United States Environmental Protection Agency

U.S. Environmental Protection Agency Clean Air Scientific Advisory Committee (CASAC) Sulfur Oxides Panel Public Meeting

Review of the Integrated Science Assessment for Sulfur Oxides – Health Criteria External Review Draft

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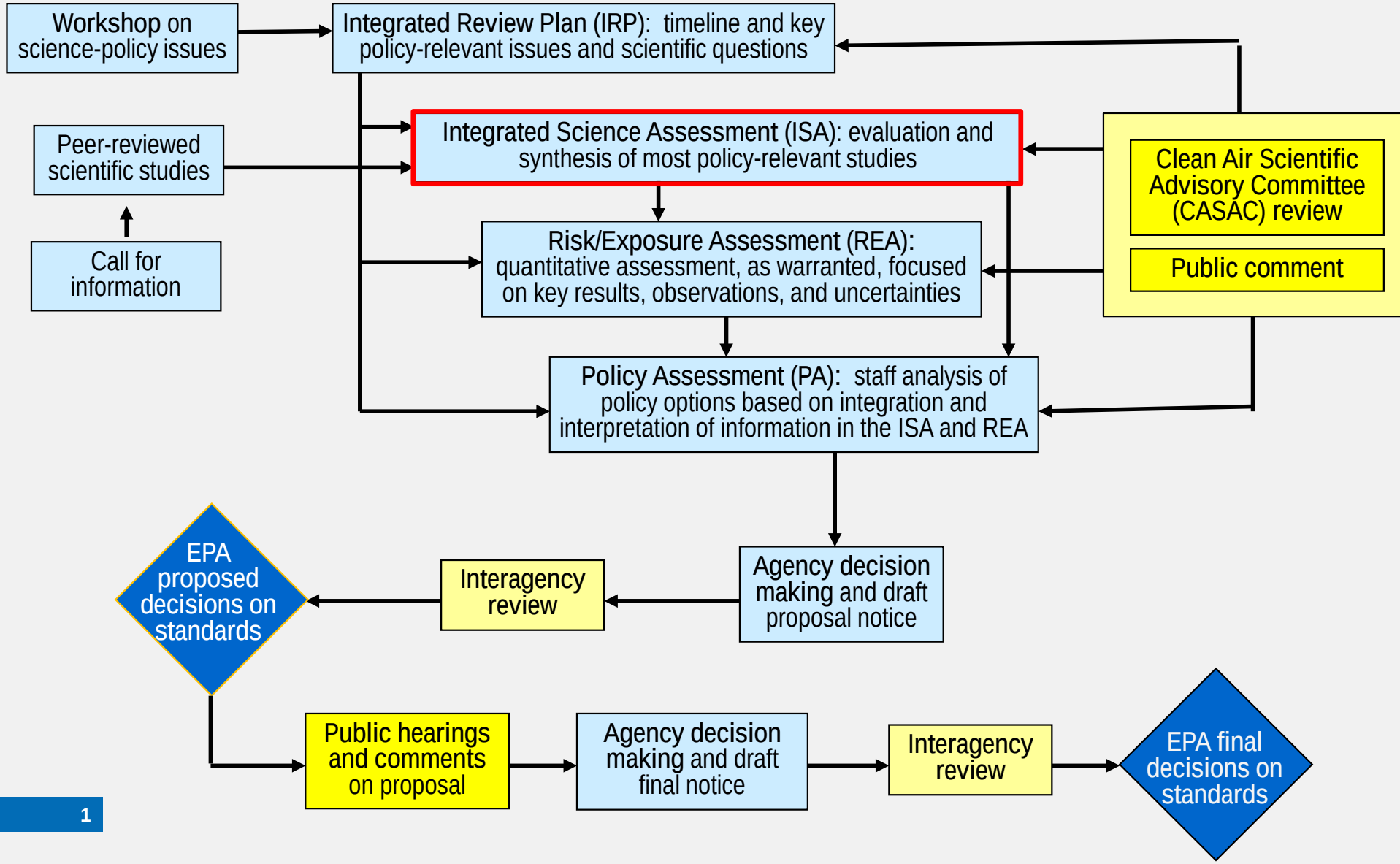
NAAQS Review Process



