Sulfur Dioxide Substance Summary

Recommendation

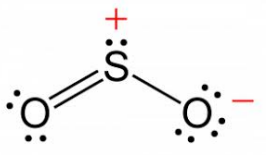
The addition of a 0.4 ppm STEL and elimination of the 2 ppm 8-hour TWA PEL for SO2 are recommended for discussion.

Physical Properties

Substance name: Sulfur dioxide

CAS: 7446-09-5 MW: 64.1

Synonyms: Sulfurous acid anhydride, sulfurous oxide, sulfur oxide

Molecular formula: SO_2 Structural formula: 

Conversion factors at 25 °C and 760 mm/Hg: 1 ppm to 2.62 mg/m^3

GHS Classification

Signal Word: Danger

GHS Hazard Statements:

Physical hazards:	Gases under pressure : Liquefied gas	H280
Health hazards:	Acute toxicity (inhalation:gas) Category 3	H331
	Skin corrosion/irritation, Category 1B	H314
	Serious eye damage/eye irritation, Category 1	H318

Physical characteristics at room temperature:

Colorless gas with a characteristic, irritating, pungent odor. [Note: A liquid below 14°F. Shipped as a liquefied compressed gas.]

Flammability and other hazards: not flammable, Vapor pressure 3.2 atm.

Upper Explosive Limit: NA Lower Explosive Limit: NA

Uses & Applications

Sulfur dioxide is an important commercial chemical. It is used to make sulfuric acid and in industries such as paper production, food production and farming, waste water treatment, and metal and oil refining. It is a refrigerant and is formed when materials containing sulfur are burned. Sulfur dioxide is used as a fungicide and acaricide on grapes.

Occupational Exposure Limits (OELs) and Other Recommendations

Table 1: Occupational Exposure Limits and Other Recommendations

Source and Date	OEL	Basis	Discussion and Assessment
Cal/OSHA Title 8	8-hr TWA PEL 2 ppm**;** STEL 5 ppm		
Fed-OSHA	8-hr TWA PEL 5 ppm		
NIOSH REL	8-hr TWA 2 ppm; STEL 5 ppm; IDLH 1600 ppm	Respiratory effects	
ACGIH TLV (2008)	8-hr TWA NA; STEL 0.25 ppm	Bronchoconstriction in asthmatics under exercise at 0.4 and 0.5 ppm but not 0.25 ppm.	A TLV-STEL of 0.25 ppm will prevent bronchoconstriction in most asthmatic individuals including during exercise.
MAK (DFG)	8-hr TWA: 1 ppm; ceiling: 1 ppm	Hypersensitivity to bronchoconstriction	Based on a 20% FEV reduction at 40 L/min, percent of workers developing bronchoconstriction at 21 L/min at 1 ml/m^3 (ppm) would be below 2%.
SCOEL (2009)	8-hr TWA 0.5 ppm; STEL 1 ppm	Irritation, chronic bronchitis	TWA intended to prevent chronic irritation (bronchitis) and increased susceptibility to airway infections. Acknowledged that asthmatic workers at higher risk.

Table 2: Other Organizational Sources Recommendations

Source and Date	Findings/ Recommendations	Basis/Source/Ref	Discussion and Assessment
OEHHA (2011)	Developmental toxicity; acute REL 0.25 ppm	OEHHA's Developmental And Reproductive Toxicity (DART) committee - State's Qualified Experts mechanism (OEHHA, 2011); acute REL based on respiratory irritation (OEHHA, 1999).	(i) adverse effects on male reproductive system such as decreased sperm quality and fecundability in humans; increased frequencies of chromosomal damage in lymphocytes of exposed workers; and adverse birth outcome among families of exposed workers; (ii) adverse effects in testes including DNA damage in male animals; (iii) decreased odds of live birth in humans; and (iv) alteration in estrous cycle, changes in pregnancy frequency and duration, and changes in offspring growth in female animals. Included under State of California-proposition 65 list as known to the state to cause reproductive toxicity.
US EPA (2017)	Respiratory effects; reproductive and developmental effects; cancer	Respiratory effects-strong causal relationship for short-term and suggestive causal relationship for long-term exposure.	Respiratory effects - bronchoconstriction (decreased lung function and increased respiratory symptoms) in exercising individuals with asthma in controlled human studies for short term exposure and in recent epidemiologic and animal toxicological studies for long-term exposure; Reproductive and developmental toxicity - some uncertainties and Little coherence or consistency among the epidemiologic and toxicological studies; Cancer - inconsistent evidence from epidemiologic and toxicological studies as well as from mode of action for genotoxicity.
NTP	-	-	-
ATSDR (1998)	Respiratory effects; some evidence of	Respiratory effects - bronchoconstriction in exercising	Association between high exposure levels in air and adverse effects on sperm in adult males; reduction in

Source and Date	Findings/ Recommendations	Basis/Source/Ref	Discussion and Assessment
	reproductive and developmental effects; and cancer.	asthmatics and in experimental animals; reproductive and developmental effects - some evidence in humans and animals; decreased infant birth weight; cancer - genotoxic effects and increase in lung cancer risk (ATSDR, 1998).	birth weight of newborn by an exposed pregnant women; increase in chromosomal aberrations and sister chromatid exchanges in exposed workers; some evidence of elevated risk of lung cancer in exposed workers and in experimental animals.
IARC (1992)	Not classifiable as to its carcinogenicity to humans (Group 3).	Inadequate evidence for the carcinogenicity in humans and limited evidence for the carcinogenicity in experimental animals (IARC, 1992).	No independent effect of sulfur dioxide seen in several cohort studies of copper smelters; no excess risk of lung cancer in a case-control study; one animal study showed significant increase in lung tumor incidence. Evaluated as Group 3.

ATSDR (1998). Toxicological profile for sulfur dioxide. US Department of Public Health – Agency for Toxic Substances and Disease Registry. https://www.atsdr.cdc.gov/toxprofiles/tp116.pdf

IARC (1992). Sulfur dioxide and some sulfites, bisulfites and metasulfites. IARC monographs on the evaluation of carcinogenic risks to humans. Vol 54. https://monographs.iarc.fr/wp-content/uploads/2018/06/mono54-7.pdf

OEHHA (2011). Evidence on the developmental and reproductive toxicity of sulfur dioxide https://oehha.ca.gov/media/downloads/proposition-65/chemicals/so2hid022511.pdf

OEHHA (1999). Acute REL. https://oehha.ca.gov/chemicals/sulfur-dioxide

U.S. EPA (2017). Integrated Science Assessment (ISA) for Sulfur Oxides – Health Criteria (Final). U.S. Environmental Protection Agency, Washington, DC, EPA/600/R-17/451. https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=338596

Health Effects

This review of health effects of sulfur dioxide relies on the summary conclusions of the Integrated Science Assessment for Sulfur Oxides – Health Criteria (USEPA, ISA 2017). ISA 2017 provides a concise review, synthesis, and evaluation of the most policy-relevant science to serve as a scientific foundation for the review of the National Ambient Air Quality Standard for Sulfur Dioxide. The ISA was initiated in 2015 with a literature review since the publication of the ISA 2008 and studies selected for inclusion in the new review. After study selection, the quality of individual studies was evaluated by U.S. EPA or outside experts in the fields of atmospheric science, exposure assessment, dosimetry, animal toxicology, controlled human exposure, epidemiology, biogeochemistry, terrestrial and aquatic ecology, and other welfare effects. Factors considered were the design, methods, conduct, and documentation of each study.

In ISA 2017, the U.S. EPA assessed the body of relevant literature, building upon evidence available during previous NAAQS reviews, to draw conclusions on the causal relationships between relevant SO_2 exposures and health effects. 1526 publications were selected for review and 999 publications were considered in ISA 2017. Once selected, EPA used a five-level hierarchy that classified the weight of evidence for causation. This weight-of-evidence evaluation is based on the integration of findings from various lines of evidence from across health and environmental effect disciplines that are integrated into a qualitative statement about the overall weight of the evidence and causality. The five descriptors for causal determination are described in Table 3. This standardized language for causality was drawn from sources across the federal government and wider scientific community, especially the U.S. EPA Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005), U.S. Surgeon General's report, The Health Consequences of Smoking (CDC, 2004), and NAS IOM document, Improving the Presumptive Disability Decision-Making Process for Veterans (IOM, 2008), a comprehensive report on evaluating causality.

Table 3: Causation categories from ISA 2017

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 recent concentrations). That is, the pollutant has been shown to result in health effects 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 MOA information). Generally, determination is based on multiple high-quality studies conducted by multiple research groups.
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.
Suggestive of, 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.
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.
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.

The causal determinations for the health effects endpoints associated with SO_2 exposure are presented in Table 4. According to EPA, these casual determinations were "informed by recent findings and whether these recent findings, when integrated with information from ISA 2008, support a change in causal conclusions. Important considerations included: (1) determining whether laboratory studies of humans and animals demonstrate an independent health effect of SO_2 exposure and what the potential underlying biological mechanisms are; (2) determining whether there is consistency in epidemiologic evidence across various methods used to estimate SO_2 exposure; (3) examining epidemiologic studies of the potential influence of factors that could bias associations observed with SO_2 exposure; (4) determining the coherence of findings integrated across controlled human exposure, epidemiologic, and toxicological studies; and (5) making judgments regarding error and uncertainty in the collective body of available studies. The table shows the causal determinations made from the current and ISA 2008 reviews. In its initial draft of ISA 2017 (USEPA 2015), EPA concluded for many of the health categories, the evidence to infer a causal relationship was suggestive but not sufficient. After comments from the Clean Air Scientific Advisory Committee Sulfur Oxides NAAQS Review Panel and public were considered, causal determinations were finalized in Table 4 (USEPA 2017). As can be seen from Table 4, the one change to ISA 2008 assessment is that the evidence for respiratory effects from long-term SO_2 exposure is now suggestive of a causal relationship.

Table 4: Causal determinations for relationships between sulfur dioxide exposure and health effects from the 2008 and 2017 Integrated Science Assessment for sulfur oxides.

