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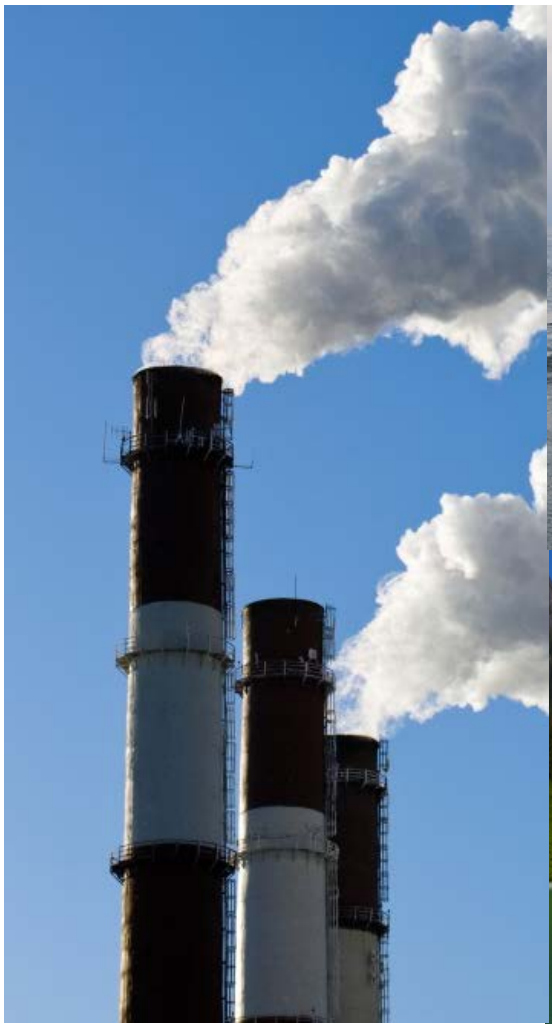
Human Health Risk Assessment for Sulphur Dioxide



Canada

Human Health Risk Assessment for Sulphur Dioxide

(CAS RN: 7446-09-5)

Analysis of Ambient Exposure to and Health Effects of Sulphur Dioxide in the Canadian Population

Water and Air Quality Bureau
Safe Environment Directorate
Healthy Environments and Consumer Safety Branch
Health Canada

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Executive Summary

The Air Quality Assessment Section, of Health Canada undertook a health risk assessment of sulphur dioxide (SO_2) in order to update the available information on adverse effects of SO_2 to human health, determine recent Canadian SO_2 exposure levels, and to inform the revision or development of Canadian ambient air quality objectives/standards.

Background

The existing National Ambient Air Quality Objectives (NAAQOs) for SO_2 were published in the *Canada Gazette, Part I*, in 1989 (Table 1).

Table 1: Existing National Ambient Air Quality Objectives for SO_2

Standard*	Concentration SO_2 (ppb)	Concentration SO_2 ($\mu g/m^3$)
Maximum acceptable level: 1-h average	344	900
Maximum acceptable level: 24-h average	114	300
Maximum acceptable level: annual average	23	60
Maximum desirable level: 1-h average	172	450
Maximum desirable level: 24-h average	57	150
Maximum desirable level: annual average	11	30
Maximum tolerable level: 24-h average	305	800

(*) At 25ºC, and 760 mmHg

Since that time a large number of publications relevant to potential human health effects of SO_2 have become available. Additionally, exposures have changed with total SO_2 levels decreasing by 96% in Canada since 1970 (Environment Canada, 2011), largely as a result of the use of alternative (low-sulphur) fuels and pollution reduction programs that limited SO_2 emissions (Chen et al., 2007).

Fine particles, including sulphate particles, were evaluated by Health Canada as part of the *Canadian Smog Science Assessment* document (Government of Canada, 2012), so for the purposes of this current assessment, only gaseous SO_2 was considered.

Environmental Concentrations of SO_2 in Canada

National Air Pollution Surveillance (NAPS) data from the most recent year available (2011) were used to model Canadian exposures. NAPS data were analyzed on an all-monitor basis, as well as stratified by urban and rural designations. Annual averages for SO_2 ranged from below the detection limit to 8.6 ppb. The 24-h averages from urban residential sites ranged from below the detection limit to 56 ppb and the 1-h averages ranged from below the detection limit to 314 ppb. The majority of NAPS monitors did not detect SO_2 on a regular basis. Additional ambient

monitoring during 2009–2011 by Airpointer monitors also indicated that SO_2 levels are typically close to the limit of detection, but there are short-lived spikes in concentrations. Shorter-term averaging times were available from the Airpointer data (e.g. 30-min and 10-min) and reflect these spikes with a maximum 10-min value of 322 ppb for a site with a nearby industrial source.

