While the new chapter is, indeed, improved, as discussed above there are still some further needs. In particular, the section on 5-minute averages is inadequate given the reliance of the REA on 5 minute data. This chapter should have CDFs for 1-hour and associated 5-minute SO<sub>2</sub> data, as well as a characterization of the correlations. The chapter would still benefit from a table of sources and their amounts. Given the discussion in Sections 3.1.5.2.1-3.1.5.2.5, this chapter should provide a scientific foundation for the relevance of the proposed mechanisms and how they are supported by observational evidence in the atmosphere.

*3. In the revision, we reduced redundancy, added summary sections and reorganized Chapter 3. In addition, discussions on potential confounding by and interactions with copollutants have been added. The 2nd draft ISA also includes additional analyses of individual-level data from human clinical studies (Sections 3.1.3. and 4.1.1) that builds upon the analysis included in the 1994 Supplement to the Second Addendum. The toxicology sections were reorganized to focus on studies using more relevant concentrations of SO<sub>2</sub> and sections were added to better discuss mode of action and potential particle-SO<sub>2</sub> interactions. We are requesting CASAC review specifically on these analyses as well as on the integration of the overall evidence from the human clinical, animal toxicological, and epidemiological studies.*

As discussed above, Sections 3.1.5.2.1-3.1.5.2.5 should be assessed for their likely importance in the atmosphere and to resulting exposures. Such sections should not be added without appropriate foundation and discussion of how likely they are to be of actual importance.

*4. The section on concentration-response relationships in Chapter 4 was reorganized and revised to include analysis of individual-level data from the human clinical studies and some additional discussion of the difficulties of discerning a threshold in population-level data. In addition, revisions were made to better characterize groups likely to be susceptible or vulnerable to SO<sub>x</sub> and the potential size of the population at risk for SO<sub>x</sub>-related health effects. Finally, revisions were made to reduce redundancy with material presented in Chapter 3. Have the revisions made to Chapter 4 improved the characterization of the potential public health impact of SO<sub>x</sub> exposure?*

*5. Revisions were made to better integrate findings from atmospheric sciences, ambient air data analyses, exposure assessment, dosimetry, and health evidence in Chapter 5. To what extent do these findings support conclusions regarding causality of SO<sub>x</sub>-related*

*health effects at relevant exposures?*

The greatly streamlined Chapter 5 is an improvement. I will take issue with the use of the studies cited suggesting that the particles act as ways to deliver SO<sub>2</sub> significantly more efficiently to the deeper lung, and that the sulfur associated with the particles is predominantly sulfate formed from chemical reactions in the atmosphere, and very little is from SO<sub>2</sub> interacting directly with dry particles. The molecular kinetics and atmospheric observations both argue against this.

## **Dr. Kent Pinkerton**

Comments on Sox ISA – 2<sup>nd</sup> Draft

**General Comments:** The second external review draft of the integrated science assessment document for Sulfur Oxides/Health Criteria is much improved over the 1<sup>st</sup> draft. The chapters are well organized and logical. The regulatory history for sulfur oxides is interesting to observe with no changes since 1969, although comments were solicited for a 1 hour standard of 0.4 ppm as well as a 5 minute standard of 0.60 ppm SO<sub>2</sub> in 1988. The current standard for sulfur oxides remains at 0.14 ppm averaged over a 24 hour period, not to be exceeded more than once per year and 0.030 ppm annual arithmetic mean with SO<sub>2</sub> as the indicator.

The authors of the document have focused each chapter to address the most relevant issues and have presented a rather thorough and updated review of the literature since the most salient features of past reports. New publications presented in the 2<sup>nd</sup> draft ISA are highly appropriate, well-presented with a balanced interpretation. The presentation of positive and negative studies is well balanced with possible interpretations provided based on a solid scientific basis.

**Question 4:** The section on concentration-response relationships in Chapter 4 was reorganized and revised to include analysis of individual-level data from the human clinical studies and some additional discussion of the difficulties of discerning a threshold in population-level data. In addition, revisions were made to better characterize groups likely to be susceptible or vulnerable to Sox and the potential size of the population at risk for Sox-related health effects. Finally, revisions were made to reduce redundancy with material presented in Chapter 3. Have the revisions made to Chapter 4 improved the characterization of the potential public health impact of Sox exposure?

### **Response:**

The concentration-response relationships are clearly presented in Chapter 4. Human clinical studies provide compelling data to demonstrate SO<sub>2</sub>-induced decrements in lung function (FEV<sub>1</sub>) and specific airway resistance (sRaw) in asthmatics following limited (10 minute) exposure to SO<sub>2</sub>. An increasing proportion of asthmatic responders to increasing levels of SO<sub>2</sub> further confirm a strong concentration-response.

Epidemiological studies, although less definitive than human clinical studies, also provide strong evidence of increasing asthma hospitalizations with increasing 1-hour maximum SO<sub>2</sub> levels ranging from 0.20 to 0.60 ppm. An important point to emphasize in both the human clinical and epidemiological studies is the observation that significant effects were noted at SO<sub>2</sub> levels beginning slightly above 0.20 ppm.

Based on the human clinical and epidemiological study findings reported in Chapter 4, it appears the approach to be implemented in the REA by the EPA of these findings is to use 0.4 to 0.6 ppm as the beginning level for consideration to derive an appropriate level

of safety to public health. Although data (especially the human clinical study) shows an increased response as SO<sub>2</sub> levels are increased in a classical a concentration-response profile, a strong rationale needs to be made for not beginning at a maximal SO<sub>2</sub> concentration of 0.20 ppm.