Health Effect Category[a] and Exposure Duration[b]	Causal Determination	
	2008 SO_X ISA[c]	2017 SO_X ISA
Respiratory effects—short-term exposure Section 5.2.1, Table 5-21	Causal relationship	Causal relationship
Respiratory effects—long-term exposure Section 5.2.2, Table 5-24	Inadequate to infer a causal relationship	Suggestive of, but not sufficient to infer a causal relationship
Cardiovascular effects—short-term exposure Section 5.3.1, Table 5-34	Inadequate to infer a causal relationship	Inadequate to infer a causal relationship
Cardiovascular effects—long-term exposure Section 5.3.2, Table 5-35	Not included	Inadequate to infer a causal relationship
Reproductive and developmental effects[d] Section 5.4, Table 5-38	Inadequate to infer a causal relationship	Inadequate to infer a causal relationship
Total mortality—short-term exposure Section 5.5.1, Table 5-41	Suggestive of, but not sufficient to infer, a causal relationship	Suggestive of, but not sufficient to infer a causal relationship
Total mortality—long-term exposure Section 5.5.2, Table 5-43	Inadequate to infer a causal relationship	Inadequate to infer a causal relationship
Cancer—long-term exposure Section 5.6, Table 5-44	Inadequate to infer a causal relationship	Inadequate to infer a causal relationship

ISA = Integrated Science Assessment; SO_X = sulfur oxides.

[a]An array of outcomes is evaluated as part of a broad health effect category: physiological measures (e.g., airway responsiveness), clinical outcomes (e.g., hospital admissions), and cause-specific mortality. Total mortality includes all nonaccidental causes of mortality and is informed by findings for the spectrum of morbidity effects (e.g., respiratory, cardiovascular) that can lead to mortality. The sections and tables referenced include a detailed discussion of the evidence that supports the causal determinations and the SO_2 concentrations with which health effects have been associated.

[b]Short-term exposure refers to time periods of minutes up to 1 mo, while long-term exposures are more than 1 mo to yr.

[c]Previous causal determinations taken from the 2008 SO_X ISA (U.S. EPA, 2008d).

[d]Reproductive and developmental effects studies consider a wide range of exposure durations.

For most health effect categories, with the exception of reproductive and developmental effects, effects are evaluated separately for short-term exposures and long-term exposures. Table 5 shows excerpts from the ISA 2017 for specific health outcomes associated with the health category.

Table 5: Health effects summaries for various endpoints from ISA 2017

HEALTH CATEGORY	Evidence Summary
Respiratory Effects, Short Term Exposure	The 2008 ISA concluded that there is a causal relationship between respiratory effects and short-term exposure to SO_2. The rationale for this causal determination was heavily based on evidence from multiple, high-quality controlled human exposure studies demonstrating decreased lung function and increased respiratory symptoms following SO2 exposures of 5−10 minutes in exercising adults with asthma…. Epidemiologic studies comprise most of the recent evidence base, and previous controlled human exposure and animal toxicological studies form the basis for characterizing and integrating evidence across disciplines. Recent epidemiologic evidence supports associations between ambient SO2 concentrations and asthma-related symptoms, hospital admissions, and ED visits, but uncertainties related to exposure measurement error and co-pollutant confounding remain.
Asthma Exacerbation	Controlled human exposure studies provide strong evidence for the effects of SO2 exposure on respiratory symptoms in adults with asthma under increased ventilation conditions. Exposures for 5−10 minutes to 0.2−0.6 ppm SO2 induced respiratory symptoms in exercising individuals with asthma, with the most consistent evidence from exposures to 0.4−0.6 ppm SO_2. Epidemiologic evidence in adults with asthma is weak, but increases in ambient SO_2 concentration are generally associated with increased risk of asthma symptoms in children. Assessing coherence specifically with controlled human exposure studies of adolescents with asthma is difficult because those studies lacked an appropriate control exposure. Limited findings support associations in children and adults with AHR and elevated IgE.
Allergy Exacerbation	Epidemiology studies found little evidence of a relationship between short-term exposure to SO2 and lung function, respiratory symptoms, or physician visits in populations with allergy. Animal studies reported that SO2 exposure enhanced allergic inflammation.
COPD Exacerbation	Across disciplines and outcomes, evidence from previous and recent studies does not clearly support a relationship between short-term SO2 exposure and COPD exacerbation. The evidence base is much smaller than that for asthma exacerbation and mostly comprises epidemiologic studies. Neither the single controlled human exposure study nor the few epidemiologic studies indicate SO2-related lung function changes in adults with COPD, and recent epidemiologic studies mostly reported no association with an array of respiratory symptoms, including sputum changes and dyspnea, which are characteristic of COPD exacerbation. Evidence is similarly inconsistent for association between short-term increases in ambient SO2 concentration and hospital admissions and ED visits for COPD.

HEALTH CATEGORY	Evidence Summary
Respiratory Infection	Recent evidence, which comes from epidemiologic studies, expands on that presented in the 2008 ISA for Sulfur Oxides and provides some, but not entirely consistent, support for an association between ambient SO2 concentrations and respiratory infection. Whereas cross-sectional studies do not consistently link SO2 exposures estimated for school or home to respiratory infections self-reported by children, some evidence points to an association with hospital admission and ED visits. Associations are observed for all respiratory infections combined and bronchiolitis but not pneumonia or otitis media. The lack of multiple studies examining the same respiratory infection outcome complicates the interpretation of the collective body of evidence, specifically because the etiologies of upper and lower respiratory infections are vastly different. ….. Information to assess the biological plausibility of epidemiologic findings is limited. There is some evidence in rodents that SO2 exposures of 0.1−1 ppm alter clearance of particles, but responses to infectious agents have not been examined in relation to ambient-relevant exposures.
Aggregated Respiratory Conditions	Recent studies add to the evidence detailed in the ISA 2008 that indicated a generally positive association between short-term SO2 exposures and respiratory disease hospital admissions and ED visits. These recent studies provide some insight into previously identified limitations (i.e., model specification, lag structure of associations, and potential seasonal differences) in the SO2-respiratory disease hospital admission and ED visits relationship…..Overall, the results of recent studies are limited in that they do not further inform the understanding of potential confounding by copollutants on the relationship between short-term SO2 concentrations and respiratory disease hospital admissions and ED visits.
Summary:	**Strong evidence indicates that there is a causal relationship between short-term SO2 exposure and respiratory effects, particularly for respiratory effects in the at-risk population of individuals with asthma …….**There is limited support for a relationship between short-term SO2 exposure and other respiratory effects, including exacerbation of COPD, allergy exacerbation, respiratory infection, respiratory effects in healthy populations, and respiratory mortality. The limited and inconsistent evidence for these non-asthma-related respiratory effects does not substantially contribute to the causal determination.
Respiratory Effects, Long Term Exposure	The 2008 ISA reviewed the epidemiologic and toxicological evidence for long-term exposure to SO2 and respiratory effects and concluded that the evidence was inadequate to infer a causal relationship. Although some positive associations with asthma prevalence, bronchitis, symptoms, and lung function were observed among children, uncertainties made it difficult at that time to assess the evidence as a whole…… Overall, the collective [2008 and 2017] evidence is strengthened by recent epidemiologic studies reporting increases in asthma incidence among children and findings of animal toxicological studies that provide a pathophysiologic basis for the development of asthma.

HEALTH CATEGORY	Evidence Summary
Development and Severity of Asthma	Recent epidemiologic evidence from a limited number of longitudinal studies report associations between asthma incidence among children and long-term SO2 exposures. Additional supportive evidence for a link between long-term SO2 exposure and the development of asthma is provided by cross-sectional studies of asthma prevalence. The longitudinal studies help reduce the uncertainty associated with the temporality of exposure and response that is inherent in cross-sectional study designs. This evidence is coherent with animal toxicological evidence of inflammation, allergic sensitization and other allergic responses, airway remodeling, and increased airway responsiveness, which are key events (or endpoints) in the proposed mode of action for the development of asthma. The animal toxicological evidence provides support for an independent effect of SO2 and strengthens the link between long-term exposure to SO2 and the development of asthma in children. Additional evidence supportive of this link comes from cross-sectional studies of respiratory symptoms and respiratory allergies among children and from natural experiments. Thus, multiple lines of evidence suggest that long-term SO2 exposure results in a coherent and biologically plausible sequence of events that culminates in the development of asthma, especially allergic asthma, in children.
Development of Allergy	There is some evidence for a potential relationship between long-term SO2 exposure and indicators of respiratory allergies and inflammation among children. Several recent cross-sectional studies examined the prevalence of respiratory allergies using different markers for respiratory allergies including IgE antibodies, rhinitis, eczema, sensitization to pollen, and hay fever related to long-term SO2 exposure…. The cross-sectional design of these studies makes these relationships uncertain with regard to the temporal relationship between exposure and outcome. Further, the exposure estimates from monitors may not adequately characterize the spatial and temporal variation in SO2 concentrations potentially leading to exposure measurement error.
Lung Function	Several studies evaluated the relationship between long-term SO2 exposure and decrements in lung function. Evidence supporting this relationship is limited because associations were inconsistent and because both PM and SO2 were at high concentrations in the same areas, which does not allow determination of individual SO2 effects. Potential confounding of long-term SO2 exposure-related decrements in lung function and lung development by other pollutants, especially PM, was evaluated in only one study. This study found an attenuation of the effect in copollutant analyses. No changes in lung function were found in long-term animal toxicological studies at relevant SO2 concentrations. The recent studies support conclusions made in the ISA 2008 (U.S. EPA, 2008d) that evidence does not strongly support an effect of long-term SO2 exposure on decreases in lung function in children.