Documents Informing the Review of the Primary SO_2 NAAQS

- Integrated Review Plan (IRP) (*completed October 2014*)
  - Provides an orientation for the new CASAC Panel regarding the history of the past reviews, decisions, and any relevant litigation
  - Highlights key policy-relevant science issues that will guide review
  - Outlines process and schedule for review
  - CASAC Panel reviewed and commented on the IRP in April 2014
- Integrated Science Assessment (ISA)
  - Concise evaluation and synthesis of the most policy-relevant science
  - Emphasis on integration of the science and on clear characterization of strengths and uncertainties of available scientific evidence
  - ISA provides the scientific foundation for …
    - Risk and Exposure Assessment
    - Policy Assessment
    - Agency decisions as reflected in proposed and final rules
  - CASAC reviews and comments on the ISA
    - Meetings are open to the public and include opportunities for public comments

Documents Informing the Review of the Primary SO_2 NAAQS (cont.)

- Risk and Exposure Assessment (REA)
  - Prior to conducting an assessment, EPA prepares an REA planning document to assess the degree to which new evidence and tools support conducting a new quantitative REA
    - If an REA is warranted, the planning document also describes the scope and methods plan for the assessment
    - EPA consults with CASAC on the REA planning document
  - The REA, if warranted, draws upon information and conclusions presented in the ISA to develop quantitative characterizations of exposures and associated risks to human health associated with recent air quality conditions and with air quality estimated to just meet the current standard(s) and, if appropriate, alternative standard(s) under consideration
  - The REA, if warranted, includes a characterization of the uncertainties associated with such estimates
  - CASAC reviews and comments on draft REAs, if conducted
    - Meetings are open to the public and include opportunities for public comments

Documents Informing the Review of the Primary SO_2 NAAQS (cont.)

- Policy Assessment (PA)
  - Provides a transparent staff analysis of the scientific basis for alternative policy options for consideration by senior management prior to rulemaking
  - Intended to help “bridge the gap” between the Agency’s scientific assessments, presented in the ISA and REA(s), and the judgments required of the EPA Administrator in determining whether it is appropriate to retain or revise the NAAQS
  - Focuses on the information most pertinent to evaluating the basic elements of the NAAQS: indicator, averaging time, form, and level
  - CASAC reviews and comments on draft PA
    - Meetings are open to the public and include opportunities for public comments

Framework for Causal Determination

- Promote consistency and transparency
- Emphasize synthesis of evidence across scientific disciplines (e.g., controlled human exposure, epidemiologic, and toxicological studies)
- Weight of evidence for causal determination
  - Causal relationship
  - Likely to be a causal relationship
  - Suggestive but not sufficient to infer a causal relationship
  - Inadequate to infer the presence or absence of a causal relationship
  - Not likely to be a causal relationship
- ISA Preamble describes this framework
  - Preamble is now stand-alone document (http://www.epa.gov/isa)
- CASAC has supported use of this framework in past ISAs

Causal Framework Description

Causal relationship	Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures (e.g., doses or exposures generally within one to two orders of magnitude of current levels). That is, the pollutant has been shown to result in health effects in studies in which chance, confounding, and other biases could be ruled out with reasonable confidence. For example: (1) controlled human exposure studies that demonstrate consistent effects; or (2) observational studies that cannot be explained by plausible alternatives or that are supported by other lines of evidence (e.g., animal studies or mode of action information). Generally, the determination is based on multiple high-quality studies conducted by multiple research groups.	Rule out chance, confounding, and other biases Consistency, coherence, biological plausibility, high-quality studies
Likely to be a causal relationship	Evidence is sufficient to conclude that a causal relationship is likely to exist with relevant pollutant exposures. That is, the pollutant has been shown to result in health effects in studies where results are not explained by chance, confounding, and other biases, but uncertainties remain in the evidence overall. For example: (1) observational studies show an association, but copollutant exposures are difficult to address and/or other lines of evidence (controlled human exposure, animal, or mode of action information) are limited or inconsistent; or (2) animal toxicological evidence from multiple studies from different laboratories demonstrate effects, but limited or no human data are available. Generally, the determination is based on multiple high-quality studies.	Multiple, high-quality studies show effects Some uncertainty remains overall
Suggestive but not sufficient to infer a causal relationship	Evidence is suggestive of a causal relationship with relevant pollutant exposures, but is limited, and chance, confounding, and other biases cannot be ruled out. For example: (1) when the body of evidence is relatively small, at least one high-quality epidemiologic study shows an association with a given health outcome and/or at least one high-quality toxicological study shows effects relevant to humans in animal species; or (2) when the body of evidence is relatively large, evidence from studies of varying quality is generally supportive but not entirely consistent, and there may be coherence across lines of evidence (e.g., animal studies or mode of action information) to support the determination.	Cannot rule out chance, confounding, other biases -Evidence is limited but supporting -Evidence is sizeable and generally but not entirely consistent
Inadequate to infer a causal relationship	Evidence is inadequate to determine that a causal relationship exists with relevant pollutant exposures. The available studies are of insufficient quantity, quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an effect.	Evidence is of insufficient quantity, quality, consistency
Not likely to be a causal relationship	Evidence indicates there is no causal relationship with relevant pollutant exposures. Several adequate studies, covering the full range of levels of exposure that human beings are known to encounter and considering at-risk populations and lifestages are mutually consistent in not showing an effect at any level of exposure.	Multiple studies consistently show no effect

