Comments for Executive Summary (SOx ISA)

- **Language needs to be revised for a broader, nontechnical audience (no jargon).**
- Do not use the same word-for-word sentences/paragraphs in Chapter 1 that were used in Executive Summary (ES), i.e., the points needs to be reiterated but reworded for the different audiences.
- *Policy-Relevant Considerations* Section (last section) is very well written and could be used as a model for other sections.
- **Correlation of maximum 5-minute SO2 concentrations with corresponding 1-hour concentrations should be summarized in ES.**
- Some of the footnotes (e.g., 2) in the first page of the ES should be elevated to the body of the text.
- Table ES-1 is useful and appropriate.
- **Definitions for short- and long-term exposures need to be consistent throughout the ES, and the entire ISA.**
- Ambient background concentrations of SO2 need to be mentioned in this section.
- Important changes made in subsequent chapters need to be incorporated in the ES (e.g., number of sites reporting 5-minute data).
- A clear definition of *new asthma onset* is needed to set it apart from *asthma exacerbation* in the ES and where it is used in the following Chapters.
- **It should be clearly stated in the ES and Chapter 1 that the controlled human exposure studies are the principal rationale behind the 2010 1h SO2 NAAQS and this standard also provides protection from chronic exposure effects.**

Comments for Chapter 1 (SOx ISA)

- Overall this Chapter adequately summarizes and integrates the key findings of subsequent chapters, and reads better than the ES.
- The summary table and references were well done.
- Summary statements in Chapter 1 could be reiterated in subsequent ISA chapters.
- **A brief rationale for why SO2 is used as the indicator for gaseous SOx needs to be provided in the introductory paragraph of this chapter.**
- **In the *Conclusion* section (1.8) the authors correctly emphasize that the current ambient air quality standard is heavily based on the results of the controlled human exposure studies, but this needs to be more strongly reflected in early sections (e.g., 1.6.1).**
- Changes made in subsequent chapters need be appropriately captured in Chapter 1.

Chapter 2

- SO_2 emission sources
  - Table with consistent source categories and emissions
  - All legends on maps should include 2000 TPY break point
  - Add discussion on SO_2 Data Requirement Rule and table and map with EPA's 01/15/16 list of large SO_2 sources (> 2000 TPY).
- Atmospheric Chemistry
  - Emphasize aqueous phase formation of sulfate (relate to respiratory track exposure)
  - Address formation of compounds other than sulfate.
    - Formation of inorganic S(IV) particulate species addressing importance of sources, ambient chemistry, and possible importance as an SO2 confounder based on epidemiological studies where smelter or integrated steel emissions were important .
    - Emission and formation of organic S(IV), e.g. bis-hydroxydimethly sulfone and alkyl sulfates, etc. as a function of emission source.

Chapter 2

- Measurement Methods
  - Combine Section 3.2.1 and Section 2.4
  - Summarize SO_2 measurement methods
  - Table with comparison studies and potential discrepancies
- Environmental Concentrations
  - Extend analysis (2010-2012) to include 2013-2014 SO_2 data
  - Examine 5-min max vs. 1-hr average data for <u>all monitors</u> from 2010-2014 (Figure 2-28)
  - Need to specify averaging period for 5-min max (below 1:1 line)
  - Add additional scatter plots, add detailed peak/mean statistics for all sites
  - Refer to previous work on peak/mean ratios

Chapter 2

- Spatial and Temporal Variations
  - Include SO_2 emissions at each NEI facility (Figures 2-14 to 2-19). This information should be used in the discussion.
    - Relate 5-min max values (> 200 ppb) to nearby facilities
  - Include national and regional maps with most recent 3-year design values.
- Co-pollutant
  - Combine Section 2.5.5 and Section 3.3.4.1
  - Correlations should be examined for the data points with high correlation coefficients
- Dispersion Modeling
  - Lagrangian puff models (CALPUFF and SCICHEM) should be considered in addition to steady-state plume models (AERMOD)
  - Model performance evaluations (MPEs) should be performed with monitoring data for each model application (where no MPE was performed or no monitors exist, the model results may be significantly biased).

Recommendations for Chapter 3

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Reorganize and rethink the approach to this chapter

- Cover each key topic in depth in one place. Avoid fragmentation.
- Define and consistently use terminology, e.g., exposure, exposure concentration
- Distinguish between overall understanding of exposure assessment or an approach to modeling (e.g. LUR) vs. content that is specific to SO2
- Remove redundancy and improve clarity
- There was an uneven level of detail across tables (i.e., the information presented in the tables vs. the discussion of the tables in the text) that should be addressed

Reorganize and rethink the approach to this chapter: Possible reorganization

1. Introduction that gives context and scope.
2. Conceptual overview of human exposure, followed by a discussion of features of SO2 and how this informs understanding and estimating exposure.
3. Applications of exposure assessment for this context (epidemiologic inference, exposure simulation for risk assessment), and the exposure metrics of interest and used in SO2 epi studies and pertinent for the risk and exposure assessment.
4. Exposure metrics relevant to the science (mostly those used in epi studies, divided into acute and chronic effect studies). Discuss modeling as appropriate.