Human Health Assessment

Based upon the US EPA *Integrated Science Assessment for Sulfur Oxides – Health Criteria* (US EPA, 2008) and an evaluation of the toxicology, controlled human exposure, epidemiology and mode of action/mechanistic literature since 2007, as well as the guidance on causal determinations as set out in Table 10.1, it has been concluded that the evidence supports a causal relationship between short-term exposure to ambient levels of SO_2 and respiratory morbidity in adults, particularly in the asthmatic subpopulation. Similarly, the literature is suggestive of a causal relationship between short-term exposure to ambient levels of SO_2 and respiratory morbidity in children. The epidemiology papers on respiratory morbidity support effects on lung function after short-term exposures to concentrations below the short-term maximum concentration identified in the NAPS data, suggesting a potential risk to the Canadian population. The effects of co-pollutants and confounding factors cannot be fully ruled out in epidemiology studies; therefore, the lowest observed adverse effect concentration (LOAEC) for lung function decrements, from controlled human exposure studies of asthmatics exposed to SO_2 for 5–10 min at increased ventilation, was used to derive a Reference concentration. Individuals in the controlled human exposure studies were found to react at a level that was below the maximum measured ambient concentration for the 10-min averaging time, which suggests that there is a potential risk to the Canadian population at current exposure levels.

The available information is suggestive of a causal relationship between short-term SO_2 exposures and all-cause and cardiopulmonary mortality at current ambient exposure concentrations, particularly in people over 40 years of age (most strongly associated with the over 65 age group). However, some inconsistency in this database and confounding of the signal in these studies is possibly indicative of SO_2 acting as a surrogate for certain sources (e.g. coal fired power plants) or reflecting effects after conversion to a particulate form.

The literature is weakly suggestive of a causal relationship with preterm birth and congenital heart malformation in babies exposed to SO_2 *in utero*. The epidemiology data on reproductive and developmental endpoints identified risks of congenital malformations and preterm delivery after SO_2 exposures during gestation at concentrations below the ambient annual maximum concentration identified in the NAPS data, suggesting a potential risk to the Canadian population at current exposure levels. However, even moreso than the case above; SO_2 may be acting in these studies as a surrogate for source or other pollutant(s) with which it is correlated.

The databases were found to be inadequate to infer a causal relationship for other endpoints, including mortality and respiratory morbidity with long-term exposures, cardiovascular morbidity with short- or long-term exposures, carcinogenicity and low birth weights.

It should be noted that there are a number of issues related to interpretation of the epidemiology literature. Most importantly, it remains difficult to determine the role of confounding co-pollutants such as $PM_{2.5}$ and PM_{10} on the effects being reported. Therefore, it is important to consider the data from controlled human exposure studies, which are available for respiratory morbidity, in conjunction with the epidemiology literature. Additional lines of evidence are also considered to

support the epidemiology findings, including evidence for potential mechanisms or modes of action and personal exposure analyses for systemic effects.

A 10-min reference concentration (RfC) of 67 ppb was derived from the controlled human exposure studies for respiratory morbidity and uncertainties, including intraspecies variability.

Public Health Impacts

Although the magnitudes of the risks of health effects associated in the epidemiology, with respect to SO_2 exposures, are relatively small, they represent important impacts on public health due to the number of people potentially affected. The subpopulations that appear to have increased susceptibility to adverse effects from SO_2 exposure represent a considerable proportion of the population, with asthmatics and the elderly alone accounting for 8.9% and 14.8% of Canadians, respectively (Statistics Canada, 2011; Asthma Society of Canada, 2012).

Similarly, with respect to the amount of SO_2-related mortality, Judek et al. (2004) estimated that 8% of total non-accidental mortality in Canadian urban census divisions between 1998 and 2000 was due to air pollution (described by a multi-pollutant model of PM, ozone, nitrogen dioxide, SO_2 and carbon monoxide), and that most of this was due to long-term exposure to ambient fine PM, which has a strong signal correlation to SO_2.

While there is currently insufficient information to relate SO_2 to specific reproductive effects, the lifelong implications of pre-term birth and various congenital issues indicates that this is an area in need of more attention.