Excerpt from Table II of Preamble to the ISA

At-Risk Framework Description

Classification	Health Effects
Adequate evidence	There is substantial, consistent evidence within a discipline to conclude that a factor results in a population or lifestage being at increased risk of air pollutant-related health effect(s) relative to some reference population or lifestage. Where applicable, this evidence includes coherence across disciplines. Evidence includes multiple high-quality studies.
Suggestive evidence	The collective evidence suggests that a factor results in a population or lifestage being at increased risk of air pollutant-related health effect(s) relative to some reference population or lifestage, but the evidence is limited due to some inconsistency within a discipline or, where applicable, a lack of coherence across disciplines.
Inadequate evidence	The collective evidence is inadequate to determine whether a factor results in a population or lifestage being at increased risk of air pollutant-related health effect(s) relative to some reference population or lifestage. The available studies are of insufficient quantity, quality, consistency, and/or statistical power to permit a conclusion to be drawn.
Evidence of no effect	There is substantial, consistent evidence within a discipline to conclude that a factor does not result in a population or lifestage being at increased risk of air pollutant-related health effect(s) relative to some reference population or lifestage. Where applicable, the evidence includes coherence across disciplines. Evidence includes multiple high-quality studies.

Excerpt from Chapter 6 of the SO_X ISA

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History of NAAQS for SO_2

Summary of Primary (Health-based) NAAQS for SO_2 1971-2010				
Final Rule	**Indicator**	**Averaging Time**	**Level**	**Form**
1971	SO_2	24-h	0.14 ppm (140 ppb)	Not to be exceeded more than once per year
		Annual	0.03 ppm (30 ppb)	Annual arithmetic average
1996	Existing primary SO_2 standards retained, without revision			
2010	SO_2	1-h	75 ppb	99th percentile of 1-hour daily maximum concentrations, averaged over 3 years
		Primary annual and 24-hour SO_2 standards revoked		

2010 Final Rule also required states to report 5-min SO_2 concentration data

Contents of the Draft SO_X ISA

- Preface: Legislative Requirements and History of the NAAQS for SO_2
- Executive Summary
- Chapter 1. Integrative Synthesis of the ISA
- Chapter 2. Atmospheric Chemistry and Ambient Concentrations
- Chapter 3. Exposure to SO_2
- Chapter 4. Dosimetry and Modes of Action for SO_2
- Chapter 5. Integrated Health Effects of Exposure to SO_2
- Chapter 6. Lifestages and Populations Potentially at Increased Risk for Health Effects of SO_2