HEALTH CATEGORY	Evidence Summary
Respiratory Infection	Evidence for prevalence of infant bronchiolitis and/or respiratory infections consists of generally positive associations found in cross-sectional studies. Thus, they provide a limited evidence base in number and design. While some animal toxicological studies reported alterations in specific host defense mechanisms, there is no evidence to support increases in bacterial or viral infections in animals exposed to SO2 at relevant concentrations
Summary	**Taken together, epidemiologic and animal toxicological studies provide evidence that is suggestive of, but not sufficient to infer, a causal relationship between long-term SO2 exposure and respiratory effects.** The strongest evidence is provided by coherence of findings of epidemiologic studies showing associations between long-term SO2 exposure and increases in asthma incidence among children and findings of animal toxicological studies that provide a pathophysiologic basis for the development of asthma. These latter studies demonstrated that repeated SO2 exposure over several weeks resulted in Th2 polarization (or other Type 2 immune responses) and airway inflammation, key steps in allergic sensitization, in naive newborn animals. In addition, repeated SO2 exposure over several weeks resulted in enhanced airway inflammation and some evidence of airway remodeling and increased airway responsiveness in allergic newborn animals. Toxicological studies involving repeated exposure to SO2 over several days provide additional evidence of these effects. However, because the toxicological evidence in animals is limited, particularly for long-term exposure, some uncertainty remains regarding an independent effect of long-term SO2 exposure on the development of asthma. In addition, potential confounding by other pollutants is unexamined, and largely unavailable, for epidemiologic studies of asthma among children. However, multiple lines of evidence suggest that long-term SO2 exposure results in a coherent and biologically plausible sequence of events that culminates in the development of asthma, especially allergic asthma, in children.
Cardiovascular Effects, Short-Term Exposure	The ISA 2008 found a lack of consistency with regard to short-term exposure to SO2 and markers of heart rate variability (HRV), cardiac repolarization, discharges of implantable cardioverter defibrillators (ICDs), blood pressure (BP), blood markers of cardiovascular disease risk, the triggering of a myocardial infarction, or ED visits or hospital admission for cardiovascular diseases. Recent epidemiologic studies add to the evidence for effects of SO2 exposure on a broader array of cardiovascular effects and mortality. Still, substantial uncertainties remain concerning exposure measurement error, the limited mechanistic evidence to describe a role for SO2 in the initiation of key events in a proposed mode of action, and potential confounding by copollutants.

HEALTH CATEGORY	Evidence Summary
Myocardial Infarction and Ischemic Heart Disease	In summary, while evidence from epidemiologic studies suggests a potential association between ambient SO2 concentrations and rates of hospital admissions or ED visits for MI or ischemic heart diseases in single-pollutant models, these associations may be the result of confounding by other pollutants…..Overall, despite some epidemiologic evidence of an association between short-term exposure to SO2 and hospital admissions and ED visits for ischemic heart disease and MI, uncertainties regarding copollutant confounding continue to impede the determination of an independent SO2 effect.
Cerebrovascular Diseases and Stroke	In summary, studies of patients with implantable cardioverter defibrillators, hospital admissions for arrhythmias, and out-of-hospital cardiac arrests do not provide evidence to support the presence of an association between ambient SO2 concentrations and arrhythmias. Most of these studies have been focused on other pollutants and, therefore, have not explored whether such an association might exist in certain subgroups.… One toxicological study also found no evidence for arrhythmias following short-term SO2 exposure. Overall, findings for the association between SO2 and cerebrovascular diseases continue to be inconsistent across studies. As for other outcomes, associations reported from single pollutant models in some locations may be at least partly due to confounding by other pollutants
Blood Pressure and Hypertension	In summary, epidemiologic studies evaluating the association between ambient SO2 concentrations and blood pressure remain inconsistent with most relying on fixed-site monitors and few examining the potential for copollutant confounding. Experimental studies provide no additional evidence for SO2-induced changes in blood pressure. The most informative studies to date found no evidence of within-person changes in blood pressure despite relatively large changes in SO2 concentrations during the Beijing Olympics. Experimental studies do not demonstrate effects of SO2 on blood pressure. As such, the current evidence does not support the presence of an association between ambient SO2 and blood pressure.
Aggregated Cardiovascular Disease	Overall, consistent associations between ambient SO2 concentrations and rates of hospital admissions or ED visits for all cardiovascular diseases have been observed. Although associations are evident in single-pollutant models in many locations, there was limited assessment of potential copollutant confounding. Therefore, this association may at least partly be the result of confounding by correlated pollutants. Additionally, most studies examined 24-h avg exposure metrics for SO2, which may not adequately capture the spatial and temporal variability in SO2 concentrations.

HEALTH CATEGORY	Evidence Summary
Summary	Overall, the available evidence is inadequate to infer a causal relationship between short-term exposure to SO2 and cardiovascular health effects. Multiple epidemiologic studies report positive associations between short-term ambient SO2 concentrations and cardiovascular outcomes, such as cardiovascular mortality, myocardial infarction and ischemic heart disease, and aggregated cardiovascular outcomes; however, substantial uncertainties remain regarding exposure measurement error and copollutant confounding. ... Controlled human exposure studies demonstrated the potential for SO2 exposure to exert an effect on the autonomic nervous system but there was a lack of supporting animal toxicological data. The available animal toxicological studies did not report effects on HR, HRV, arrhythmia, or blood pressure following short-term SO2 exposures. In addition, limited and inconsistent mechanistic evidence, including evidence pertaining to key events in a proposed mode of action, offered only limited insight for the role of SO2 in the triggering of cardiovascular diseases. Although multiple recent epidemiologic studies add to the evidence available for the current review, the additional studies do not substantially reduce uncertainties related to copollutant confounding. Moreover, there continues to be a limited experimental evidence to provide biological plausibility to strengthen the inference of causality for SO2-related cardiovascular effects.
Cardiovascular Effects, Long-Term Exposure	The 2008 ISA for Sulfur Oxides included one epidemiologic study, which reported an increased risk of cardiovascular events in association with long-term exposure to SO2…. No new toxicological studies in humans or animals have been published since the 2008 ISA for Sulfur Oxides. Overall, the biological plausibility and independence of the SO2 effect observed in epidemiologic studies remains an important uncertainty.
Myocardial Infarction and Ischemic Heart Disease	Overall, these epidemiologic data do not provide support for an association of long-term SO2 exposure with IHD or more broadly defined categories of cardiovascular disease. There is uncertainty related the independent effect of SO2 on the cardiovascular system. Further, the exposure assessment techniques applied in the studies were subject to varying degrees of error depending on the method. Uncharacterized spatial variability in the exposure estimate has the potential to bias the health effect estimate.
Cerebrovascular Diseases and Stroke	In summary, the epidemiologic studies do not provide evidence to support an effect of long-term SO2 exposure on stroke morbidity. Findings are not generally consistent across studies and there are uncertainties related to the potential for exposure measurement error and confounding by co-pollutants
Arrhythmias and Cardiac Arrest	The ISA 2008 for Sulfur Oxides (U.S. EPA, 2008d) concluded that the evidence available at the time did not suggest that SO2 has an effect on cardiac arrhythmias. There continues to be essentially no epidemiologic or toxicological evidence suggestive of such a relationship. One animal toxicological study evaluated arrhythmia frequency in rats following short-term SO2 exposure and reported no significant changes in spontaneous arrhythmias (irregular, delayed, or premature beats).
Summary	Overall, the evidence is inadequate to infer a causal relationship between long-term exposure to SO2 and cardiovascular health effects.

HEALTH CATEGORY	Evidence Summary
Reproductive and Developmental Effects	The ISA 2008 concluded the evidence was inadequate to infer a causal relationship with reproductive and developmental effects. Epidemiologic studies included in the ISA 2008 examined impacts on reproductive outcomes including preterm birth, birth weight, intra-uterine growth retardation, birth defects, infant mortality, and neonatal respiratory hospitalizations. While positive associations were observed in the previous ISA 2008, there was little biologic plausibility for these associations provided by supporting toxicological literature. Interpretation of those results was also limited by the lack of control for potential confounding by copollutants, the small number of studies, and uncertainty regarding exposure. Overall, the number of studies examining associations between exposure to ambient SO2 and reproductive and developmental outcomes has increased substantially since publication of the ISA 2008, yet evidence for an association with individual outcomes remains relatively limited and key uncertainties have not been reduced.
Fertility, reproduction, and pregnancy	While studies of fertility, reproduction, and pregnancy are limited in number, generally, SO2 exposures appear to have no association with these outcomes. A group of studies examining hypertensive disorders during pregnancy report inconsistent results, with the majority observing no association with SO2 exposure
Fetal Growth	In summary, there is inconsistent evidence for increased odds of fetal growth restriction with exposure to SO2 during pregnancy, and the evidence lacks consistency in fetal growth definition/metric and in exposure timing. No recent animal studies evaluating fetal growth were identified. Studies examining the association between SO2 and fetal growth can be found in ISA 2008.
Preterm weight	In summary, there is some evidence for an association between exposure to SO2 and preterm birth particularly with near-birth exposure windows. Studies examining PTB primarily used average daily SO2. The one study that examined 1-h max SO2 found no associations for PTB. Recent studies do not provide evidence to help reduce uncertainty related to exposure measurement error, copollutant confounding, or the biological mechanism by which SO2 could cause preterm birth. No recent animal studies evaluating preterm birth were identified.
Birth weight	In summary, there is some evidence that LBW may be associated with SO2, while evidence for an association with change in birth weight is inconsistent. Overall, the results of studies of LBW and birth weight remain inconsistent and these do not provide evidence to help reduce uncertainty related to exposure measurement error, copollutant confounding, or the biological mechanism by which SO2 could cause these effects.
Fetal Mortality	In summary, although few in number, studies of fetal mortality and SO2 show elevated associations for both short- and long-term exposures. However, these studies are limited by the uncertainties associated reproductive and developmental outcomes identified in the 2008 SOX ISA. No recent animal studies evaluating fetal mortality were identified.

HEALTH CATEGORY	Evidence Summary
Developmental	There is some evidence for an association between gestational and early life exposure to SO2 and respiratory health effects that extend into early childhood, although evidence is limited and exposure windows are uncertain.
Other Developmental Effects	Studies examining other developmental exposures are limited in number.
Summary	Overall the evidence is inadequate to infer a causal relationship between exposure to SO2 and reproductive and developmental outcomes. There are several well-designed, well-conducted epidemiologic studies, many described in papers published since the previous ISA, that indicate an association between SO2 and reproductive and developmental health outcomes; the bulk of the evidence exists for adverse birth outcomes. For example, several high quality studies reported positive associations between SO2 exposures during pregnancy and fetal growth metrics. However, the evidence is not entirely consistent, and has not substantially reduced any of the uncertainties connected with the associations observed between exposure to SO2 and birth outcomes that were identified in the previous ISA…. There is insufficient information on potential modes of action of SO2 on reproductive outcomes at relevant exposure levels for this ISA… Overall, many uncertainties remain when evaluating the evidence for these health endpoints; therefore, the evidence is inadequate to infer a causal relationship between exposure to SO2 and reproductive and developmental outcomes.
Mortality, Short-Term Exposure	The ISA 2008 concluded that the collective evidence is "suggestive of a causal relationship" between short-term SO2 exposure and mortality. Overall, the number of studies that examined the relationship between short-term SO2 exposure and mortality was sparse and there was limited data available to inform the potential for copollutant confounding. Since the completion of the ISA 2008, epidemiologic literature that has examined the association between short-term SO2 exposure and mortality has expanded. However, similar to the collection of studies evaluated in the ISA 2008, most of the recent studies do not focus specifically on the SO2-mortality relationship but instead on PM or O_3. Recent multicity studies evaluated since the completion of the ISA 2008 continue to provide consistent evidence of positive associations between short-term SO2 exposures and total mortality.
Summary	Although the body of evidence is larger, key uncertainties and data gaps still remain, which contribute to the conclusion that the evidence for short-term SO_2 exposures and total mortality is suggestive of, but not sufficient to infer, a causal relationship… However, questions remain regarding whether SO_2 has an independent effect on mortality, which can be attributed to: (1) the limited number of studies that examined potential copollutant confounding, (2) the relative lack of copollutant analyses with PM2.5, (3) and the evidence indicating attenuation of SO_2-mortality associations in copollutant models with NO_2 and PM_{10}.