Conclusions and Recommendations

In conclusion, the human health assessment has identified potential health risks to the Canadian population from exposures to ambient concentrations of SO_2, which are below the current National Ambient Air Quality Objectives. It is therefore recommended that the current National Ambient Air Quality Objectives be revised or new Ambient Air Quality Objectives or Standards be introduced with consideration of the following:

- The strongest evidence of causality was between short term SO_2 exposures and respiratory morbidity, based largely on the 5-10 minute controlled human exposure studies. A 10-min human health reference concentration of 67 ppb has been identified in the assessment.
- The more recent literature also adds to the weight of evidence for a “suggestive of causal” relationship between non-accidental and cardiopulmonary mortality risks and short-term exposures to SO_2.
- Additional endpoints (reproductive/developmental) have been identified based on the more recent literature. Although these endpoints have also been designated as having a weakly “suggestive of causal” relationship with SO_2 exposures, the database is limited.
- Intermittent spikes in exposures are linked to respiratory morbidity and are suspected for most other endpoints, including reproductive/developmental. Current Canadian monitoring data support that Canadians are likely to be exposed to intermittent spikes in concentrations. Mechanistic and personal exposure modeling also support intermittent spikes in exposure as being relevant to the health effects observed.

- There is “inadequate evidence to infer a causal relationship” between long term exposures of SO_2 and health effects.

1.0 Introduction

The Air Quality Assessment Section, Air Health Effects Assessment Division, Safe Environments Directorate of Health Canada undertook a health risk assessment for sulphur dioxide (SO_2) in 2012. The purpose of this analysis is to:

- update the available information on adverse effects of SO_2 to human health since the US EPA assessment;
- determine Canadian exposure levels;
- identify new trends in the literature on adverse health issues that have come to light since the US EPA assessment; and
- inform the revision or development of ambient air quality objectives/standards.

Environment Canada is developing a complementary environmental status review report for SO_2 that will provide a summary of the environmental effects and information on the emissions, sources and ambient concentrations of this air pollutant.

The following sections describe the context for development of this risk assessment, as well as a description of the process behind how the content is organized, and the objectives of the assessment.

1.1 Canadian Air Quality Policy Context

Ambient air quality management in Canada is a shared responsibility among provincial, territorial, federal, and in some cases municipal governments. With respect to SO_2, in particular, in 1969, the Government of Canada established the Air Pollution Control Division in what was then called the Department of National Health and Welfare. For better coordination of air pollution control and to facilitate pollution reduction measures, an *ad hoc* Federal-Provincial Committee on Air Pollution was also established; this committee was transferred to the Department of the Environment in 1971 and continued to work under the newly implemented *Clean Air Act* (1971) (Health Canada, 1976). A subcommittee of the Federal-Provincial Committee on Air Pollution set about developing recommendations for National Ambient Air Quality Objectives (NAAQOs).

The *Clean Air Act* was subsumed into the *Canadian Environmental Protection Act* (1988) and the NAAQOs for SO_2 (Table 1.1) were consolidated and published in the *Canada Gazette, Part 1*, in 1989.

Table 1.1: Existing NAAQOs for SO_2

Standard*	Concentration SO_2 (ppb)	Concentration SO_2 ($\mu g/m^3$)
Maximum acceptable level: 1-h average	344	900
Maximum acceptable level: 24-h average	114	300
Maximum acceptable level: annual average	23	60
Maximum desirable level: 1-h average	172	450
Maximum desirable level: 24-h average	57	150
Maximum desirable level: annual average	11	30
Maximum tolerable level: 24-h average	305	800

(*) At 25ºC, and 760 mmHg

In the 1990s, the role of SO_2 in the formation of particulate matter (PM), acid deposition and visibility deterioration began to receive increasing attention. Evidence of significant health effects of fine PM ($PM_{2.5}$) began to mount, along with improved understanding of the significant role of SO_2 in the formation of fine PM, which is a primary component of smog. Smog and acid deposition are now parallel drivers for SO_2 management agreements and programs.

1.2 Government Regulation of Air Pollutants

Governments at various levels in Canada can assess air pollutants and set ambient air quality objectives or standards. These represent goals for outdoor air quality that protect public health, the environment, or aesthetic properties of the environment. Ambient air quality objectives or standards are primarily effects-based, but are also reflective of technological, economic and societal considerations, and they guide federal, provincial, territorial and municipal governments in making risk management decisions related to air quality concerns.