Once again, similarities between human clinical and epidemiological studies should be emphasized, although I would agree that the human clinical studies provide the most compelling evidence in considerations for setting the standard for SO<sub>2</sub>.

The difficulty in establishing a threshold in population-level data is well presented in Chapter 4. Human clinical studies are likely to be the best source for setting risk levels, but epidemiological studies continue to provide strong supportive evidence as well. It is questionable whether one should consider non-linear concentration-response relationships to SO<sub>2</sub> levels, based on epidemiological studies, especially those studies illustrated in figures 4-4 and 4-5. These studies demonstrate effects beginning in the 0.2 to 0.3 ppm level. I would suggest (as somewhat already stated in the text of Chapter 4) it is important to not over-interpret these epidemiological findings as being non-linear. To do so, would also require an explanation in the Schwartz et al study (1994) (Figure 4-5) for a negative odds ratio at a low level (0.10 ppm) of SO<sub>2</sub> and a non-linear increase in the odds ratio as levels of SO<sub>2</sub> increase to 0.4 ppm.

Chapter 3 contains a comprehensive overview the scientific literature along with a complete and thorough review of new studies published since the previous review. The presentation and stated interpretation and conclusions of this data in general are logical and balanced. The summaries found at the end of each section in Chapter 3 are helpful reminders and a reasonable and rational reflection of the section conclusions.

Chapter 4 is written to address critical issues of public health impact as discussed above. The chapter contents are presented in such a fashion to utilize critical data presented in Chapter 3 without being redundant. The definition and significance of susceptible and vulnerable populations is discussed. These are important factors that require a clear explanation in order to identify the appropriate populations at risk. Should these two populations identified as “susceptible” and “vulnerable” have overlap, is this also a critical component in estimating the appropriate size of the population at risk.

Excellent examples of epidemiological studies are presented to further confirm sensitivity of children with asthma to SO<sub>2</sub>. Similar sensitivity in adults has not been found. Genetic factors related to health outcomes were also considered with regard to air pollutants as an important factor to consider in future studies. A study by Winterton and colleagues (2001) has found a significant association between SO<sub>2</sub> and the homozygous wild-type allele for TNF-alpha.

Within chapter 4 is also presented a number of studies to examine age-related susceptibility with a good balance of studies and outcomes. The tables and figures throughout the chapter are highly complimentary to the text. To estimate the size of the

population at risk is an important determinant, but will need to incorporate the appropriate parameters.

In summary, this is an excellent chapter. Since the standard has not changed since its original inception in 1969-71, if the potential decision by EPA in the REA is to suggest changes in the standard to promulgate a 5-10 minute peak or 1-hour maximal level of SO<sub>2</sub>, this potential to recommend a very different standard from the current standard needs to be clearly justified in this chapter or in the REA.

Specific comments:

Page 4-2, line 26: please state the meaning of sRaw in the text

**Dr. Edward M. Postlethwait**

Comments on SO<sub>x</sub> ISA – 2<sup>nd</sup> Draft

The second draft of the SO<sub>x</sub> ISA is clearly improved. Suggested points for consideration include:

1. Much of the document focuses on the potential impacts of short term, relatively higher concentration exposures. In this regard, it is important to describe and/or illustrate the characteristics of short term spikes. This may be important for exposure/risk predictions since it is assumed that 5-10 minute exposures will be modeled as steady state exposure conditions but in the real world such spikes may, for example, be very sharp rather than the square wave exposure patterns that are generally employed in most human clinical investigations.
2. Do the tables which include compilations of relative risks computed from population studies include points which are not statistically significant? If so, then there may be an unintentional bias in representing potential health impacts. If none significant results are to be presented, they should be identified as such to appropriately inform the reader.
3. While the human clinical studies of asthmatics show apparent thresholds at SO<sub>2</sub> levels between 0.4 and 0.6 ppm, other data may suggest that some individuals may respond at lower concentrations. Thus it is recommended that predictive estimates utilize concentrations below the proposed benchmark 0.4 ppm level.
4. The above highlights an appreciable challenge for conducting risk estimates in that some population studies suggest effects occur at levels well below those observed during clinical studies. The ISA would clearly be strengthened by an improved integration/synthesis regarding the potential genesis of effects threshold differences, especially since the chapter on dosimetry clearly describes that > 90% of inhaled SO<sub>2</sub> is scrubbed in the upper airways so that during environmentally relevant exposures only very small amounts of SO<sub>2</sub> would penetrate to anatomic regions involved in bronchoconstrictive events. Thus at least an attempt to clarify the apparent discrepancies is warranted.
5. The concluding language in the various health effects sections relating exposures to the various biological endpoints of interest would be strengthened by more internal consistency. For example, it is stated that there is sufficient evidence “to infer a causal relationship between respiratory morbidity and short-term exposure to SO<sub>2</sub>”, which is unequivocal based on clinical studies. However, in other sections statements regarding causality have the caveat “at current ambient levels.” Thus, while asthmatics, and likely most individuals, will respond at some threshold exposure level, whether this occurs at ambient levels is not consistently addressed. Because of the dearth of more current data and the confounding associated with multipollutant

exposures in population studies, the ISA would benefit by more thorough discussion of the potential for SO<sub>2</sub> to induce biological effects versus those effects that are/can be detected under ambient conditions.

**Dr. Jonathan M. Samet**

Comments on SOx 2nd Draft ISA

General Comments:

Overview:

This second draft Integrated Science Assessment (ISA) has been redrafted following the initial review by CASAC. Along with the draft ISA for Nitrogen Oxides, it represents the second use of the new evidence review approach by the Environmental Protection Agency. As such, it remains critical that a useful model be established for future reviews.