HEALTH CATEGORY	Evidence Summary
Mortality, Long-Term Exposure	In past reviews, a limited number of epidemiologic studies assessed the relationship between long-term exposure to SO2 and mortality in adults. The ISA 2008 concluded that the scarce amount of evidence was "inadequate to infer a causal relationship" (U.S. EPA, 2008d. …. Consistent with the conclusion of the ISA 2008, the collective evidence informing the association between long-term SO2 exposure and mortality continues to be limited. Despite the improved consistency of the associations between long-term exposure to SO2 and both respiratory and total mortality with the inclusion of recent cohort studies, these studies do not address uncertainties identified in the ISA 2008.
Summary	The majority of the limited evidence informing the association between long-term exposure to SO2 and mortality from U.S. cohort studies was included in the 2008 SOX ISA. A recent cohort study of male truck drivers provided some additional evidence for an association between long-term exposure to SO2 and both respiratory mortality and total mortality, while updates to the ACS and Veterans cohort studies provides some limited evidence for an association with total mortality, although none of these recent studies help to resolve the uncertainties identified in the ISA 2008 related to copollutant confounding or the geographic scale of the analysis.
Cancer	Similar to studies of SO2 concentrations and lung cancer in the previous ISA, recent studies of SO2 concentrations and lung cancer have provided inconsistent results with two of the largest studies reporting null results. Studies of bladder cancer appear to find no association between SO2 concentrations and bladder cancer incidence but a study of SO2 concentration and bladder cancer mortality reported a positive association. Limited information is available regarding other cancers. Animal toxicology models of SO2 inhalation exposure show SO2 acting as a promoter or cocarcinogen, with one study showing increased lung tumor formation in a lung tumor-prone animal model.
Summary	The overall evidence for long-term SO2 exposure and cancer is inadequate to infer a causal relationship. This conclusion is based on the inconsistent evidence from epidemiologic studies, as well as mixed evidence within the animal toxicology and mode of action framework for mutagenesis and genotoxicity.

Integrated Science Assessment (ISA) For Sulfur Oxides – Health Criteria (Final)

ISA 2017 found that the scientific evidence only supports a causal relationship for SO2 and short-term respiratory effects. This finding is based largely on controlled human studies that were the basis for this finding in ISA 2008. New studies since ISA 2008 are suggestive of a relationship between SO2 and long-term respiratory effects are largely longitudinal epidemiological studies of asthma in children and adolescents. The evidence from longitudinal studies is coherent with animal toxicological evidence of allergic sensitization, airway remodeling, and increased airway responsiveness, which are key events (or endpoints) in the proposed mode of action for the development of asthma. However, the epidemiologic studies of asthma development in children have not clearly characterized potential confounding by other pollutants or mixtures of pollutants. This uncertainty was present in the previous review, and there is no new information from incidence studies to help reduce this uncertainty. The uncertainties in the epidemiologic evidence base is

reduced, in part, by the biological plausibility provided by findings from experimental studies that demonstrate SO2-induced effects on key events or endpoints that are part of the proposed mode of action for the development of asthma [i.e., allergic sensitization, airway remodeling and increased airway responsiveness]. However, because the toxicological evidence in animals is limited, particularly for long-term exposure, some uncertainty remains regarding an independent effect of long-term SO2 exposure on the development of asthma. As such, ISA 2017 concluded that epidemiologic and animal toxicological studies provide evidence that is suggestive of, but not sufficient to infer, a causal relationship between long-term SO2 exposure and respiratory effects. The strongest evidence is provided by coherence of findings of epidemiologic studies showing associations between long-term SO2 exposure and increases in asthma incidence among children and findings of animal toxicological studies that provide a pathophysiologic basis for the development of asthma.

To augment the 2017 ISO assessment, a limited review of recent SO2 publications was conducted (Table 6). This review was restricted to animal toxicological studies to address a principal information deficiency cited in ISO 2017. This is not a comprehensive literature survey but does provide some insight into possible mechanisms of SO2 toxicity. The studies are categorized into four health effects. A common observation throughout these studies is a dose-response relationship between multiple proinflammatory markers and toxic responses in tissues throughout the body such as a decline in membrane structure, apoptosis, and signaling pathways. These and other studies suggest that these toxic responses from SO2 are a consequence of oxidative stress well known to occur with SO2 intake. A LOAEL or NOAEL is identified for each study, however these studies were generally not conducted with dose ranges or sample sizes sufficient for hazard assessment.

Table 6: Recent animal studies of sulfur dioxide

Effect, Author, & Year	Exposure	Results	Conclusions
Reproductive			
Zhang, 2016	24 male Wister rates exposed to 15 ppm SO2, 4 hrs/day	No significant increase in BW between treated and control but BW increase in SO2-trreated rates was slower than controls over 8 weeks; after 8 weeks, mean percentage of testis weight to body weight (g/g) in treated rats significantly greater than controls ($p<0.05$, 1% vs. 0.9%).	LOAEL: 15 ppm. The changes in the testis and in serum testosterone may be one of the pathways that lead to low sperm motility of male rats.

Effect, Author, & Year	Exposure	Results	Conclusions
Zhang, 2016	8-week old Kumning Mice were exposed 12 per group to 5 ppm SO_2 for 3 hrs/day for 8 weeks.	Body weight, spermatozoa count and malformation percentage and blood-testis barrier (BTB) assessed by QRT-PCR and western blot analysis. No effect on body weight or body weight gain. Sperm count ($p<0.01$) and malformation ratio ($p<0.001$) significantly less than control. mRNA levels of only 1 of ten BTB proteins was significantly less than controls ($p <0.05$) whereas 5 of 10 BTB proteins showed reduced expression by western blot analysis.	LOAEL: 3 ppm. Sperm count and testis histology affected significantly by SO_2. Authors concluded that histological results showed that SO_2 loosened the normal array of spermatogenic cells and increased the gap within seminiferous tubules.
Li, 2018	10 C57BL/6 mice exposed for 6 hrs/day for 30 days to 1.75 ppm SO2.	Sperm count, malformation and morphology significantly different from controls ($P < 0.05$). SO2 caused a significant increase in apoptosis index in the testes of mice ($P < 0.01$) compared to controls. Markers of oxidative damage were significantly higher in SO2 group compared to controls ($p < 0.05$).	LOAEL: 1.75 ppm. Resuslts suggest that SO2 effects male reproduction by inducing testicular ROS generation, promoting spermatogenic cell apoptosis, and possibly inhibiting testosterone synthesis/secretion.
Neurological			
Sang, 2009	Male Wistar rats (10 per group) exposed to 0, 5, 10 and 20 ppm SO2 for 6 hrs/day for 7 days.	Hippocampal DNA-protein cross links and protein carbonyl levels were elevated significantly above controls in the mid and high-level SO2 exposed group ($p < 0.05 – 0.001$). Mid and high level SO2-exposed groups had significantly higher caspase-3 activity and TUNEL staining than controls ($p < 0.05 – 0.001$).	NOAEL: 5 ppm. Oxidative stress (as assessed by PCO content) in the hippocampus increased in a dose-dependent manner. Increased caspase-3 activity and the number of immunostaining neurons suggest that SO2 resulted in apoptosis in the hippocampus. The authors suggested that the accumulation of carbonyl in the hippocampus indicated that free radicals formed from SO2 exceeded the defensive capacity of the antioxidant system.

Effect, Author, & Year	Exposure	Results	Conclusions
Sang, 2010	Three groups were exposed to 2.5, 5, and 10 ppm SO2 for 6 hrs/day for 7 days.	Vasoconstrictive protein (ET-1) mRNA and protein expression in rat cortex increased significantly after SO2 exposure: 1.64-, 3.72-, and 6.27-fold of control at 2.5, 5 and 10 ppm, respectively ($p < 0.05$, $n = 6$). Pro-inflammatory enzyme (iNOS and COX-2) mRNA and protein expression in rat cortex increased significantly at 5 and 10 ppm SO2. Adhesion molecules (ICAM-1) mRNA and protein expression increased significantly at 2.5, 5 and 10 ppm ($p < 0.05$, 0.01). Similar significant increases were observed in a rat ischemic stroke model after 6 h/day 2 week exposure to 2.5, 5 and 10 ppm.	LOAEL: vasoconstriction 2.5 ppm; inflammation 5.0 ppm. ET-1 concentration in the cerebrospinal fluid was elevated in stroke patients (Chen et al., 2001). In the present study, the upregulation of ET-1 expression in rat cortex suggests the reduction of cerebral blood and a tendency to ischemic injuries via endothelial dysfunction following SO2 inhalation.
Yao 2015	Male Wistar rats (20 per group). Exposed to 1.3 and 2.7 ppm SO2 for 6 hrs/d for 90 days, respectively.	Hippocampus analyzed for expression of memory related kinases and inflammatory markers. For memory kinases, no significant difference was observed in total CaMKIIα expression, while PKA, PKC and p-CaMKIIα protein expression, was significantly reduced at 7 mg/m3 compared to control. mRNA level and protein expression of the proinflammatory cytokines TNF-α, IL-1β and IL-6 were significantly higher in both SO2 groups compared to controls ($p<0.05$, $P<0.01$).	LOAEL: 1.3 ppm. Attenuated PKA, PKC and CaMKII activation and increased inflammatory cytokine release were observed. These inflam-matory signals could disrupt the synaptic signaling and lead to prolonged aberrant transmission between hippo-campal synapses resulting in synaptic dysfunction and impairment of spatial learning and memory.
Wang, 2017	SO2 in ambient air (15 ppm SO2, 3 hrs/day).	Compared with the control group, brain histological structures were damaged in all exposed group. The ratio of tailing and tail length in brain cells from exposed groups as determined by the COMET assay were significantly greater than controls ($P < 0.01$).	LOAEL: 15 ppm. The possible mechanism involved may be the cation of modified cytosines to form uracil.
Pulmonary			