Other key points

- Consider adding a glossary of exposure-related terms. Could expand upon the current list of acronyms and definitions (pp xii of the document) for this purpose.
- Clearly define exposure error. In these definitions, distinguish the metric one would prefer to use, from how well the given metric is measured, specifically 1) exposure measurement error that comes from the uncertainty of the exposure metric being used relative to an uncertain version of that metric, and 2) a different target parameter of interest in the epidemiologic study than one might prefer.
- Models have uncertainty. Their results are not true values. More complex models don't necessarily reduce or eliminate uncertainty.
- Separate references to 2008 ISA that don't need to be fully reviewed in this document, from references that are newly available and incorporated here

Other key points page 2

- Don't perpetuate misleading literature by referencing correlations derived from data with many below LOD values (which are sometimes confusingly represented as negative concentration values). This is misleading and should not be captured in the document even if it is reported in the peer-reviewed literature.
- Ensure an accurate definition of exposure is being used that does not conflate exposure with dose. Omit material not relevant to exposure.
- Chapter 2 vs. Chapter 3:
  - CH2: Focus on measurements in the context of
  - CH2: In-depth description of deterministic models (e.g. AERMOD, CMAQ)
  - CH3: Cover statistical models for exposure assessment for application to epidemiology. It should only have a brief mention of deterministic models, only in the context of exposure and risk assessment. Refer to Chapter 2 for the details of deterministic modeling.

Chapter 4

- Introduction of dosimetry nomenclature and concepts would be helpful
- Obesity is important factor in dosimetry vis-à-vis ventilation and airway deposition. Importantly, obesity also effects the relative degree of oral and nasal ventilation (To get a complete picture of biological response, studies of interactive effects between obesity and SO2 exposure are needed)

- Cast extrapulmonary effects in the proper light (i.e., there is much less experimental evidence that such effects occur with SO2 as there is with ozone and particles).
- Be aware of recent insights into innate immunity in epithelium that may provide a pathway for short time response to SO2.

- Overall summary including knowledge gaps and what can we learn about biological response (airway and extrapulmonary) from general behavior of other air pollutants, especially those that evoke oxidative stress and neural irritation/activation would be useful.

Chapter 5

- The authors are to be commended for a chapter that summarizes and distills a very large literature. That said, some of the epidemiological evidence presented in the chapter could be more accurately characterized. The precision of effect estimates needs to be made clear in a consistent manner. Currently, different sections of the chapter (e.g., respiratory and cardiovascular) treat precision of effect estimates differently.
- The reviewers agree with the causal determination for respiratory effects of short-term exposure and the suggestive determination for respiratory effects of long-term exposure. We also agree with the inadequate determination for cardiovascular effects of long-term exposure and the suggestive determination for total mortality and short-term exposures. We are not convinced the evidence has sufficiently changed since the 2008 ISA to upgrade the determination from inadequate to suggestive for total mortality, reproductive/developmental effects, and cancer and long-term exposure.

- Because of the potential for co-pollutant, especially PM2.5, confounding of observed effects of both short-term and long-term exposures to SO2 in epidemiological studies, there is still considerable uncertainty about the role of SO2. Unless there are new studies that address this uncertainty, either experimental or epidemiological with adjustment for co-pollutant confounding, we recommend retaining an inadequate determination.
- The chapter is lengthy. A suggestion about how to potentially shorten the chapter is to focus on the key studies that are relevant to the assessment of the evidence using the causal framework. Both the text and the tables could be revised in such an approach. If unnecessary detailed descriptions of less relevant studies can be eliminated then more emphasis could be placed on a careful evaluation, synthesis and integration of the studies that provide the strongest evidence, including details that would allow a more rigorous assessment of study quality, especially for epidemiological studies.

- Measurement error in exposure assessment for epidemiological studies is treated superficially. The text leads readers to conclude that measurement error always leads to a bias toward the null, but bias away from the null can also occur, particularly in studies of long-term exposure. This should be stated clearly in the relevant sections. The revised treatment of measurement error suggested for Chapter 3 can be referenced in Chapter 5.
- The chapter is inconsistent in how it discusses co-pollutant correlations. For example, in the respiratory section SO2 correlations with other criteria pollutants are repeatedly described as “low to moderate,” yet in the cardiovascular section, the correlations are described as “moderate to high” with other pollutants. In general, the chapter needs more depth regarding the effects of multi-pollutant exposures. Co-exposure to other pollutants is currently treated as adding to uncertainty. While this is an important issue, exposure to mixtures of pollutants in the “real world” also may have greater health impact than exposure to single pollutants in controlled human exposure studies.

- It is important to note that only mild-moderate asthmatic subjects who were both relatively young and healthy have been studied in controlled human exposure studies and thus the results of these studies may not be representative of the responses of more at-risk individuals.
- Obesity has not been considered as an effect modifier regarding short-term exposures and asthma exacerbations.
- Discussion of E-R function shapes (e.g., linearity) is overly confident given the very limited empirical exploration of this issue for most outcomes.

Chapter 6

1. Further clarify terminology-populations can be “at risk” of higher SO2 related effects because:

   – They spend more time in areas with ambient concentrations that are harmful to health (based on where they live or time outdoors for example).

   – They experience a greater internal dose when exposed to a given ambient concentration (because of ventilation rate, or exercise activities for example) and hence suffer a greater adverse effect.

   – They have other factors that act synergistically with the air pollution exposure to enhance its adverse effect (e.g. age, sex, SES, race, genetic predisposition, existing disease behaviors like smoking or diet, weight)

   - These three types of factors may also themselves cluster and intercact

   -Consider whether these categories would be helpful in framing and structuring the chapter

- Further clarification of tables
  - Criteria used to determine presence of effect modification (stat sig? magnitude of difference?)
  - Clarify symbols
- Consider expanding on descriptive information on pops at risk
  - E.g. Expand table 6-2 to include children, include descriptives of prevalence of outdoor activities for various subgroups
- Better integration with chapters 5
  - Move appropriate sections from chapter 5 to chapter 6