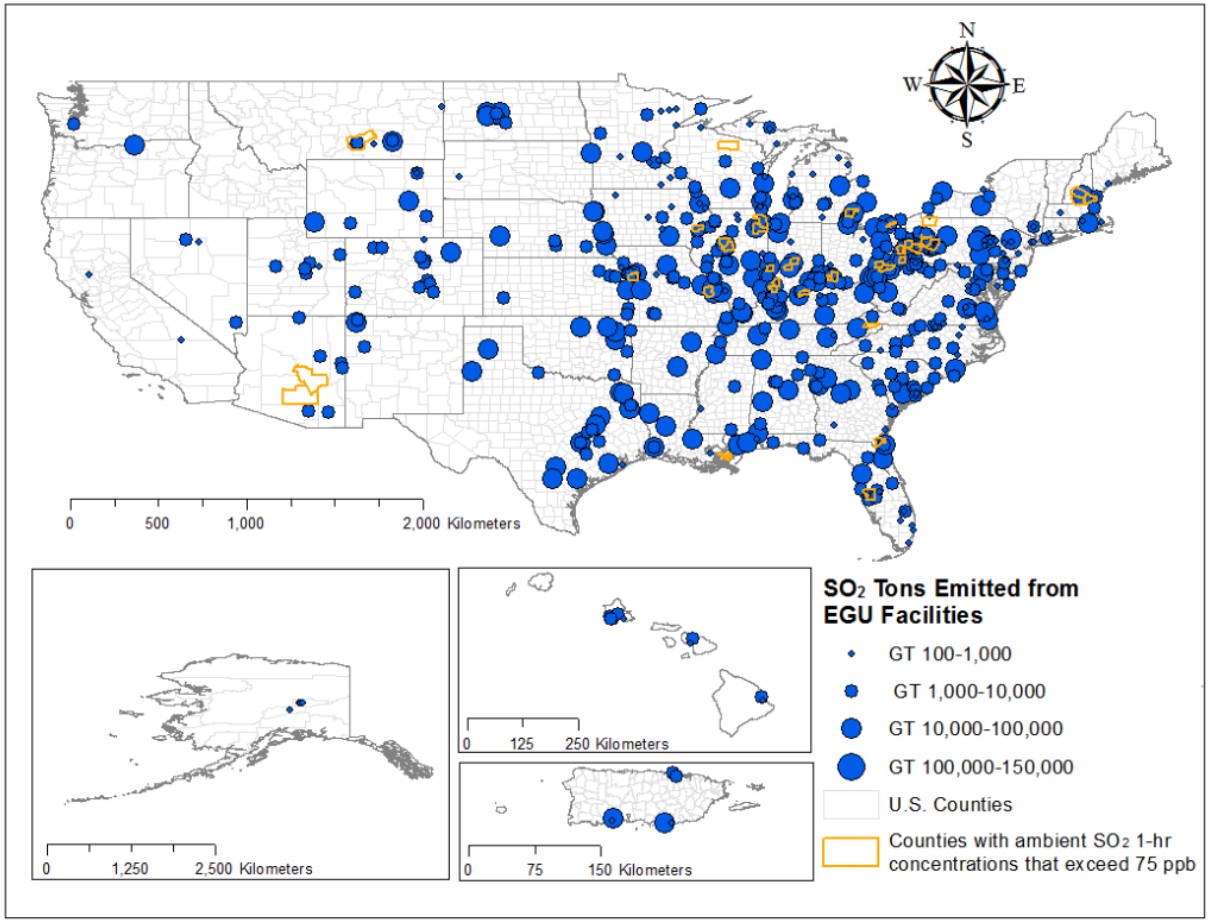
- ISA Preamble: now an online stand-alone companion document as part of an effort to streamline this and future ISAs (http://www.epa.gov/isa)

- SO_2 is the most important gaseous sulfur oxides (SO_X) species in ambient air, and the health literature focuses on SO_2; thus, the ISA focuses on SO_2 health effects
  - Particulate forms of SO_X are considered in the PM NAAQS reviews
  - Ecological effects of SO_X are considered together with those of NO_X in a separate NOx/SOx welfare NAAQS review

Atmospheric Chemistry and Ambient Concentrations

- Nearly 80% of 2013 anthropogenic SO_2 emissions came from electric utilities (63%) and industry (15%), mainly from fossil fuel combustion
  - Natural sources include volcanoes and oxidation of biogenic reduced sulfur compounds
- U.S. mean 1-hr daily max concentration from 2010-12 was 9 ppb; 99th percentile was 105 ppb
  - Between 1990-2012, 99th percentile 1-hr daily max SO_2 concentrations declined 72%
- U.S. mean 5-min hourly max concentration, newly required in 2010, was 3 ppb; 99th percentile was 31 ppb
- Analysis of 6 urban areas showed some near-source monitors with 5-min hourly max SO_2 concentrations of 200 ppb or more
  - 5-min hourly max and 1-hr concentrations were correlated
  - The ratio of 5-min hourly max concentration to the corresponding 1-hr value generally ranged between 1 and 3, with high ratios observed at sites with higher concentrations
- Dispersion modeling can be used to estimate SO_2 concentrations in locations where monitoring is not practical or sufficient