Effect, Author, & Year	Exposure	Results	Conclusions
Qin, 2016	Groups of male rats (n=6) exposed to 0, 1.33 ± 0.15, 2.70 ± 0.43, and 5.43 ± 0.79 ppm SO_2 for 4 hrs/d for 30 days.	Histopathology indicated mitochondrial damage occurred in cardiac myocytes in a dose-dependent manner. These structural changes correlated with loss of mitochondrial function as the COX activity, ΔΨm, and ATP content were dramatically decreased in dose-dependent manner in rat hearts. With the exception of ATP content at the lowest dose, all parameters were statistically lower than controls at every dose (*P < .05, **P < .01, ***P < .001). Mitochondrial DNA content and RNA levels associated with protein expression were all statistically lower than controls (*P < .05, **P < .01, ***P < .001) though not in a dose-dependent manner.	LOAEL: 1.33 ppm. These results demonstrated that long term low-dose exposure to SO_2 promoted the damage of mitochondria structure in cardiac myocytes.
Developmental			
Woerman, 2013.	Pregnant Sprague–Dawley dams and their pups were exposed to 5 ppm SO_2 for 1 h daily throughout gestation and 6 days postnatal.	In Vivo: no significant difference in litter size or weight. HR, recorded from unanaesthetized and unrestrained pups, was significantly elevated (P < 0.05) following SO_2 exposure (424 ± 9 b.p.m.; n = 10) compared with control animals (374 ± 12 b.p.m.; n = 11), an increase of 13.4%. Reflex control of HR in SO2-treated rats was less than half of that of controls (p< 0.05). In Vitro: SO2 had no effect on inhibitory neurotransmission to Cardiac Vagal Nerves (CVN) but significantly reduced glutamatergic EPSC frequency. Spontaneous glutamatergic EPSCs were significantly (P < 0.05) diminished in SO_2-exposed animals (2.1 ± 0.3 Hz, n = 11 animals) compared with control (4.3 ± 0.8 Hz, n = 5 animals) pups, a decrease of 51.2%.	LOAEL: 5 ppm. Perinatal exposure to SO_2 increased baseline HR, in combination with reduced reflex control. This indicates the site of action of SO_2 exposure is likely on excitatory glutamatergic neurons and pathways prior to CVNs in the brainstem cardiorespiratory network. Authors suggest loss of excitatory neurotransmission to CVNs would be responsible for a withdrawal of parasympathetic cardio-inhibitory vagal activity to the heart, resulting in an elevated basal HR, both of which were present in *in vivo* recordings from treated pups.

Recommendation

Addition of a new 0.4 ppm STEL and elimination of the 2 ppm - 8-hr TWA PEL are recommended for discussion.

SO_2 exposure has been demonstrated to induce clinical features of asthma exacerbation, including decreased lung function [e.g., decreased forced expiratory volume in 1 sec (FEV_1) or increased specific airway resistance (sRaw)], and increased symptoms (e.g., wheezing, cough, shortness of breath), as well as some subclinical effects such as inflammation. In a recent review of the health effects of SO_2 (ISA 2017) an increase in sRaw of 100% or a decrease in FEV_1 of 15% were considered to constitute a moderate or greater decrement in lung function for a majority of asthmatics. In general, bronchoconstriction to this level (+100% sRaw; -15% FEV) is commonly seen in experimental studies at ventilation rates of approximately 40 L/min with the percent of asthmatics responding dependent on the concentration of SO_2. As shown in Table 7, this respiratory decrement can be seen in some asthmatics at concentrations as low as 0.2 ppm. Table 7 also shows that the percent of asthmatics responding increases with concentration and in some individuals the respiratory decrement is substantially higher (> +100% sRaw and -15% FEV1).

Table 7: Percentage of adults with asthma in controlled human exposure studies experiencing sulfur dioxide-induced decrements in lung function and respiratory symptoms (Table 5.2 from ISA 2017)

SO_2 Conc (ppm)	Exposure Duration (min)	n	Ventil-ation (L/min)	Cumulative Percentage of Subjects (Number of Subjects)[a] ↑sRaw / ↓ FEV_1	≥100% / ≥15%	≥200% / ≥20%	≥300% / ≥30%	Study	Respiratory Symptoms: Supporting Studies
0.2	5	23	~48	sRaw	9% (2)[b]	0	0	Linn et al. (1983b)	Limited evidence of SO_2-induced increases in respiratory symptoms in some people with asthma: (Linn et al. (1990); Linn et al. (1988); Linn et al. (1987); Schachter et al. (1984); Linn et al. (1983b))
	10	40	~40	sRaw	7.5% (3)[c]	2.5% (1)[c]	0[c]	Linn et al. (1987)[c]	
	10	40	~40	FEV_1	9% (3.5)[c]	2.5% (1)[c]	1% (0.5)[c]	Linn et al. (1987)[c]	
0.25	5	19	~50–60	sRaw	32% (6)	16% (3)	0	Bethel et al. (1985)	
	5	9	~80–90	sRaw	22% (2)	0	0	Bethel et al. (1985)	
	10	28	~40	sRaw	4% (1)	0	0	Roger et al. (1985)	
0.3	10	20	~50	sRaw	10% (2)	5% (1)	5% (1)	Linn et al. (1988)[d]	
	10	21	~50	sRaw	33% (7)	10% (2)	0	Linn et al. (1990)[d]	
	10	20	~50	FEV_1	15% (3)	0	0	Linn et al. (1988)	
	10	21	~50	FEV_1	24% (5)	14% (3)	10% (2)	Linn et al. (1990)	
0.4	5	23	~48	sRaw	13% (3)	4% (1)	0	Linn et al. (1983b)	Stronger evidence with some statistically significant increases in respiratory symptoms: Balmes et al. (1987)[f], Gong et al. (1995) (Linn et al. (1987); Linn et al. (1983b)) Roger et al. (1985)
	10	40	~40	sRaw	24% (9.5)[c]	9% (3.5)[c]	4% (1.5)[c]	Linn et al. (1987)[c]	
	10	40	~40	FEV_1	27.5% (11)[c]	17.5% (7)[c]	10% (4)[c]	Linn et al. (1987)[c]	
0.5	5	10	~50–60	sRaw	60% (6)	40% (4)	20% (2)	Bethel et al. (1983)	
	10	28	~40	sRaw	18% (5)	4% (1)	4% (1)	Roger et al. (1985)	
	10	45	~30	sRaw	36% (16)	16% (7)	13% (6)	Magnussen et al. (1990)[f]	
0.6	5	23	~48	sRaw	39% (9)	26% (6)	17% (4)	Linn et al. (1983b)	
	10	40	~40	sRaw	34% (13.5)[c]	24% (9.5)[c]	19% (7.5)[c]	Linn et al. (1987)[c]	
	10	20	~50	sRaw	60% (12)	35% (7)	10% (2)	Linn et al. (1988)	
	10	21	~50	sRaw	62% (13)	29% (6)	14% (3)	Linn et al. (1990)	
	10	40	~40	FEV_1	47.5% (19)[c]	39% (15.5)[c]	17.5% (7)[c]	Linn et al. (1987)[c]	
	10	20	~50	FEV_1	55% (11)	55% (11)	5% (1)	Linn et al. (1988)	
	10	21	~50	FEV_1	43% (9)	38% (8)	14% (3)	Linn et al. (1990)	

1.0	10	28	~40	sRaw	50% (14)	25% (7)	14% (4)	Roger et al. (1985)[e]	Clear and consistent increases in SO_2-induced respiratory symptoms: (Linn et al. (1990); Linn et al. (1988); Linn et al. (1987); Linn et al. (1983b)), Gong et al. (1995), Horstman et al. (1988)
	10	10	~40	sRaw	60% (6)	20% (2)	0	Kehrl et al. (1987)	

Conc = concentration; FEV_1 = forced expiratory volume in 1 sec; n = sample size; sRaw = specific airway resistance; SO_2 = sulfur dioxide.

[a]Data presented from all references from which individual data were available. Percentage of individuals who experienced greater than or equal to a 100, 200, or 300% increase in specific airway resistance, or a 15, 20, or 30% decrease in FEV_1. Lung function decrements are adjusted for the effects of exercise in clean air (calculated as the difference between the percent change relative to baseline with exercise/SO_2 and the percent change relative to baseline with exercise/clean air).

[b]Numbers in parenthesis represent the number of subjects experiencing the indicated effect.

[c]Responses of people with mild and moderate asthma reported in Linn et al. (1987) have been combined. Data are the average of the first- and second-round exposure responses following the first 10 min period of exercise. In some cases, the average had a first decimal place value of 5, which is reported in the table to avoid a high bias in values due to rounding. **In all other cases, the calculated percentages were rounded to the nearest integer.**

[d]Analysis includes data from only people with mild (Linn et al., 1988) and moderate (Linn et al., 1990) asthma who were not receiving supplemental medication.

[e]One subject was not exposed to 1 ppm due to excessive wheezing and chest tightness experienced at 0.5 ppm. For this subject, the values used for 0.5 ppm were also used for 1.0 ppm under the assumption that the response at 1.0 ppm would be equal to or greater than the response at 0.5 ppm.

[f]Indicates studies in which exposures were conducted using a mouthpiece rather than a chamber.

The respiratory decrement in the controlled human studies with SO_2 was frequently accompanied by respiratory symptoms following exposures of 5−10 minutes, with elevated ventilation rates at concentrations of 0.4−0.6 ppm. A fraction of the population in these studies (~5−30%) was also observed to have decrements in lung function at lower SO_2 concentrations (0.2−0.3 ppm). Although the degree of lung function decrements (> +100% sRaw and -15% FEV1) are considered moderate, they were less likely to be accompanied by respiratory symptoms at these lower concentrations (ISA 2017). To evaluate whether the respiratory decrement in this population was significantly different from controls, a statistical analysis of a subset of the ISA 2017 studies was performed (Johns, 2010). The subset of studies was from a research group that conducted several of the human volunteer studies (Linn et al., 1983, 1987, 1988, 1990; Roger et al., 1985). Though a smaller group of measures, this analysis does reduce some uncertainty through the use of the same exposure protocol (chamber), individual subject responses, and similar breathing rates (40-50 L/min).