In this regard, I still find the second draft ISA to be deficient. While changes have been made, the approach to evidence identification, review, and synthesis remains inadequately specified. In the revised Chapter 1, while the Agency has begun to more formally set out criteria for evidence evaluation and standard approaches for classifying the strength of evidence for causation, the overall approach still needs development and its application in the subsequent chapters of the ISA is not sufficiently thoughtful. My responses to the charge questions follow:

Question 1:

This question asks whether the framework set out in Chapter 1 is appropriate and adequately applied, and whether the Agency's approach for causal inference needs to be strengthened. The Agency, in developing its approach, has relied on a number of recent reports that offer models, including the approach taken in the Surgeon General's Reports and the conceptual framework set out in the recent Institute of Medicine document, *Improving the Presumptive Disability Decision-Making Process for Veterans*. These documents along with the others that are cited do provide useful approaches. The Agency's adoption of a five-level set of descriptors of strength of evidence is appropriate and should prove useful for decision-making based on the degree of certainty provided by scientific evidence considered. Through its application, the Agency will be able to refine the review and synthesis process and, in particular, set precedents for responding to evidence reaching different levels of certainty for causation. For example, would evidence reaching the "suggestive" level be a sufficient foundation for altering a NAAQS?

There are still limitations of Chapter 1, however. The discussion of association versus causation is not well formulated and the authors are not clear in discussing key concepts that affect interpretation of epidemiological data. For example, confounding and effect modification are addressed rather superficially, as is measurement error. I urge the staff to continue to refine this material, because it will become a model for future ISAs. The authors comment on the complexity of determinants of health and of response to an environmental agent, such as sulfur dioxide. However, their approach to doing so is limited and Figure 1-1 is presented with little explanation.

The discussion of uncertainty is brief and needs expansion. A more systematic approach to describing uncertainty would be useful, both around determination of causation and with regard to the quantification of effect. This important issue is handled in only one page.

I was concerned by the application of the approach for causal inference in subsequent chapters. The discussion is limited around evidence synthesis, particularly in Chapter 3. There needs to be a better template for assuring standardization of discussion of the strength of evidence.

Charge Question 4:

The revised Chapter 4 adequately sets out the quantitative information from the human clinical studies. The plots are clear in showing the observed concentration-response relationships. The epidemiological data are also described, although the findings cannot be so readily summarized.

The chapter offers definitions of “susceptible” and “vulnerable” that need some strengthening. Is a susceptible population as defined or one that has a steeper exposure-response relationship than a non-susceptible population? The definition given here emphasizes response at a lower concentration than in the general population. The distinction between susceptibility and vulnerability lies in a greater biological response for susceptible individuals and a greater risk for exposure (higher exposure?) in a vulnerable population. Later in the chapter this distinction becomes blurred.

**Specific Comments:**

<b>Page #</b>	<b>Line #</b>	<b>Comment</b>
1-5	1	Need introduction here that a hierarchy of evidence may be identified and that for some pollutants human clinical studies may provide the most compelling evidence, e.g., CO, but not for all, e.g., PM.
1-5	6	Delete “can”
1-5	8	A panel study is a cohort study
1-5	9	“...occasionally in epidemiology:” and offer the opportunity to investigate a change in exposure.
1-5	15	“species” and the model used
1-6	5	“The results are” delete and substitute “observed risk represents”
1-6	8	The alternatives are chance and bias
1-6	8	“subjects in a population” usually volunteers
1-7	3	Randomization needs better description: of exposure (pollutant <u>vs</u> sham or of people (pollutant or sham).
1-7	6	Delete randomness, substitute “the role of chance”

Page #	Line #	Comment
1-7	16	“Nutritional deficits” Such as?
1-7	17	“from epidemiological studies” Not inferred from epi studies alone.
1-7	19	Delete statistical
1-7	24	Delete “with”, substitute of
1-7	25	Effect modification can also be examined with models
1-8	1	“possible mechanisms” and the distributions of these factors in the population under study.
1-8	4	“In multivariate analyses...” true? On what basis? References?
1-8	10	But not necessary
1-12	10	Delete “the absence of”, Substitute not meeting
1-13	1	“recent publications” All relevant?
1-14	19	“The complex molecular and...” What does this mean?
3-1	7	Delete “nature”, substitute role
3-1	21	May provide evidence
3-2	9	And to precisely characterize exposure/response
3-2	23	Delete “test”, not a test-an application
3-3	2	“thus, <del>attempts</del> results of models that attempt to distinguish
3-3	11	Delete errors, substitute problems
3-3	14	Why?
3-3	22	“reliability” or validity?
3-8	25	How were studies selected?
5-2	20	“led to the conclusion that <del>it</del> ” Substitute the evidence.
5-2	26	<del>The</del> , substitute An immediate response
5-2	27	“bronchoconstruction, <del>this response is mediated</del> ”
5-3	1	Depending on concentration
5-3	8	“human clinical studies (finding reporting of <del>reporting</del> respiratory symptoms)”
5-3	12	“5-20%” Of asthmatics
5-4	24	“internal coherence” What is this?
5-6	6	How do they provide plausibility?
5-9	12	“much uncertainty remains” What does this mean? What kind of uncertainty?
5-11	17	“Individuals in, substitute having a chronic”
5-12	4	“data support the finding...” Not the proposed language

## **Dr. Richard Schlesinger**

### Comments on SO<sub>x</sub> ISA – 2<sup>nd</sup> Draft

Overall, the 2<sup>nd</sup> draft improves on the 1<sup>st</sup> in integrating the various disciplines. However, there is still room for improvement in some of the sections as noted below. In many cases, the various disciplines are not really integrated but rather separate discussions of each are just placed in the same section. A true integration would interweave the epi with mechanistic support from the controlled studies.