Federal, provincial and territorial governments work together in partnership under the framework of the Canadian Council of Ministers of the Environment (CCME). In 2012, Canadian Environment Ministers agreed to take further action to protect the health of Canadians and the environment with measures to improve air quality in Canada through a comprehensive new Air Quality Management System (AQMS). The AQMS includes the establishment of Canadian Ambient Air Quality Standards (CAAQSs) for air pollutants of concern, new base-level industrial emissions requirements for major industrial sectors and equipment groups, the management of the air quality at the local and regional levels, and a collaborative process to address mobile source emissions. Where air quality is particularly poor, provinces and territories may require further emission reductions from industrial and non-industrial sources of pollution to manage air quality issues. The AQMS will also address the transboundary movement of air pollutants

between provinces and territories, and between Canada and the United States (US). The *Canadian Environmental Protection Act, 1999* (CEPA, 1999) provides the federal government with broad authority to address atmospheric emissions of substances that have negative impacts on health and the environment. The *Canadian Environmental Protection Act* was first promulgated in 1988, and was revised and renewed as a new Act in 1999. The focus of CEPA, 1999 is pollution prevention and the protection of the environment and human health as a means to promote sustainable development. Health Canada and Environment Canada share responsibility under CEPA, 1999 to assess and manage the threats that pollutants may pose; Health Canada focuses on risks to human health, while Environment Canada focuses on risks to the environment. Sulphur dioxide, along with other air pollutants, has been declared "toxic" under CEPA, 1999, meaning that these pollutants are "entering or may enter the environment in a quantity or concentration or under conditions that: have or may have an immediate long-term harmful effect on the environment or its biological diversity" (CEPA s64(a)) and "constitute or may constitute a danger in Canada to human life or health" (CEPA s64(c)).

1.3 Inclusion Criteria for Assessment Information

This *Human Health Risk Assessment for Sulphur Dioxide* uses the US EPA's 2008 *Integrated Science Assessment for Sulphur Oxides – Health Criteria* as a basis from which the updated assessment departs. Data reviewed in this assessment were identified in searches including *PubMed* and focus on the years 2008–2011, though some older studies have been included to enhance discussion of toxicokinetics and to provide additional background reference material. Additionally, a number of 2007 studies that were not in the US EPA 2008 document were included here to account for any gap between the cessation of literature searching and the publication date of the US EPA document.

The individual papers identified for the update periods were critiqued for study design, methodology and analytical technique before inclusion. In general, more weight has been given to studies where the exposure was expected to be relevant to ambient exposures in Canada in terms of composition, sources, levels and environmental conditions.

1.4 Content of the Assessment

The *Human Health Risk Assessment for Sulphur Dioxide* builds upon the most recent US assessment and critically evaluates relevant information that has become available since 2008. Evaluation and interpretation of this information is essential to establishing the weight of evidence for the various health effects associated with SO_2 exposure**,** and for establishing whether population health impacts can be expected from current ambient exposures.

Following the introductory section, the physical-chemical properties of SO_2 are presented in Section 2. Section 3 covers the known environmental sources of SO_2 to the Canadian environment, while Section 4 provides an assessment of the reported environmental concentrations of SO_2 in Canada and elsewhere, as well as a brief overview of its environmental fate.

Exposure of the general population to ambient SO_2 is covered in Section 5, and Section 6 discusses the dosimetry of inhaled SO_2 in the respiratory tract, as well as the toxicokinetics of this pollutant.

Section 7 reviews the scientific literature related to health effects of SO_2 exposure, including odour detection, irritation, and the results of epidemiological, controlled human exposure and toxicological assessments of respiratory morbidity, cardiovascular morbidity, mortality, carcinogenicity, mutagenicity, and reproductive and developmental endpoints associated with both acute and chronic exposure to ambient SO_2.

Since SO_2 is also produced in the body (i.e. endogenously), Section 8 discusses the relationship between endogenous sulphur status and the applied dose, using both acute and chronic modelling scenarios. The objective of this section is to determine whether the biological plausibility of the epidemiological observations of systemic effects can be supported by the modelled applied dose. Section 9 addresses the mechanisms or modes of action, by which SO_2 may exert the adverse effects observed in the literature.

A discussion of SO_2 as a cause of adverse human health effects (Section 10) and a risk characterization (Section 11) integrate key information from the prior chapters on exposure, dosimetry, and health effects of SO_2. Overall document conclusions are presented in Section 12.

1.5 Objectives of the Assessment

The information and conclusions presented in the *Human Health Risk Assessment for Sulphur Dioxide* are intended to provide scientific guidance to decision-makers in the review and/or development of air quality policies, including NAAQOs and CAAQSs. By identifying SO_2-related health risks to the Canadian population, this document will facilitate development of risk management strategies to reduce the risk of SO_2 to the health of Canadians. The information it contains will also provide context for international negotiations related to reduction of the transboundary and transcontinental flow of air pollutants. The knowledge gaps identified in this assessment are intended to provide direction for future scientific research so that the available information expands to better support future policy decisions.