In this analysis, the concentration-respiratory response relationship was evaluated using all available individual subject lung function data from studies wherein mild and moderate asthmatics were exposed for 5-10 min to multiple SO_2 concentrations during exercise with unencumbered breathing. For each study evaluated, subjects were classified as responders or non-responders based on the magnitude of SO_2-induced increase in sRaw and decrease in FEV_1 experienced at the highest exposure concentration (0.6 or 1.0 ppm SO_2). By categorizing the subjects this way, overall mean variance for each group is minimized as the subjects are divided into two groups based on SO_2 sensitivity. Statistical comparisons were made between multiple concentrations: five concentrations for responders and non-responders for sRaw, and three concentrations for responders and non-responders for FEV1. The comparisons are between the mean increase in SRaw from breathing clean air and from breathing the SO_2 concentrations. Taking into account multiple comparisons using

the Bonferroni procedure, the critical alpha levels for sRaw and FEV1 are therefore 0.05/10 (= 0.005) and 0.05/6 (= 0.0083), respectively.

The analysis found, among responders, SO_2 exposure was shown to increase sRaw by 10.2, 19.5, 25.4, 75.7, and 68.0 percent after exposure to 0.2, 0.25, 0.3, 0.4, and 0.5 ppm SO_2, respectively, and was shown to decrease FEV1 by 5.0, 7.6, and 17.4 percent after exposure to 0.2, 0.3, and 0.4 ppm SO_2, respectively (Table 8). These comparisons are to the subject's sRaw when exposed to clean air at the same breathing rate. In this analysis, none of the SO_2 exposure concentrations < 0.6 ppm resulted in statistically significant bronchoconstriction among non-responders. However, among responders, statistically significant increases in sRaw were demonstrated at SO_2 concentrations of 0.4 and 0.5 ppm ($P < 0.001$), with marginally significant effects at a concentration of 0.3 ppm SO_2 ($P = 0.009$). Statistically significant decreases in FEV1 were demonstrated at concentrations of 0.3 and 0.4 ppm SO_2 ($P = 0.005$ and < 0.001, respectively). The responder asthma group is likely more sensitive to exercised-induce asthma and the exercised-induced SRaw increase too high to distinguish a significant effect of 0.2 and 0.3 ppm SO2. Note that upper bound sRaw levels were similar in responders and nonresponders between 0.2 and 0.3 ppm and only at 0.4 ppm SO2 and above do sRaw levels drastically rise in responders (see Table 8).

Table 8: Percent change in post- versus pre-exposure measures of sRaw and but FEV_1 relative to clean air control after 5–10 min exposures to SO_2 during exercise (Johns, 2010)

			sRaw			
				95% Confidence Limits		
	SO_2 Conc (ppm)	Number of Exposures	% Increase	Lower	Upper	P value
Responders	0.2	36	10.2	-3.6	24	0.147
	0.25	14	19.5	-4	43.1	0.104
	0.3	25	25.4	6.5	44.3	0.009
	0.4	36	75.7	53.4	98	**<0.001**
	0.5	14	68	33.2	102.8	**<0.001**
Non-responders	0.2	67	7.9	-4.9	20.7	0.227
	0.25	14	12.6	-10.5	35.7	0.286
	0.3	16	16.4	-5.2	38.1	0.137
	0.4	67	16.2	1.8	30.6	0.028
	0.5	14	14.7	-12.3	41.7	0.285

			FEV_1			
				95% Confidence Limits		
	SO_2 Conc (ppm)	Number of Exposures	% Increase	Lower	Upper	P value
Responders	0.2	37	5	8.9	1.1	0.012
	0.3	20	7.6	13	2.3	**0.005**
	0.4	37	17.4	21.3	13.6	**<0.001**
Non-responders	0.2	43	0.4	4.3	5.2	0.854
	0.3	21	3.6	9.6	2.5	0.252
	0.4	43	4.3	9.2	0.6	0.086

One factor not addressed in the ISA 2017 analysis of the asthma studies is the effect of breathing rate on response to SO_2. To evaluate this, 18 studies from the EPA analysis in which increase in sRaw was determined were consolidated and scaled by multiplying the SO_2 concentration and breathing rate used in the study to provide a measure of integrated exposure (IE). A plot of the percent of asthamtics responding (+100% sRaw) (y-axis) versus IE (x-axis) from the studies shows a linear relationship between exposure and sRaw increase with no apparent effect of exposure time on the relationship (Figure 1). The linear equation for this relationship is:

$$\% \text{ Responding} = 0.21(IE) - 0.90. \quad \text{(Eq. 1)}$$

This relationship shows that there is an IE at which no response will occur. This is consistent with what is understood about SO_2 inhalation – at tidal (rest) and low activity breathing, most of the breath enters the lungs through the nasal passages which effectively scrub SO_2 from the air whereas at higher activity, oral breathing increases wherein air passes directly into the lung with little loss of SO_2. Several studies of sedentary exposure of asthmatics to SO_2 at 0.5 ppm for periods up to 3 hours have found no difference in sRaw and FEV_1 in the same subjects when breathing clean air (Tunnnicliffe 2003; Jaeger 1979).

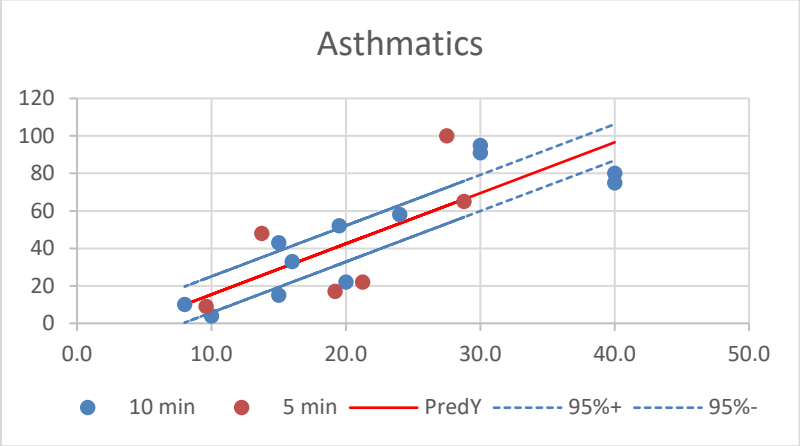


Figure 1: % Asthmatics responding (Y-axis, +100 sRAW) as function of IE (X-axis).

To relate the response rates in asthmatics to its occurrence in the population, the rates observed in the asthmatic studies were converted to population rates by extrapolating the population size from the number of asthmatics in a study. Based on a California asthma incidence of 7.8% (https://ww.cdc.gov/nchs/fastats/asthma.htm), asthma study size (9-45, n= 18, Table 7) was divided by this incidence to estimate the population from which the asthma study subjects were drawn. The number of responding asthmatics (+100% s RAW) in each study was then divided by this population estimate to calculate the population response. For example,

N asthmatics responding (sRAW ↑ 100%)	N asthmatics in study	% Asthmatics Responding	Estimated study population	% Population Responding
2	23	9	295	0.7

Replotting a population response as a function of IE gives the following figure:

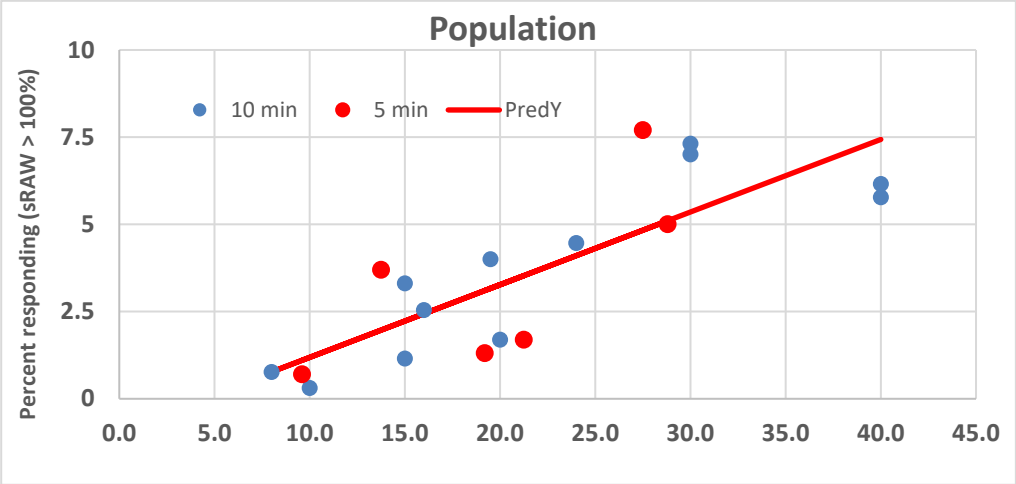


Figure 2: % Population responding (Y-axis, +100 sRAW) as function of IE (X-axis)

% responding corresponds to the percent of exposed persons who will experience a sRaw increase of 100% at a given SO2 concentration and breathing rate.

Using Equation 1, the population responses for a range SO_2 concentrations and breathing rates were calculated (Table 9). The breathing rates used in this analysis correspond to the 50 and 95 percentile rates for sedentary, light, moderate and heavy activity intensities developed by OEHHA using a time-activity-ventilation (TAV) analysis and an energy expenditure derivation (OEHHA, 2012). Based on the equation, $S0_2$ concentrations and breathing rates that give an IE of 4.3 or greater will result in a +100% sRaw increase in the population.

Activity	BR (L/min) mean; 95%	% Population Response		
		0.25 ppm	0.40 ppm	0.50 ppm
Sedentary	5.3	-0.6	-0.5	-0.3
	7	-0.5	-0.3	-0.2
Light	12.5	-0.2	0.1	0.4
	16.2	-0.1	0.5	0.8
Moderate	27	0.5	1.4	1.9
	37.7	1.1	2.2	3.0
Heavy	50.2	1.7	3.3	4.3
	73.2	2.9	5.2	6.7

Table 9: Estimated percent of population experiencing +100% sRaw increase at different breathing rates and SO_2 concentrations.

Table 9 shows that breathing rate will be an important determinant of whether asthmatics experience respiratory decrement when exposed to SO_2. Asthma symptoms are known to be brought on by exercise and studies in asthmatics exposed to clean air at elevated breathing rates have induced significant changes in sRaw and FEV_1. The data from Horstman (1988) are provided to illustrate this point (Table 10). In both the clean air ("0.0") and SO_2 control groups, the group mean sRaw

increases by about 65% after breathing clean air at 40 L/min for 10 minutes but the standard deviation indicates that some control subjects experienced +100 sRAW. Such individuals likely have moderate/severe asthma and would be highly sensitive to SO_2.