The inclusion of a section on mixtures, i.e., 3.1.5, is an improvement, but it is not clear why that section was placed where it was. I think that a section on mixtures and the potential for interaction related to all health outcomes from SO<sub>2</sub> for all exposure scenarios should be developed and placed at the end of the chapter prior to the Conclusions.

Table 5-3 is excellent and provides a very nice summary overview of the conclusions of the ISA and comparison to the previous Criteria Document.

### Specific Issues

1. Section 3.1.3 is titled, Respiratory Effects Associated with Peak Exposure. In reality, this is a discussion of studies that involve exposures for 1 hr or less to single levels of SO<sub>2</sub> without any baseline in animal and human clinical evaluations. Thus, the use of the term peak may be misleading since this may imply some higher level relative to some lower baseline. This section should also be renumbered as follows:
  - 3.1.3.1 Clinical Studies
  - 3.1.3.2 Animal Studies
2. Section 3.1.4 discusses Epi studies and this should be reflected in the section heading. Furthermore, lines 7-21 on page 3-17 should be moved to section 3.1.2.
3. Section 3.1.4.3 is an attempt to integrate animal, human clinical and epi studies.
4. Page 3-48, lines 15-17. The inconsistency may be due to the fact that the specific nature of the interaction may depend upon the specific co-pollutant.
5. Section 3.1.6 seems to be out of place here. Perhaps the material could be integrated into other sections.

6. Section 3.2. title should perhaps read “systemic” rather than “other.”
7. The conclusions in section 3.2.2. are not totally consistent with the statements made on page 3-59, lines 24-27. In one case, the evidence is noted as inconsistent while in the other it is noted to be inadequate.
8. On page 4-1, add “and vulnerable” following susceptible on line 10.
9. The comment on page 4-12, lines 1-2, that epi studies suggest that people with preexisting respiratory diseases are more susceptible to effects from SO<sub>2</sub> contradicts the comment on page 4-11, lines 12-13.
10. The sentence on lines 17-19 on page 4-20 is not clear.

## Dr. Christian Seigneur

Comments on SO<sub>x</sub> ISA – 2<sup>nd</sup> Draft

**Charge Question 2.** *Have these revisions to Chapter 2 improved its assessment of the currently available scientific knowledge on atmospheric sciences and exposure and its relevance to the evaluation of human health effects presented in later chapters?*

The second version of the ISA for the health criteria of sulfur oxides shows significant improvements compared to the first draft version. Comments made last year on the discussion of the physico-chemical processes that govern the evolution of sulfur oxides in the atmosphere have been addressed in this revised version. Therefore, the following comments on the second version tend to address points of detail or clarification rather than fundamental issues.

### Chapter 2. Source to tissue dose

Section 2.2, p. 2-3: “Because the saturation vapor pressure of H<sub>2</sub>SO<sub>4</sub> is extremely low, it will be removed rapidly by transfer to the aqueous phase of aerosol particles and cloud drops”. This is true only if aqueous particles or cloud drops (or fog droplets) are present. For example, under dry conditions, gaseous sulfuric acid may be transferred to particles to form dry particulate ammonium sulfate.

p. 2-20: The SO<sub>2</sub> and sulfate concentration maps shown in Figures 2-8 and 2-9 originate from the CASTNET data using some spatial interpolation methodology. Note that EPA’s Clean Air Market Division (CAMD) has developed some data fusion approach that combines the CASTNET data with a CMAQ simulation to produce concentration maps that are improved compared to the simple CASTNET interpolation maps (CAMD contact: Melissa Rury).

### Annex B

CTMs are sometimes referred to as chemistry-transport models (e.g., p. B-15, line 1), sometimes as chemical-transport models (e.g., Title of Section B-5). It may be preferable to use a single term throughout the document.

p. B-7, lines 12-13: The statement that transportation related sources only have a minor contribution to SO<sub>2</sub> ambient levels suggests a strong east-coast bias. In California, where point sources have low SO<sub>2</sub> emissions compared to the eastern U.S., ships can be a major contributing source to SO<sub>2</sub> concentrations. As a matter of fact, it would be appropriate to highlight the recent State of California regulation on sulfur content authorized for diesel fuel of ships that are within the proximity of the Californian coast.

p. B-17, line 6: The Weather Research & Forecast (WRF) model is now the preferred meteorological model; add it in the parentheses before RAMS.

p. B-22, line 14: The discussion points out that a plume-in-grid treatment affects the simulation results for ozone concentrations. This effect is due to the improved treatment of the NO<sub>x</sub> emissions when using a subgrid-scale representation of major point sources. In reality, the plume-in-grid treatment redistributes the ozone concentrations with little effect on the overall ozone budget (e.g., Karamchandani et al., Development and application of a state-of-the-science plume-in-grid model, *J. Geophys. Res.*, **107**, 4403-4415, 2002). Since the document focuses on SO<sub>x</sub>, it should be noted that a plume-in-grid treatment of SO<sub>x</sub> (and NO<sub>x</sub>) emissions has a significant effect on secondary sulfate (and nitrate) formation that may lead to up to 15% less sulfate (or nitrate) formation from those major point sources treated with a subgrid scale representation within the 3-D grid-based model (Karamchandani et al., Plume-in-grid modeling for particulate matter, *Atmos. Environ.*, **40**, 7280-7297, 2006).