Geographic Distribution of SO_2 Emissions from EGUs



- Electricity Generating Units (EGUs) are the main source of SO_2
- These sources are primarily in the Eastern U.S., especially in the Ohio River valley
- SO_2 concentrations follow a similar pattern
- Volcanic emissions can lead to local high concentrations (e.g., Hawaii)

ISA Fig 2-2

Charge Questions for Chapter 2

Chapter 2 describes scientific information on sources, atmospheric chemistry, and measurement and modeling of ambient concentrations of gaseous sulfur oxides.

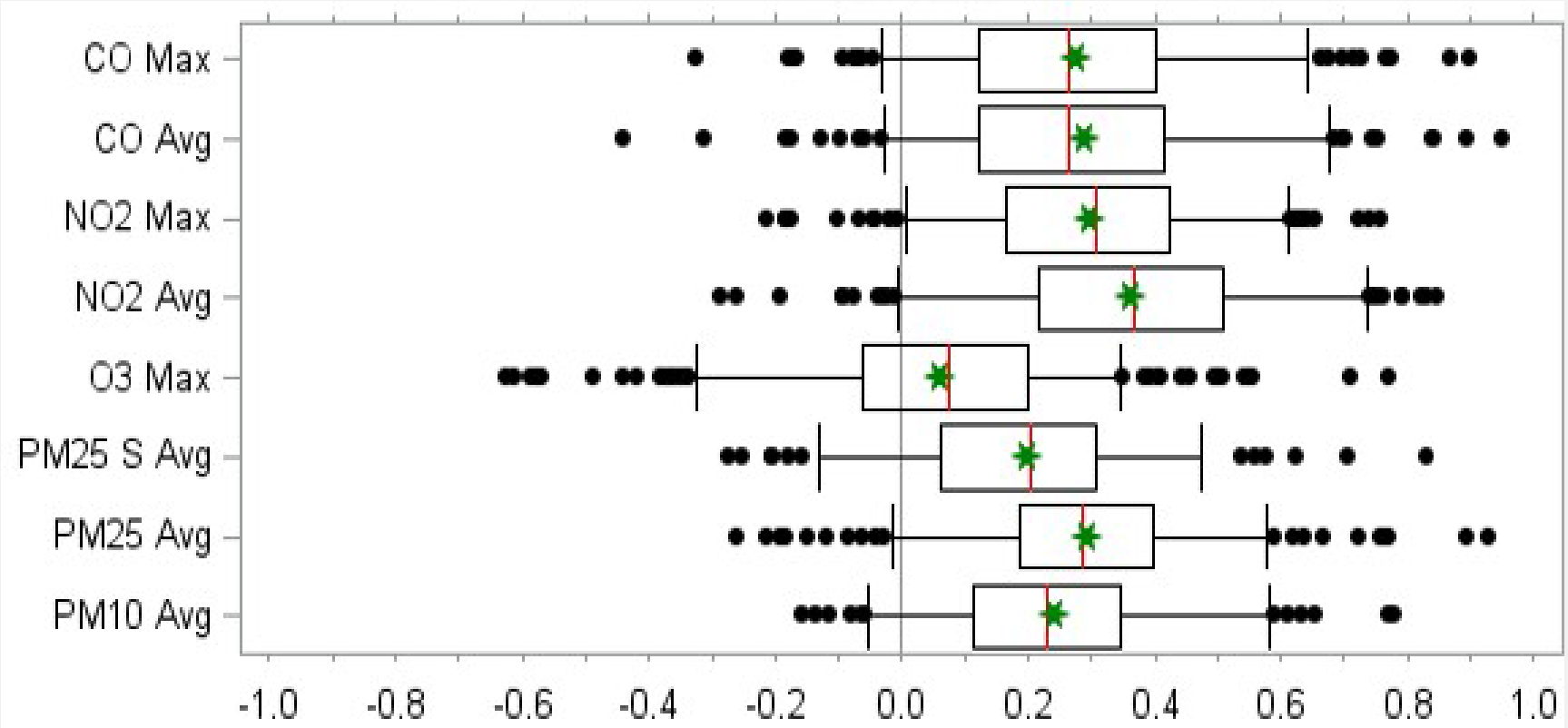
- To what extent is the information presented regarding sources, chemistry, and measurement and modeling of ambient concentrations accurate, complete, and relevant to the review of the SO_2 NAAQS?
- Please comment on the extent to which available information on the spatial and temporal trends of ambient SO_2 concentrations at various scales has been adequately and accurately described. In particular, what is the extent to which the analyses of recently available 5-min SO_2 concentration data are informative in considering relationships between 5-min and 1-hr SO_2 concentrations?
- How informative is the analysis of correlations between SO_2 and co-occurring pollutant concentrations for interpretation of epidemiologic studies?