Pre- and Postexposure SRaw (cm H_2O × sec) for All Durations of Exposure to Both Clean Air and 1.0 ppm SO_2[Λ]

	Duration (min)									
	Clean Air					1.0 ppm SO_2				
Measurement	0.0	0.5	1.0	2.0	5.0	0.0	0.5	1.0	2.0	5.0
Pre	7.1 (3.3)	7.2 (3.0)	7.1 (3.2)	6.9 (2.7)	6.6 (2.7)	7.1 (2.8)	6.7 (2.9)	7.0 (2.3)	7.2 (3.0)	6.6 (2.8)
Post	11.6 (6.0)	13.5 (10.5)	14.3 (10.66)	14.7 (11.0)	16.0 (11.9)	12.2 (9.1)	12.5 (10.6)	15.1 (9.6)	24.1 (20.6)	36.3 (20.8)

[Λ]Values are means (± S.D.).

Table 10: (from Horstman, 1988) Mean pre- and post-exposure sRaw in asthmatics after breathing clean air and 1.0 ppm SO2 for 0, 0.5, 1, 2, and 5 minutes.

To assess the interaction between breathing rate and SO_2 it would be useful to have a measure of the effect of breathing rate alone on respiratory function in asthmatics. Unfortunately ISA 2017 did not report response rates for the control groups from the asthmatics studies. Asthma responses for control groups in many of the published studies were reported as a group mean so determining a response rate is not feasible. In an analysis of mostly the same studies used by ISA 2017, Johansson (2016) graphically displayed the mean control sRaw increases from the asthmatic studies (red oval, Figure 3). The mean control sRaw increase exceeds +100 sRAW in several studies.

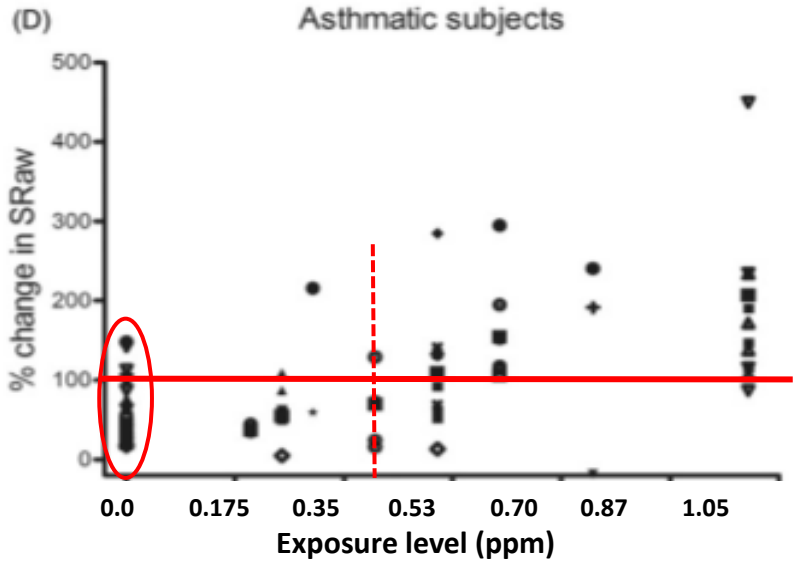


Figure 3: Mean % change in sRaw from studies reviewed in Johansson (2016).

SRaw increases obtained from the controlled human subject studies may reflect the sensitivity of those with asthma to irritants. Asthmatics are broadly categorized into three groups – moderate/severe, mild and atopic – that reflect the inherent status of the disease within the subject and their sensitivity to irritants and allergans and even physical exertion. Physical exertion separate from exposure to any agent will cause respiratory decrement in some sensitive asthmatics. The study by Linn (1987) provides some insight into the percentage of these sensitive individuals within the broader class of asthmatics. This group conducted many of the asthmatic studies that are used in the ISA 2017 assessment. This study is unique in that it classified subjects into 4 groups – normal, atopic, mild, and moderate/severe – with fairly good numbers per group (16-24). Subjects were exposed to clean air (0.0) and SO_2 (0.2 – 0.6 ppm) in a chamber for 1 hour during which they alternated between 10-min of exercise and rest. Stress test results were used to assign each individual subject an appropriate ergometer work load during exposures, sufficient to increase ventilation to about 40 L/min. Data in Table 11 shows that for the S group (severe asthmatics) breathing clean air (0.0), sRaw increase is 73% (5.68/7.82) and 97% (7.55/7.82) whereas for other groups, sRaw increase never exceeds 50%. The data also show that sRaw only exceeds 100% moderate/severe and mild asthmatics at 0.4 ppm and above.

SPECIFIC AIRWAY RESISTANCE (Cm H_2O-s): GROUP MEAN MEASUREMENTS AND RESULTS OF ANALYSES OF VARIANCE

		SO_2 Concentration (ppm)			
Measure	Group	0.0	0.2	0.4	0.6
Round 1					
Preexposure	N	3.99	4.75	4.49	4.26
	A	4.40	4.63	4.66	4.60
	M	5.37	5.40	5.36	5.44
	S	7.82	7.82	7.69	8.10
Change early in exposure*	N	+0.93	+0.53	+0.50	+0.78
	A	+0.79	+1.13	+1.45	+2.23
	M	+1.55	+2.07	+6.92	+8.30
	S	+5.68	+3.55	+8.28	+16.27
Change late in exposure*	N	+1.06	+0.42	+0.65	+0.75
	A	+0.90	+0.82	+1.29	+1.13
	M	+1.11	+1.91	+3.89	+6.17
	S	+7.55	+6.07	+7.21	+12.16
Round 2					
Preexposure	N	4.26	4.75	4.39	4.46
	A	4.96	4.66	4.40	4.59
	M	4.92	5.10	6.70	4.61
	S	7.78	7.87	7.67	7.51
Change early in exposure*	N	+0.57	+0.49	+0.72	+0.65
	A	+0.25	+0.97	+0.97	+1.22
	M	+1.33	+2.28	+1.64	+8.99
	S	+3.65	+3.93	+7.80	+12.80
Change late in exposure*	N	+0.62	+0.28	+0.54	+0.69
	A	+0.41	+0.53	+0.97	+0.83
	M	+1.11	+1.91	+1.08	+5.42
	S	+4.26	+5.13	+7.17	+10.27

Table 11: Mean sRaw increase in four groups of human subjects: normal (N), atopic (A), mild asthma (M), severe asthma (S). Shaded areas are the baseline sRaw in severe athmatics before exposure

and increases (denoted by "+") after 1-hr exposure on two different treatment days. A + value greater than baseline indicates >+100% sRaw increase.

While many subjects in this study experienced significant bronchoconstriction and symptoms, most were able to complete the exposure protocol. The study did report the number of subjects who could not complete the exercise:

> **"Mean exercise intensity, as measured by heart rate and minute volume, did not vary with $S0_2$ exposure level or clinical status. The overall mean minute volume was 43 L.** ….**Thus, for the most part, subjects maintained their intended work output despite $S0_2$-associated symptoms and bronchoconstriction. In 1.9 % of individual exposures, work was reduced because of symptoms**. This occurred twice in clean air, once in 0.2 ppm, 3 times in 0.4 ppm, and 7 times in 0.6 ppm. One normal, 1 atopic, and 6 moderate/severe asthmatic subjects experienced at least one such incident."

This observation indicates that while most subjects could maintain their breathing rate and workload, several could not. The percentage of controls in clean air that could not maintain the workload can be interpreted as the response rate for breathing clean air at 40 L/min – 2.4% of the population will experience significant respiratory effects while breathing 40 L/min. For example,

SO_2 2	Failed Test	N	% Responding
0	2	85	2.4
0.2	1	85	1.2
0.4	3	85	3.5
0.6	7	85	8.2

Data from Horstman (1986) provide a similar estimate for the response rate from breathing clean air (Table 12). Basal (sRAW) and exercised-induced bronchoconstriction (EIB) was determined in 12 asthmatics by having the subjects breath clean air at 40 L/min for 10 minutes. Two subjects (10 and 12) exceeded +100 sRAW. Using the previous conversion, 12 asthmatics represent a population of 154 (12 / 0.078) and a population response rate of 1.3 % (2/152) to breathing air at 40 L/min. Averaging Linn and Horstman gives an estimated population response rate to breathing 40 L/min for 10 min of 1.85%.

Subject Characteristics[A]

Subject No.	Age (yr)	Ht. (cm)	Wt. (kg)	BSA (m^2)	B	C	D	E	F	G	FEV_1/FVC[H]	SRaw[I]	EIB[J]	Mech.[K]
1	37	194	86.1	2.17	–	533	2038	O	T, E, Pb	14	65	5.93	2.4	1.85
2	23	175	71.1	1.86	–	455	171	O	T	-	71	6.07	0.9	4.60
3	25	188	79.1	2.05	+	98	338	O	M	2	57	6.71	5.9	1.60
4	28	172	75.6	1.89	+	64	44	O	T, E, Pb	2	79	4.77	3.2	4.25
5	30	175	72.4	1.87	+	240	384	O	M	13	60	8.34	13.5	2.30
6	28	187	77.8	2.03	+	94	253	D	M, T	3	73	4.00	0.8	1.55
7	37	180	68.4	1.87	+	248	255	D	E, T, H	2	60	9.41	6.4	3.30
8	27	185	74.9	1.98	+	98	522	D	B, F, G, P	7	87	5.31	0.0	6.55
9	36	181	86.5	2.07	–	170	150	W	M	2	73	13.73	10.9	0.80
10	22	189	75.7	2.02	–	472	692	D	A, T	1	51	5.86	31.2	1.20
11	28	175	66.6	1.81	–	320	699	O	M, T, E, Pb	5	65	5.16	2.6	4.60
12	22	174	62.6	1.76	+	490	610	O	T	2	56	7.92	34.5	1.30

Table 12: sRaw increases (EIB) in 12 asthmatic subjects breathing 40 L/min for 10 min.