p. B-25: It is true that compensation of errors may lead to good model performance for the wrong reasons and that the performance evaluation of individual model components is desirable. Therefore, it would be appropriate at this point to mention the effort made to evaluate the aqueous chemistry component of SO<sub>x</sub> models either in the laboratory (Waltrop et al., *J. Atmos. Chem.*, **12**, 1-17, 1991) or in the atmosphere (Daum et al., *Atmos. Environ.*, **18**, 2671-2684, 1984). Also, the evaluation of reactive plume models against aircraft data should be addressed.

p. B-25: This section only discusses regional and global CTM for SO<sub>x</sub> and does not present any information on plume dispersion models that are used to estimate local (e.g., within 50 km) impacts of major SO<sub>x</sub> emission sources. Since a plume dispersion model (AERMOD) will be used to conduct the Risk and Exposure Assessment, it is desirable to have a section in the Annex that presents this type of models, their limitations and available performance evaluation results.

## **Dr. Frank E. Speizer**

Comments on SOx ISA – 2<sup>nd</sup> Draft

Chapter 1 :

Page 1.6, Figure 1-1. I do not find this particular figure that useful. Perhaps Gee & Payne-Sturges, 2004 have sufficient text that accompanies the figure to make it useful, but simply putting it out without adequate descriptors do not help. I could imagine many of the arrows going in both directions if not in opposite directions. My suggestion would be either to expand the text of abandon the figure.

Page 1-6, section 1.3.3 the first sentence I this section needs to be modified. There is another alternative way of stating what is being said. After all there are no clinical studies of tobacco smoke and lung cancer. The studies are all epidemiological “association” studies. But the consistency and reproducibility and the magnitude of the associations are so overwhelming that there are no alternative tenable explanations (there were early on but these have all but gone away).

Page 1-14, last box in table from previous page. I think it would be worth putting a limit on “any level of exposure” Perhaps something like reasonable level or at least in human non-toxicological levels.

Page 1-15 end of section 1.3.8. Two issues that are not discussed here, (will need to be addressed somewhere) but I thought should be part of this overall assessment of causality are “uncertainty” and “margin of safety”. There are a various interpretations of each and laying out some definitions, even if they might be different definitions used by different people, would be useful. What constitutes a level of uncertainty that is acceptable to all, 90% of regulators, 50% of regulators etc? Similarly, are there percents of uncertainty that are judged by advocacy groups that are different? With regard to margin of safety ditto. Is it 20% margin, 50%, 100%, 500%. A discussion up front in the document might be a useful exercise and might put CASAC, Staff, and administrative policy makers all on same page.

Focus Question 1.

I think the cataloging of the descriptions of how causation might be determined is reasonable. The issue really isn't how we generally understand how epidemiology, clinical studies and animal toxicology data are used. More important issues are the ones raised in my last point above. I know there have been focus group discussions on the topic and there may even be some published research on the subject. The more I think about it the more important it seems to me that it be part of this chapter. Adding this material would substantially change the discussion and perhaps aid in what will be a difficult discussion in subsequent chapters when causation gets interpreted in making recommendations for standards.

Additional Comments related to other Chapters.

Figure 3-1, Page 3-12: This is an important figure that should be more thoroughly discussed. The figure indicates, from one of the larger early studies that there are marked discrepancies in the responsiveness of individual subjects. About 25% of the subjects were essentially unresponsive in terms of airway sensitivity below 2 ppm and another 25% were responsive below 0.5 ppm. Thus, in assessing group data it is obviously the case that within any group the responders and the non-responders need to be considered separately if at all possible. In this study of asthmatics, in which the presumption would be that the response pattern would be random across the group, this clearly was not the case. I am sure that I and others argued in the past that this raises concern that in attempting to justify a short term standard the fact that which 25% of the asthmatic population would be affected cannot be determined prior to exposure argues for consideration in the setting of a standard with an adequate margin of safety. I would contend that 25% of the population of asthmatics is a larger fraction of the most sensitive population than one should be comfortable to ignore in setting a short term standard. This argument did not win the day in 1994. The data since that time has further established the issue that there are what might be called “super sensitive” groups of people and the whole issue of both what proportion of the population should be protected and what the margin of safety should be will need to be revisited. In this case margin of safety is not a surrogate for uncertainty of effect but a measure of the size of the population to be protected.

In reaching a conclusion on page 3-46 the general impression is that the evidenced is suggestive. However, not taken into account in reaching these conclusions is the evidence that not all subjects within any given population are equally sensitive to the impact of SO<sub>2</sub>. In my mind this phenomena tips the balance that regulation of short term exposure is necessary.

This point is made even more effectively in Section 4.1.1 on page 4.2-3 along with figure 4-1. Given that sRaw is measured as doubling and FEV<sub>1</sub> change is measured as 15% decrease the range of changes from 0.2ppm to 0.6 is quite substantial and is consistent with a significant adverse effect that will need to be modeled in the risk assessment.

A better job needs to be done in indicating that subgroups of subjects appear to be more sensitive and may be driving the overall assessments in any specific study. These subgroups appear to exceed 5% to 13% for sRaw and FEV<sub>1</sub> respectively, at the lowest levels of exposure tested (0.2 ppm). The lack of a threshold at these (relatively) high levels of exposure as compared to “background of less than 15ppb makes straightforward extrapolation uncertain. I am sure there are people who are sensitive at these lower levels but finding an appropriate level and population at risk will be difficult.

With regard to long term exposure and mortality the larger (and better) conducted US studies are consistent but when assessed in the context of all studies that might be interpreted as negative leave the impression that the results are inconsistent and therefore no prudent declaration of causal association can be made. This seems slightly off base as there is adequate reasoning given as to why some studies might be positive and some negative and one simply cannot sum the total of studies.