2.0 Physical–Chemical Properties[1]

Name:	Sulphur dioxide
CASRN:	7446-09-5
Molecular formula:	SO_2; O=S=O
Molecular weight:	64.064 g/mol
Colour:	Colourless gas or liquid
Odour:	Strong, irritating, and pungent
Boiling point:	-10.05°C
Melting point:	-75.5°C
Corrosive:	Corrosive when hydrated/oxidized
Specific gravity:	2.619 g/L
Water solubility:	Soluble
Solvent solubility:	Soluble
Index of refraction:	1.3396 at 25°C (water = 1.33)
Vapour density:	2.264 at 0°C (air = 1)
Vapour pressure (mmHg):	2538 at 21.1°C
Vapour pressure (kPa):	230 at 10°C; 330 at 20°C; 462 at 30°C
Henry's Law constant:	8.10×10^{-4} atm- m^3/mol at 25°C; or 0.048 (mol/L) air/(mol/L) water at 37°C and 1 atm pressure (US EPA, 2008)
Hydroxyl radical reaction rate constant:	$<1.0 \times 10^{-18}$ cm^3/molecule-sec at 25°C
Oxidized:	Catalytically oxidized by air to SO_3

[1] The reference for Section 2.0 is the Hazardous Substances Data Bank (National Library of Medicine, USA) unless otherwise indicated.

3.0 Sources of Sulphur Dioxide

Overall, emissions of SO_2 from natural sources are estimated to be small compared to industrial sources. However, there are exceptions on the local scale where exposures from natural sources may be higher than industrial sources (e.g. near volcanic activity, wildfires or marine environments).

3.1 Natural Sources

SO_2 represents a small fraction of the sulphur species emitted by natural sources (other species include dimethyl sulphate, hydrogen sulphide, sulphur oxide, and the general category of total reduced sulphur).

Volcanoes, forest fires, and wildfires are the largest natural sources of SO_2 emissions. The US EPA (2008) reported that SO_2 in volcanic plumes can range in the tens of parts per million. Volcanic sources may result in SO_2 exposures, and Canadians might be affected by volcanic sources from Canada and the US, namely from the Pacific Northwest, Alaska, and to a lesser degree, Hawaii (US EPA, 2008). Forest fires and wildfires result in SO_2 release when the sulphur bound in amino acids of vegetation gets oxidized during combustion. Reduced sulphur gases are also emitted by marine organisms, as well as by anaerobic bacteria in marshes and estuaries.

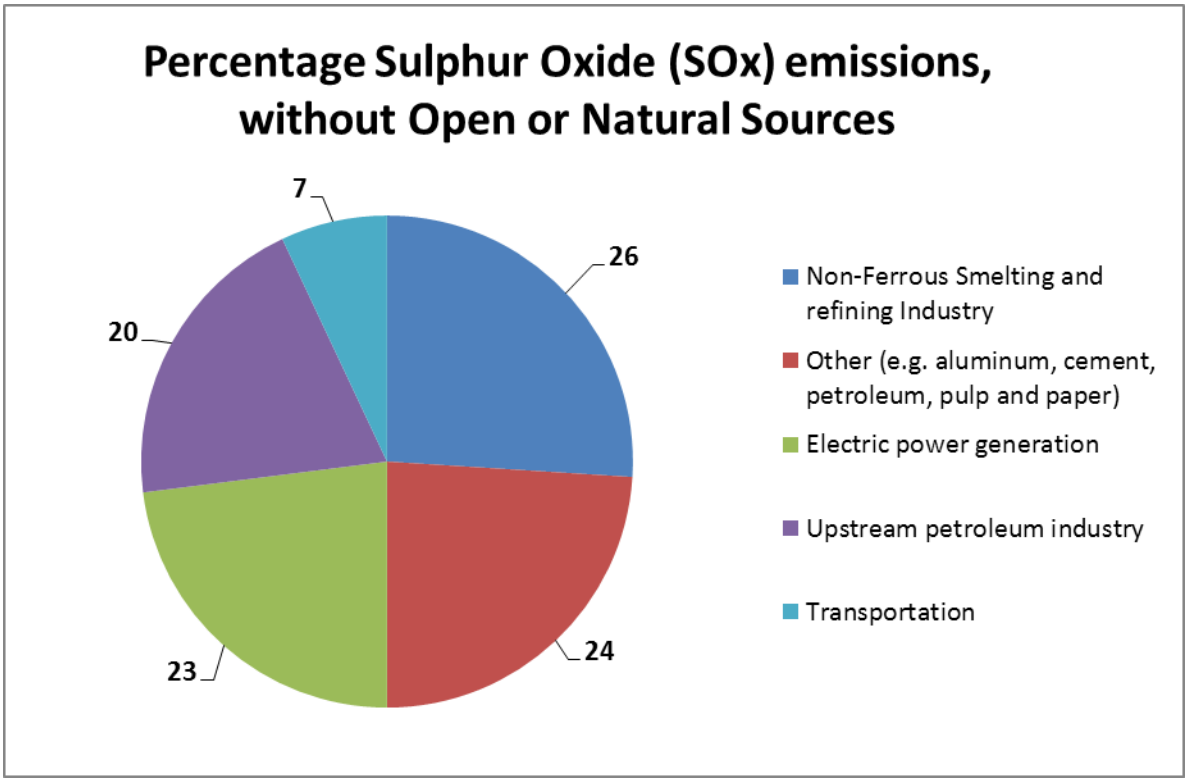
In Canada, Environment Canada (2013) reported that estimated total SO_2 emissions in 2011 from natural sources (forest fires) were approximately 100 tonnes; however, estimates were not available for other potential natural sources (e.g. marine organisms or anaerobic bacteria), likely due to difficulties in quantifying such releases. Natural sources such as forest fires also vary from year to year.