Exposure to Ambient SO_2

- SO_2 concentrations have high spatial variability on urban scales
  - Effect estimates can be attenuated with decreased precision for epidemiologic studies of short-term SO_2 exposure
  - Effect estimates can be biased in either direction and have decreased precision for epidemiologic studies of long-term SO_2 exposure
- Personal SO_2 monitors have low sensitivity relative to current ambient concentrations
  - Difficult to evaluate relationship between ambient concentrations and personal exposures
  - However, when personal exposures are above detection limits, exposure is moderately correlated with ambient concentration
- Models can provide more detailed exposure estimates but require additional input data, assumptions, and computational resources

Exposure to Ambient SO_2

- Ambient daily SO_2 concentrations are generally not highly correlated with other criteria pollutants, although high correlations are observed at some AQS monitors
- Low correlation with other pollutants increases confidence that observed health effects are due to SO_2



ISA Fig 2-35

24-h avg Pearson Correlation Coefficient , 2010-12

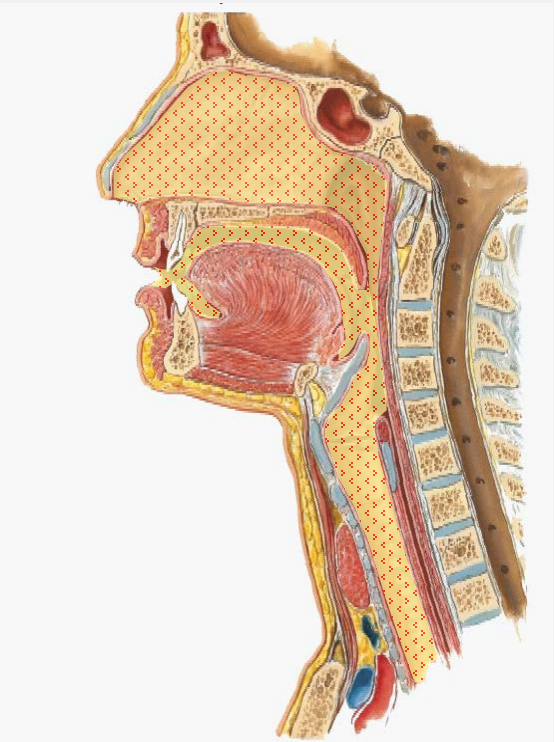
Charge Questions for Chapter 3

Chapter 3 describes scientific information on exposure to ambient SO_2 and implications for epidemiologic studies.

- To what extent is the discussion on methodological considerations for exposure measurement and modeling clearly and accurately conveyed, appropriately characterized, and relevant to the review of the SO_2 NAAQS?
- Please comment on the accuracy, level of detail, and clarity of the discussion regarding exposure assessment and the influence of exposure error on effect estimates in epidemiologic studies of the health effects of SO_2.