## Summary and Conclusions Chapter

The conclusion about the “very few monitors” Page 5-2, line 16 suggests that one strong recommendation in this chapter is that an expanded network of monitors are needed. This may or may not be true depending upon the distribution seen at existing monitors in that with a 1 hour mean of 13ppb and a 99<sup>th</sup> percentile value of 120-700ppb little information is supplied other than the conclusion given that the max is not contributing to the mean. Some full distributions might help lead to the conclusion as to how much additional monitoring is necessary outside potential known hotspots.

Having the key finding summarized and reproducing the summarizing tables from the appendices is useful.

**Dr. Lianne Sheppard**

Comments on SOx 2nd Draft ISA

*Overall assessment:* This document is much improved from the previous version. Generally it flows better and more closely attains its goal of presenting an integrated science assessment of SO<sub>2</sub> and its effect on health.

*Charge question 1:* The Chapter 1 framework is reasonable.

*Charge question 2:* Chapter 2 is better.

- There is better characterization of the spatial distribution of SO<sub>2</sub> monitors, but the discussion is still lacking in the sense that there is no stratification of analyses by micro vs. neighborhood scale monitors. This is an important feature to take into account in the interpretation of epidemiological studies. What fraction of monitors in each area falls in these categories? How many areas with SO<sub>2</sub> monitors lack any neighborhood scale monitors?
- Section 2.5 is a good addition and a good effort was made in 2.5.4 to discuss important features of exposure assessment for epidemiological studies. The availability of neighborhood scale monitors should be brought into this discussion, as well as the reactivity of SO<sub>2</sub>.

*Charge question 3:* Chapter 3 is much more readable and well organized.

*Charge question 4:* The revision to the concentration-response modeling discussion is reasonable. Discussion of vulnerable and susceptible groups is reasonable, but could possibly still benefit from a catalogue (e.g. in a table) of all potential vulnerabilities and susceptibilities that warrant consideration. The public health impacts section appears to be incomplete. While the gradation of responses and the prevalence of respiratory disorders tables are useful, these are not linked to provide any inference about degree of public health importance of SO<sub>2</sub> exposure in the population.

*Charge question 5:* There is good integration in Chapter 5.

*Specific comments:* To be added.

**Dr. George Thurston**

Comments on SO<sub>x</sub> 2nd Draft ISA

*1. The framework for causal determination and judging the overall weight of evidence, is presented in Chapter 1. Is this the appropriate approach? Is it appropriately applied in the case of SO<sub>x</sub>? How could the framework or its application be refined?*

RESPONSE: Yes, I feel the staff has done an excellent job of properly incorporating and explaining both the weigh of evidence criteria and the causality inference framework.

*2. The discussion of the atmospheric chemistry of SO<sub>x</sub> has been expanded to provide a better characterization of the spatial heterogeneity of urban SO<sub>2</sub> concentrations and correlations of SO<sub>2</sub> with other pollutants. We also included new sections describing the regulatory network and siting criteria with maps of SO<sub>2</sub> and other monitors. A brief section describing the available 5-minute SO<sub>2</sub> data was also included. In addition, the relationships between outdoor, indoor, and personal exposure to SO<sub>2</sub> were clarified with additional details on sources of exposure error. Have these revisions to Chapter 2 improved its assessment of the currently available scientific knowledge on atmospheric sciences and exposure and its relevance to the evaluation of human health effects presented in later chapters?*

RESPONSE: Yes, this is much improved, but I would like to see a better representation of the trends in short-term SO<sub>2</sub> concentrations (i.e., 1-hr maximum). While there has clearly been improvement in annual average SO<sub>2</sub> concentrations, as would be expected given the advent of the acid rain control program, these efforts have focused on lowering overall tons of SO<sub>2</sub> emissions, and not on lowering maximum impacts. So the question remains, have we seen a reduction in peak SO<sub>2</sub> exposures near major sources? As such, I would ask that plots of the distribution of 1-hour maximum values (for which many more sites are available than for 5-minute peaks) over time to better elucidate how much improvement we are making in lowering peak SO<sub>2</sub> exposures.

Another issue I have with Chapter 2 is the inadequate coverage of the PM-SO<sub>2</sub> interaction, and the potential for the co-presence of PM to increase lung dosage and health effects of SO<sub>2</sub> over and above that indicated by controlled animal and human populations using pure SO<sub>2</sub> gas, without associated PM (which would be the case in the real world). While the document includes research by Amdur on page 2-60, it does not include her work very clearly showing the way that co-presence of PM along with SO<sub>2</sub> increases the impact of acute SO<sub>2</sub> exposure. While these studies are discussed in Chapter 3, they are probable even more important to mention here as well, as they are important to our understanding of SO<sub>2</sub> doses in the real world. Now, while SO<sub>2</sub> has a relatively low Henry's law constant, and it might therefore be expected that little will be stored as sulfite in the aqueous phase in a naturally occurring aerosol, but the Amdur studies conversely imply that this SO<sub>2</sub>-PM interaction is a strong one, so the document

needs to more thoroughly investigate this mechanism, and better sort out its possible role in enhancing the effects of ambient SO<sub>2</sub>. This might very well be an important consideration in trying to extrapolate from controlled studies to effects in populations, as, if ignored, it may well mean that the human health effects of elevated SO<sub>2</sub> exposures will be underestimated, and the SO<sub>2</sub> concentrations required for a response would be underestimated, as well. This consideration also points to the greater relevance of using epidemiology for risk assessment, rather than controlled exposures to subjects, since epidemiology will have already incorporated such PM-SO<sub>2</sub> interactions that happen in the real world, but not in controlled exposure environments lacking PM.