3.2 Anthropogenic Sources

In Canada, Environment Canada (2013) reported that estimated total SO_2 anthropogenic emissions in 2011 were approximately 1 million tonnes (without including open sources such as agriculture, waste, and prescribed burning). Estimates of emissions from open and natural sources are much smaller (<1% of total emissions) than estimates of other emissions, and these sources are considered to be uncontrollable through conventional means; therefore these sources have not been included in Figure 3.1. The primary anthropogenic sources for all sulphur oxides (SO_x) in Canada are described by percentage emission in Figure 3.1, and comprise:

- base metal smelters;
- fossil-fueled electric power generation plants;
- upstream oil and gas industry (e.g. natural gas plants);
- other industrial sources (e.g. aluminum smelting and refining, cement plants, petroleum refineries, pulp and paper mills); and
- transportation sources (e.g. ships, airplanes).

Figure 3.1: 2011 Percentage sulphur oxide emissions (without open or natural sources)



Source: (Environment Canada, 2013)

3.3 Endogenous Sources

Please refer to Section 8 for a discussion of endogenously generated SO_2.

4.0 Environmental Levels and Environmental Fate

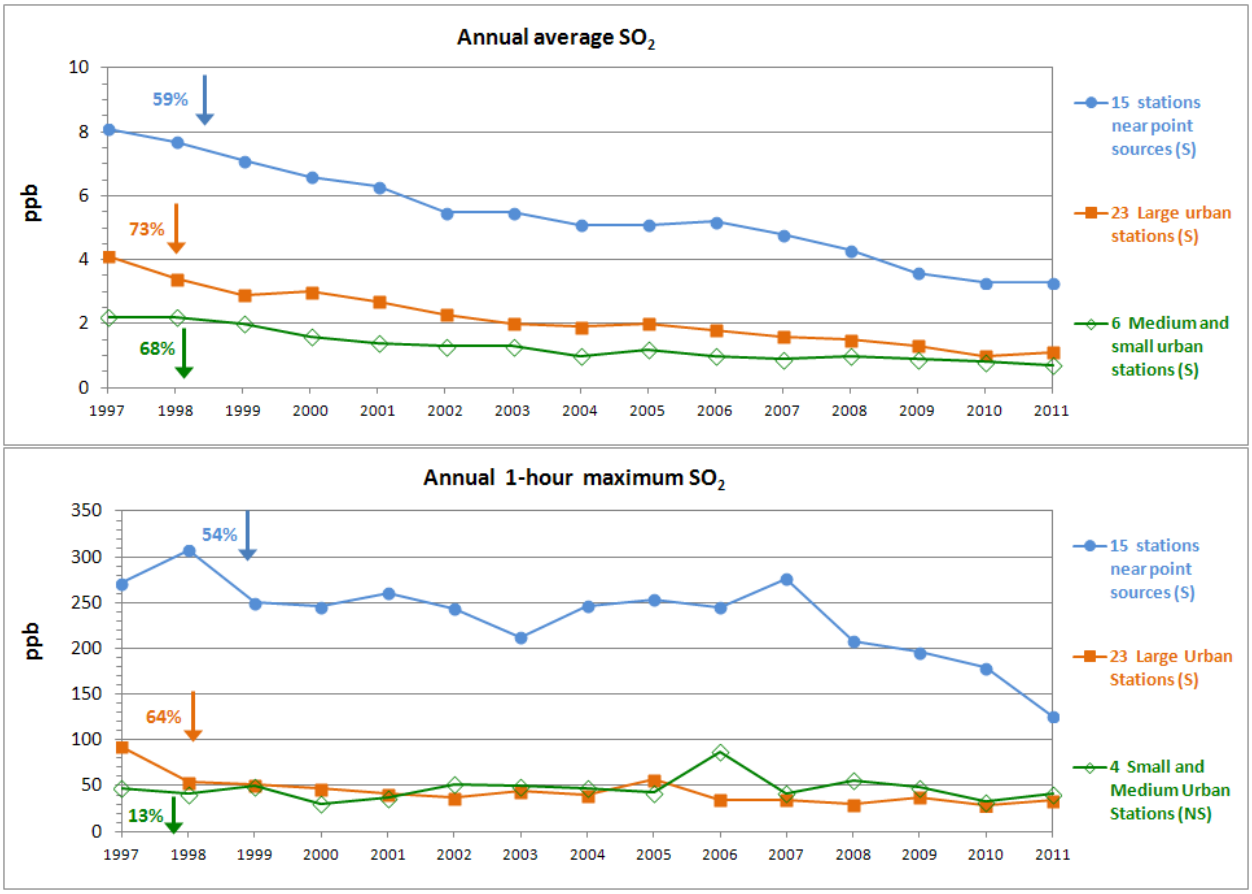
4.1 Environmental Levels

The ambient concentrations of SO_2 presented in this report were retrieved from the Canada-wide Air Quality Database (CWAQD) maintained by Environment Canada. The CWAQD contains data originating from several networks, the most important of which is the National Air Pollution Surveillance (NAPS) program, a cooperative arrangement among the federal, provincial, territorial and municipal governments that has been in existence since 1969. The CWAQD also contains data from the Canadian Air and Precipitation Monitoring Network (CAPMoN) operated and maintained by