Subtracting a breathing-induced response rate of 1.85% from the response estimates in Table 9 gives the following rates:

Activity	BR (L/min) mean; 95%	% Population Response		
		0.25 ppm	0.40 ppm	0.50 ppm
Moderate	27	-1.35	-0.45	0.05
	37.7	-0.75	0.35	1.15
Heavy	50.2	-0.15	1.45	2.45
	73.2	1.05	3.35	4.85

This analysis indicates that there will be appreciable respiratory effects to SO_2 only at 0.4 ppm and above. When correcting for sRaw increases due to breathing air at 40 L/min, a positive response from 0.25 ppm SO_2 will only be observed at a very high breathing rate (73.2 L/min). At 0.4 ppm, a positive response occurs at the 95% of moderate activity and at heavy activity.

As discussed previously, the breathing rates used in this analysis are taken from OEHHA technical guidance for exposure assessment (OEHHA, 2012). OEHHA relied on a U.S. EPA study that used existing data on minute ventilation rates (in ml/min or ml/kg-min) for a range of activities to assign Metabolic Equivalent values depending on the intensity level of activity.A Metabolic Equivalent (MET) is the ratio of the work metabolic rate to the resting metabolic rate. One MET is defined as 1 kcal/kg/hour and is roughly equivalent to the energy cost of sitting quietly. A MET also is defined as oxygen uptake in ml/kg/min with one MET equal to the oxygen cost of sitting quietly, equivalent to 3.5 ml/kg/min. METs link energy requirements of activity to the required oxygen uptake needed to maintain that energy level so activity-level breathing rates can be derived from MET values. Based on OEHHA's guidance, the following activity levels correspond to these MET levels and breathing rates. The 50 and 95 percentile values are shown.

Activity Level	MET	Breathing Rate (L/min)	
		50%	95%
Sedentary/Passive	< 1.5	5.3	7.0
Light Intensity	1.5 < 3.0	12.5	16.2
Moderate Intensity	3.0 < 6.0	27.0	37.7
High Intensity	> 6.0	50.2	73.2

CDC has assigned MET values to 501 job categories based on the American Time Use Survey collected as part of the annual census (https://epi.grants.cancer.gov/physical/MET/#atus). Figure 4 shows the frequency of these job categories by MET. Few work activities as defined by the CDC exceed breathing rates of 40 L/min.

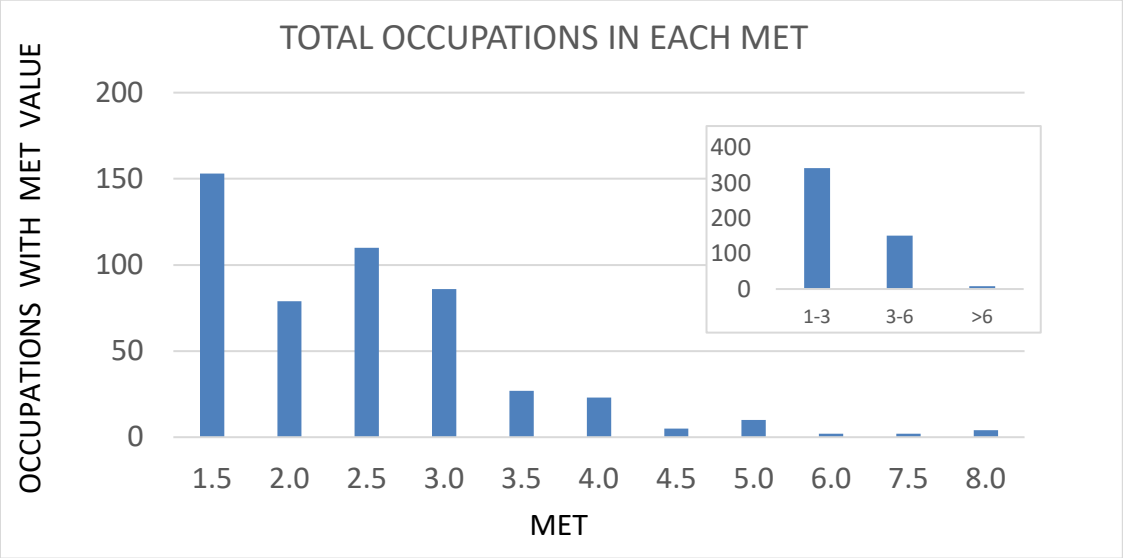


Figure 4: Number of occupations with specified MET value. From https://epi.grants.cancer.gov/physical/MET/#atus

Conclusion: Statistically significant changes to sRaw and FEV1 in controlled human studies were observed at 0.4 ppm at breathing rates from 40 to 50 L/min (Table 8). The frequency of occupations with breathing rates above 40 L/min (8) suggests that few workers will be effected though these high-breathing rate occupations (construction, oil and gas extraction/refinery, agriculture, structural steel) are associated with SO_2 exposure.

CERS Usage Information

Pending

Measurement Information

	OSHA Method	NIOSH Method
	ID 200 or ID 104	3800 or 6004
Validated detection level	104: 2.5 ppm (60-L air volume)	3800: 0.35 ppm (Direct reading)
	200: 1.36 ppm (12-L air volume)	6004: 0.2 ppm (100-L air sample)

Using NIOSH 6004, a 15 minute air sample at 1.5 LPM results in a 22.5 L sample. The range is 6004 11 to 200 µg SO2 per sample. Therefore, using 11 ug per sample and a 22.5 L sample volume yields an 11 ug per sample, or 0.489 ug/L or 0.489 mg/m3. Since 1 ppm = 2.62mg/m3, 0.489 mg/m3 = 0.187 ppm.

Based on this data, the method could achieve a 0.2 ppm detection limit and is analytically feasible.

Recommended Workplace Controls and Feasbility Issues

The Division is seeking stakeholder input on these subjects.

References

Horstman, D; Roger, LJ; Kehrl, H; Hazucha, M (1986). Airway sensitivity of asthmatics to sulfur dioxide. Toxicology and Industrial Health 2:289-298.

Horstman, DH; Seal, E, Jr; Folinsbee, LJ; Ives, P; Roger, LJ (1988). The relationship between exposure duration and sulfur dioxide-induced bronchoconstriction in asthmatic subjects. AIHA Journal 49:38-47.

Jaeger MJ, Tribble D, Wittig HJ (1979). Effect of 0.5 ppm sulfur dioxide on the respiratory function of normal and asthmatic subjects. Lung 156(2):119-27.

Johns, DO; Svendsgaard, D; Linn, WS (2010). Analysis of the concentration-respiratory response among asthmatics following controlled short-term exposures to sulfur dioxide. Inhalation Toxicology 22:1184-1193.

Li X, Yi H and Wang H (2018). Sulphur dioxide and arsenic affect male reproduction via interfering with spermatogenesis in mice. Ecotoxicology and Environmental Safety 165:164-173, 2018.

Linn, WS; Avol, EL; Peng, RC; Shamoo, DA; Hackney, JD (1987). Replicated dose-response study of sulfur dioxide effects in normal, atopic, and asthmatic volunteers. American Review of Respiratory Disease 136:1127-1134.

Linn, WS; Venet, TG; Shamoo, DA; Valencia, LM; Anzar, UT; Spier, CE; Hackney, JD (1983). Respiratory effects of sulfur dioxide in heavily exercising asthmatics: A dose-response study. American Review of Respiratory Disease 127:278-283.

OEHHA, (2012). Technical Support Document for Exposure Assessment and Stochastic Analysis, FINAL, August, 2012. https://oehha.ca.gov/media/downloads/crnr/chapter32012.pdf

Qin G, Wu M, Wang J, Xu Z, Xia J, Sang N (2016). Sulfur Dioxide Contributes to the Cardiac and Mitochondrial Dysfunction in Rats. Toxicol Sci. 151(2):334-46. https://academic.oup.com/toxsci/article/151/2/334/2241016

Roger, LJ; Kehrl, HR; Hazucha, M; Horstman, DH (1985). Bronchoconstriction in asthmatics exposed to sulfur dioxide during repeated exercise. Journal of Applied Physiology 59:784-791

Sang N, Hou L, Yun Y, Li G (2009). SO2 inhalation induces protein oxidation, DNA-protein crosslinks and apoptosis in rat hippocampus. Ecotoxicol Environ Saf. 72(3):879-84.

Sang N, Yun Y, Li H, Hou L, Han M, Li G (2010). SO2 inhalation contributes to the development and progression of ischemic stroke in the brain. Toxicol Sci. 114(2):226-36. https://academic.oup.com/toxsci/article/114/2/226/1672928

Tunnicliffe WS, Harrison RM, Kelly FJ, Dunster C, Ayres JG (2003). The effect of sulphurous air pollutant exposures on symptoms, lung function, exhaled nitric oxide, and nasal epithelial lining fluid antioxidant concentrations in normal and asthmatic adults. Occup Environ Med. 60(11):15. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1740413/

U.S. EPA (2017). Integrated Science Assessment (ISA) for Sulfur Oxides – Health Criteria (Final). U.S. Environmental Protection Agency, Washington, DC, EPA/600/R-17/451. https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=338596

U.S. EPA (U.S. Environmental Protection Agency) (2008d). Integrated science assessment for sulfur oxides: Health criteria [EPA Report]. (EPA/600/R-08/047F). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment- RTP. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=198843

Wang C, Liang C, Ma J, Manthari RK, Niu R, Wang J, Wang J, Zhang J (2018). Co-exposure to fluoride and sulfur dioxide on histological alteration and DNA damage in rat brain. J Biochem Mol Toxicol. 32(2). https://www.researchgate.net/publication/322072078

Woerman AL, Mendelowitz D (2013). Perinatal sulfur dioxide exposure alters brainstem parasympathetic control of heart rate. Cardiovasc Res. 99(1):16-23. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3687747/

Yao G, Yue H, Yun Y, Sang N (2015). Chronic SO2 inhalation above environmental standard impairs neuronal behavior and represses glutamate receptor gene expression and memory-related kinase activation via neuroinflammation in rats. Environ Res. 137:85-93. http://ir.nsfc.gov.cn/paperDownload/1000009439725.pdf

Zhang J, Zheng F, Liang C, Zhu Y, Shi Y, Han Y, Wang J (2016). Sulfur dioxide inhalation lowers sperm quality and alters testicular histology via increasing expression of CREM and ACT proteins in rat testes. Environ Toxicol Pharmacol. 47:47-52.

Zhang J, Li Z, Qie M, Zheng R, Shetty J, Wang J (2016). Sodium fluoride and sulfur dioxide affected male reproduction by disturbing blood-testis barrier in mice. Food Chem Toxicol. 94:103-11.