*3. In the revision, we reduced redundancy, added summary sections and reorganized Chapter 3. In addition, discussions on potential confounding by and interactions with copollutants have been added. The 2nd draft ISA also includes additional analyses of individual-level data from human clinical studies (Sections 3.1.3. and 4.1.1) that builds upon the analysis included in the 1994 Supplement to the Second Addendum. The toxicology sections were reorganized to focus on studies using more relevant concentrations of SO<sub>2</sub> and sections were added to better discuss mode of action and potential particle-SO<sub>2</sub> interactions. We are requesting CASAC review specifically on these analyses as well as on the integration of the overall evidence from the human clinical, animal toxicological, and epidemiological studies.*

RESPONSE: While this section makes advances, Section 3.1.5.2.5 is wholly inadequate. It ignores the major implication of these interactions: that exposure studies that do not include the potentiating effects of PM on SO<sub>2</sub> exposures will very likely have both underestimated the size of SO<sub>2</sub> effects and the overestimated the SO<sub>2</sub> levels at which such effects may be experienced in the co-presence of particles (i.e. in the real world).

*4. The section on concentration-response relationships in Chapter 4 was reorganized and revised to include analysis of individual-level data from the human clinical studies and some additional discussion of the difficulties of discerning a threshold in population-level data. In addition, revisions were made to better characterize groups likely to be susceptible or vulnerable to SO<sub>x</sub> and the potential size of the population at risk for SO<sub>x</sub>-related health effects. Finally, revisions were made to reduce redundancy with material presented in Chapter 3. Have the revisions made to Chapter 4 improved the characterization of the potential public health impact of SO<sub>x</sub> exposure?*

RESPONSE: Again, in this chapter, there is little acknowledgement of the fact that many of the clinical and animal studies were done using pure SO<sub>2</sub>, without co-PM exposures, as would occur in the real world. This is especially critical in section 4.3.2, where the clinical studies are used to indicate benchmarks of effects. Such a choice of levels at which various effects would occur must take into account the documented effects that PM would have on the size and threshold of effects by SO<sub>2</sub>. For example, based on the work of Amdur and others, a conservative factor to adjust for the copresence of PM might well be applied to estimate the levels at which such clinical symptoms might occur in the real world.

*5. Revisions were made to better integrate findings from atmospheric sciences, ambient air data analyses, exposure assessment, dosimetry, and health evidence in Chapter 5. To what extent do these findings support conclusions regarding causality of SO<sub>x</sub>-related health effects at relevant exposures?*

RESPONSE: The big issue that needs more discussion is why the epidemiology shows health effects associations at much lower concentrations than do the clinical studies. The paragraph at the top of page 5-11 does discuss one likely explanation of this apparent paradox: the effects of the fact that “aerosol particles act as carriers and deliver sulfur-containing compounds more effectively to the lower respiratory tract”. However, more discussion is needed here of the fact that this may well account for why epidemiological associations are found at SO<sub>2</sub> concentrations well below where effects are documented by clinical studies using pure SO<sub>2</sub> exposures.

**Dr. James Ultman**

Comments on SO<sub>x</sub> ISA – 2<sup>nd</sup> Draft

### **General Comments**

This second draft of the ISA provides a significant improvement over the first draft, both with respect to content and chapter organization.

Apparently, the framing questions that originally appeared on page 1-2 in the first draft of the ISA have been deleted from the second draft. The answers to several (but not all) of these questions can be culled from the final “Conclusions” section on page 5-12 of the revised document. Given the importance of these questions in informing the REA as well as the final rulemaking, EPA staff should consider reinserting the questions into Chapter 1 and then explicitly answering them in Chapter 5.

### **Comments on Chapter 2 and Charge Question #1**

#### General

A major improvement in this chapter is the new material on monitor locations, particularly those 108 sites where 5-minute averages have been recorded.

I am, however, puzzled by the statement on lines 1-2 of page 2-32 that: “Although these 5-minute data meet AQS minimum quality assurance requirements...these data (are) very difficult to use precisely.” This appears to be the rationale for not including any actual data from these sites in the document.

In fact, this very set of data, is used in the first draft REA to model the relationship between peak and short-term ambient SO<sub>2</sub> concentrations. I suggest that disconnect between the ISA and REA be remedied by including some data, in either a tabular or graphical form, regarding the peak and 1-hour short-term concentration data obtained from the monitors listed in tables 2-6 and 2-7. Is it possible, for example, to examine and compare the relationships between the two concentration averages over time at various sites?

The text indicates that ambient monitors are allowed to be sited at any vertical location between 2 and 15 meters above the ground (pg. 2-9 lines 3-4). Yet, there is virtually no discussion of vertical SO<sub>2</sub> gradients nor the errors such gradients introduce when using ambient concentration as a surrogate for ground-level concentration. For example, ground-level concentrations near point sources will be much lower than concentrations recorded from monitors high off the ground. It would be beneficial for the ISA to provide a better qualitative and quantitative appreciation of this.

## Specific Comments

### **Page; lines**

**2-3; 10 & 12** Define terminology (OH for hydroxyl free radical and HO<sub>2</sub> for hydroperoxyl radical) immediately after the equation in which they first appear.

**2-9; 3-4** How large a difference between monitored concentrations is a variation of 2-15 m difference in monitor height likely to introduce? How does this difference depend on distance to the point source?