Environment Canada, as well as data collected by provincial, territorial and municipal monitoring stations that are not part of the NAPS program. The NAPS program measures ambient air pollutant concentrations with over 1,000 monitors at 286 stations in 203 communities. NAPS data include continuous SO_2 measurements reported hourly (Demerjian, 2000). The data are precise enough to allow for the assessment of source–receptor relationships relevant to industrial and mobile sources in the vicinity of each monitoring station.

Ambient concentrations of SO_2 can be affected by several factors, including the proximity of local emission sources, the local weather conditions and geological formations such as mountains. Therefore, extrapolation of local air quality data to the national context requires models that can account for spatial distribution patterns, making it difficult to characterize air quality on a large scale. A further consideration when modelling SO_2 concentrations is the fact that SO_2 is rapidly oxidized in the atmosphere, and as such, monitor-to-monitor correlations are weak unless they are in proximity to the same source. Currently, in Canada, annual averages from the NAPS sites in 2011 ranged from below the detection limit to 8.6 ppb (see Table 5.3). Since 1970, total SO_2 levels have decreased by 96% in Canada (Environment Canada, 2011), largely as a result of the use of alternative (low-sulphur) fuels and pollution reduction programs that limited SO_2 emissions (Chen et al., 2007).

Recent trend analysis demonstrated that SO_2 concentrations in Canada have continued to decrease between 1997 and 2011, as illustrated in Figure 4.1. NAPS stations were classified as large urban ((LU) population, ≥100,000), medium urban ((MU) population, 30,000–100,000), small urban ((SU) population, 1,000–30,000), non-urban (NU) and point-source-influenced (PS).