Dosimetry

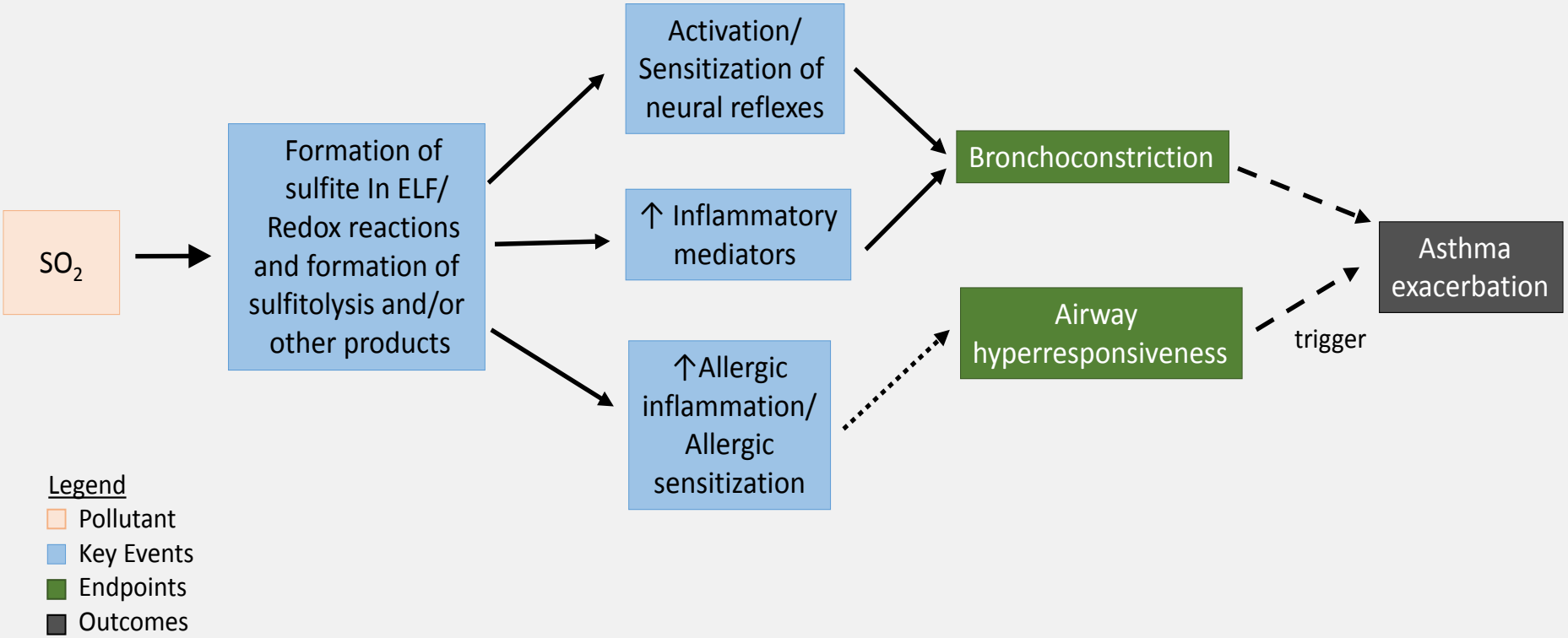
- SO_2 is readily absorbed in nasal passages under resting conditions
- Oronasal breathing during exercise increases SO_2 penetration into the lower respiratory tract
- Greater oronasal breathing occurs in children and in individuals with asthma or allergic rhinitis
- SO_2 forms products in the epithelial lining fluid; a major product is sulfite, which is highly reactive
- At any given time following inhalation, the majority of SO_2-derived products are found in the respiratory tract, but a fraction moves rapidly into the circulation
- Transformation of sulfite to nonreactive sulfate mainly occurs in the liver; sulfate is excreted via urine
- Other sources of sulfite in the body are ingested foods and beverages and catabolism of sulfur-containing amino acids



Oronasal breathing

Mode of Action for Asthma Exacerbation by SO_2

Proposed Mode of Action Linking Short-term Exposure to SO_2 and Respiratory Effects



Pathways indicated by a dotted line are those for which evidence is limited to findings from experimental animal studies, while evidence from controlled human exposure studies is available for pathways indicated by a solid line. Dashed lines indicate proposed links to the outcome of asthma exacerbation.

Charge Questions for Chapter 4

Chapter 4 characterizes scientific evidence on the dosimetry and modes of action for SO_2. Dosimetry and modes of action are bridged by the absorption and reaction of SO_2 in the epithelial lining fluid to form SO_2-derived products (e.g., sulfite and/or S-sulfonates) that are widely distributed throughout the body.

- To what extent is the discussion of the chemistry of inhaled SO_2 and the processes of absorption, distribution, metabolism, and elimination accurate, complete, and relevant to the review of the SO_2 NAAQS?
- Please comment on the discussion comparing endogenously generated and ingested sulfite with that derived from inhaled ambient air.
- To what extent are the discussion and integration of the potential modes of action underlying the health effects of exposure to sulfur oxides presented accurately and in sufficient detail? Are there additional modes of action that should be included in order to fully characterize the underlying mechanisms of sulfur oxides?