**2-14; 1** Make sure that SLAMS and NAMS acronyms have been previously defined.

**2-23; 9** I assume that you mean “the Pearson correlation coefficients (r) for concentration data from multiple monitors taken as pairs in these CMSA’s...”

**2-26; 9-11** 104 sites +15 sites is greater than the total of 108 sites mentioned in the previous sentence.

**2-41; 5** Given the importance of exercise in promoting health effects in asthmatics, it is important that this be included as a personal activity in this list.

**2-41; 17-21** Incomplete, run-on, sentence.

**2-58; 14** For clarification, it would be helpful to add a phrase indicating that the Henry’s Law constant is inversely proportional to solubility.

### **One-way flow versus cyclic flow---**

**2-59; 4-5** What the text refers to as “total respiratory tract absorption” is presumably the retained dose of SO<sub>2</sub> over a complete respiratory cycle.

**2-59; 18-20** In these experiments, the upper airways were isolated from the lower respiratory tract, and absorption was measured during one-way flow (as opposed to the bidirectional flow that occurs during a complete respiratory cycle). This was also the case for other investigations that are cited later on pages 2-59 and 2-60.

**2-63; 6-8** It is precisely because of desorption during exhalation that cyclic flow experiments report smaller absorption efficiencies than one-way flow experiments. This explanation should be worked into the discussion.

**Dr. Ronald E. Wyzga**

Comments on SOx ISA – 2<sup>nd</sup> Draft

**Charge question 3:** In the revision, we reduced redundancy, added summary sections and reorganized Chapter 3. In addition, discussions on potential confounding by and interactions with copollutants have been added. The 2<sup>nd</sup> draft ISA also included additional analyses of individual-level data from human clinical studies (Sections 3.1.3 and 4.1.1) that builds upon the analysis included in the 1994 Supplement to the Second Addendum. The toxicology sections were reorganized to focus on studies using more relevant concentrations of SO<sub>2</sub> and sections were added to better discuss mode of action and potential particle-SO<sub>2</sub> interactions. We are requesting CASAC review specifically on these analyses as well as on the integration of the overall evidence from the human clinical, animal toxicological and epidemiological studies.

**Response to charge question:** By and large I applaud the efforts undertaken in the revision. It increases the presentation and discussion of the human clinical studies, which I believe are extremely informative about the health effects of SO<sub>2</sub>. The focus is clearly upon respiratory responses, especially among asthmatics. I previously had sent the Agency staff several papers of human clinical studies, which have hopefully aided in this effort. They provide comprehensive input to aid our understanding of responses of asthmatics exposed to SO<sub>2</sub> in the chamber. To some extent the results presented in the ISA could have been extended to indicate the importance of other factors, such as the influence of routine asthma medication and weather upon response.

I believe the document was largely successful in integrating results across scientific disciplines although I note that several highlighted toxicological studies do utilize exposures orders of magnitude higher than those which occur in the ambient environment. (e.g., 0.8-6mg/m<sup>3</sup> and 1-2ppm SO<sub>2</sub>). Special note should be made of the fact that these concentrations are extremely high and not representative of those that occur in the real world. The copollutant issue in epidemiological studies is a difficult one to address largely because few studies address this issue systematically, making it difficult to resolve this issue definitively. I would urge the document to ask for more systematic investigation of this issue within individual studies.

**Overall comments:** This document is substantially improved over the previous draft; it considers the informative human clinical studies in more detail and correctly focuses upon respiratory health, especially asthma issues. I believe that relatively small changes in the document are needed. I give my specific comments below, which generally ask for further clarification or greater articulation of the presented material.

**Specific comments:**

p. 2-23, ll. 9-20: perhaps some discussion about the dependence of exposure to SO<sub>2</sub> on whether an individual (monitor) is in the plume from a point source is warranted.

p. 3-11; ll. 7-18: Another reason for the similarity in response between mild and moderate/severe asthmatics is that the latter were not able to exercise as intensely as the mild asthmatics. It should also be noted that studies (e.g., Gong et al., 1996; Gong et al./ 2001; Linn et al. 1988) have shown that medicated asthmatics were not sensitive to SO<sub>2</sub> exposure.

p. 3-15, ll. 11: insert “exercising, non-medicated” before asthmatics.

P. 3-16, l. 3: Linn et al., 1983 reported a significantly increased response among asthmatic subjects utilizing a mouthpiece for exposure as opposed to those with unencumbered breathing. This reference can be cited here.

p. 3-35, l. 10: “statistically”

p. 3-43, ll. 10-19: Systematic examinations of the potential influence of co-pollutants on study results are rare. Studies often consider a limited set of co-pollutant with no discussion about why other co-pollutants are not considered. It would be useful to indicate the need for more systematic review of this issue within a study.

p. 3-45, ll. 1-7: It should be noted that the panel studies found responses at ambient levels only when asthmatics were exercising.

p. 3-46, l. 31: reference should be given.

p. 3-47, ll. 14-20: It should be noted that exposure was by mouthpiece. See comments for p. 3-16.

p. 3-49, ll. 16 and following: It should be noted that the exposure levels in the studies cited in this section were extraordinarily high. This comment applies to section 3.15.2.5.

p. 3.55, ll. 21-22: It should be noted that controlled human studies did not find responses in adult atopics. (Linn et al., 1987).

p. 4-2, l. 1: Measurement error can also serve to linearize dose-response estimates.

p. 4.4, ll. 10-11. See comment for page 4-2.

p. 4-11, ll. 4-13: It might also be noteworthy to indicate that asthmatics on routine medication do not appear to respond to SO<sub>2</sub> while exercising.