Health Effects of SO_2

Health Effect Category and Exposure Duration	Causal Determination	
	2008 ISA	2015 Draft ISA
Respiratory effects – Short-term exposure	**Causal**	**Causal**
Respiratory effects – Long-term exposure	Inadequate	*Suggestive*
Cardiovascular effects – Short-term exposure	Inadequate	*Suggestive*
Cardiovascular effects – Long-term exposure	Not included	*Inadequate*
Reproductive and developmental effects	Inadequate	*Suggestive*
Total mortality – Short-term exposure	Suggestive	Suggestive
Total mortality – Long-term exposure	Inadequate	*Suggestive*
Cancer – Long-term exposure	Inadequate	*Suggestive*

Short-Term Exposure and Respiratory Effects: Causal

- Clearest evidence comes from controlled human exposure studies of exercising individuals with asthma and 5-10 minute exposures to SO_2
  - Bronchoconstriction observed among some asthmatic adults with 5-10 minute exposures of 200-300 ppb
  - Bronchoconstriction, frequently accompanied by respiratory symptoms, observed among a greater percentage of asthmatics at concentrations of 400 ppb and above, with a clear concentration-response

- Animal toxicological studies have reported increased airway resistance with short-term exposures of 160-1,000 ppb
- Consistent and coherent evidence from epidemiologic studies showing generally positive associations between 24-h avg or 1-h daily max SO_2 concentrations and respiratory symptoms, emergency department visits, and hospital admissions

Other Health Effects of SO_2

- For long-term exposure and respiratory effects, the evidence is **suggestive** of a causal relationship
  - There is limited evidence from epidemiologic and toxicological studies for a possible relationship between long-term SO_2 exposure and the development of asthma
- Evidence is also **suggestive** of a causal relationship for cardiovascular effects (short-term exposure), total mortality (short- and long-term exposure), reproductive and developmental effects, and cancer
  - Generally, only limited evidence is available for outcomes categorized as "suggestive", with uncertainties regarding exposure measurement error and biologically plausible mechanisms for observed effects
- Evidence is **inadequate** to infer a causal relationship for long-term exposure and cardiovascular effects
  - Inconsistent evidence for any one endpoint; exposure measurement error
- For several health outcomes, the causal determination changed from "inadequate", as detailed in the 2008 SO_X ISA, to "suggestive" due to evaluation of a small body of new evidence and refinement of the causal framework with input from CASAC

Charge Questions for Chapter 5

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

- To what extent does this chapter accurately reflect the body of evidence from previous and recent epidemiologic, controlled human exposure and toxicological studies? What are the views of the panel on the integration of this evidence and the relative emphasis placed on each source of evidence?
- Considering the discussion of the strengths and limitations of the evidence in the text and tables within Chapter 5, to what extent is the causal framework appropriately applied to evidence for each of the health effect categories to form causal determinations?
- The conclusions in the draft SO_X ISA regarding the respiratory effects of SO_2 exposure rely heavily on controlled human exposure evidence demonstrating effects of short-term peak exposures. Interpretation of the epidemiologic studies is more complicated due to the longer averaging time used in these studies. Please comment on the extent to which the evidence pertaining to the lowest concentrations associated with effects is appropriately characterized.

At-Risk Populations and Lifestages

- Consistent with the 2008 SO_X ISA, there is **adequate evidence** to conclude that **people with asthma** are at increased risk for SO_2-related respiratory effects
- Evidence is suggestive of increased risk for SO_2-related respiratory effects for children and older adults
- Evidence is inadequate to determine whether other factors result in increased risk, including genetic background, sex, socioeconomic status, race/ethnicity, obesity, cardiovascular disease, and diabetes

Charge Questions for Chapter 6

Chapter 6 evaluates scientific information and presents conclusions on factors that may modify exposure to SO_2, physiological responses to SO_2 exposure, or risk of health effects associated with SO_2 exposure. Consistent with previous ISAs for ozone, lead, and oxides of nitrogen, conclusions on these at-risk factors inform at-risk lifestages and populations.

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

Charge Questions for Executive Summary and Chapter 1

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

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

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