Figure 4.1: Trends in annual mean and 1-h maximum SO_2 (ppb) 1997–2011*

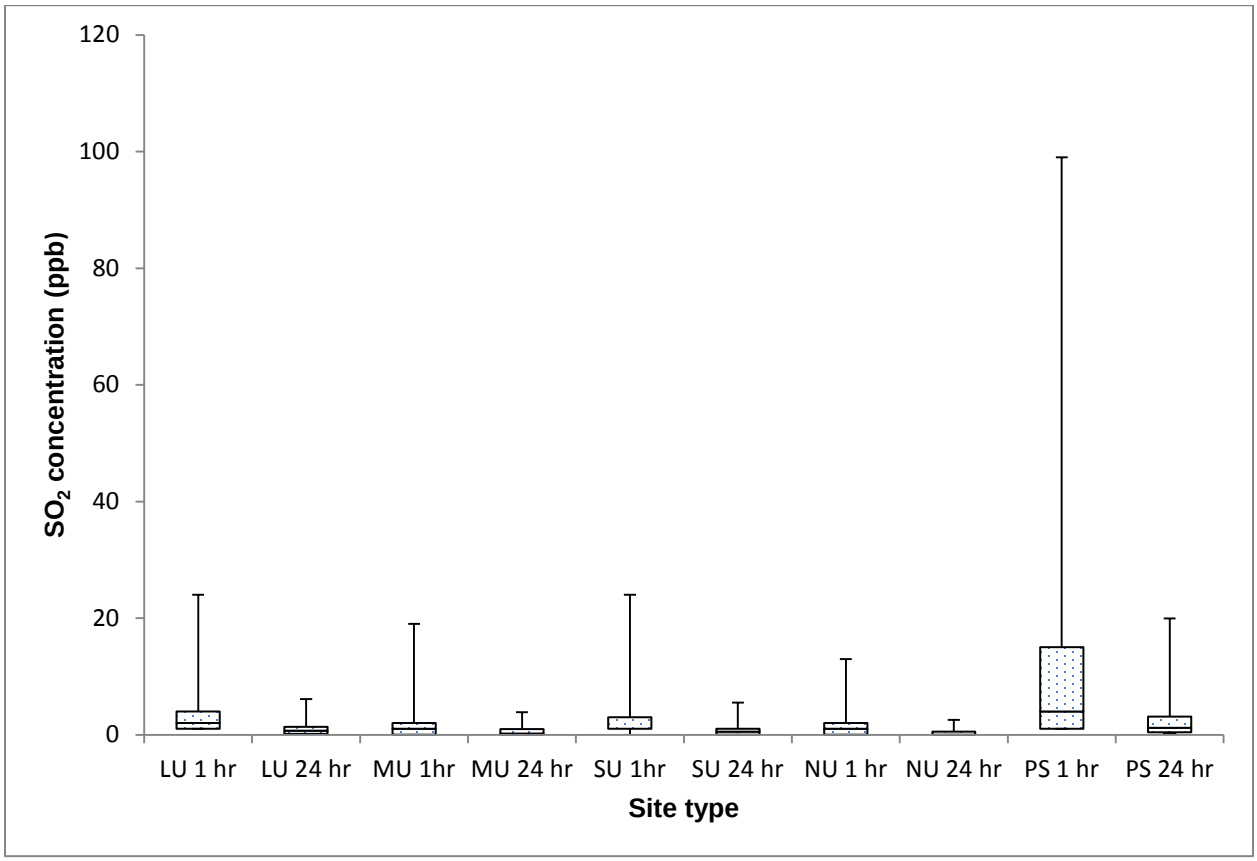


*The charts do not include data from the Témiscaming (Québec) station, which only had data for the period 1999 to 2009. The percentage number is the difference in concentration between 2011 and 1997 on a percentage basis; a downward arrow indicates that concentrations in 2011 were lower than in 1997. (S) and (NS) mean that the trend is statistically significant (95% CI) and non-significant, respectively.

As shown in Figure 4.1, sites with a point source continue to have higher annual average and annual 1-h maximum concentrations of SO_2 in comparison to non-point-source sites; however, concentrations have significantly decreased over time for point-source, large, medium and small urban sites. As Figure 4.1 illustrates, annual means were quite low as of 2011; however, when considering shorter time periods and upper bound values like the 1-h maximum, much higher values are observed, especially for sites with a point source, although these values are also decreasing over time.

Figure 4.2 shows SO_2 concentrations (as median, 2nd, 25th, 75th and 98th percentiles) for 1-h daily maximum and 24-h averaging times. The highest SO_2 concentrations were generally measured at sites with nearby point sources.

Figure 4.2: Distribution of 1-h daily maximum and 24-h average SO_2 by site type (2011) (Boxplot shows median, 2nd, 25th, 75th and 98th percentiles)



* large urban ((LU) population, ≥100,000), medium urban ((MU) population, 30,000–100,000), small urban ((SU) population, 1,000–30,000), non-urban (NU) and point-source-influenced (PS).

The differences between rural and urban SO_2 concentrations have been explored by Environment Canada and in the published literature. Arain et al. (2009) noted that urban areas often have higher temperatures and lower wind speeds than rural areas. Higher temperatures are due to thermal trapping by large buildings and release of heat from anthropogenic sources. Increased surface roughness, increased surface length and friction contribute to reduced wind speeds. These two factors may explain the observed buildup of gaseous pollutants in urban areas, resulting in higher exposure concentrations in these areas. Additionally, differences in the size and number of sources may also account for the differences between rural and urban concentrations.

In the Canadian experience, urban levels are generally higher than rural levels; however, some rural sites have exhibited higher SO_2 concentrations than some urban sites, likely due to higher industrial emissions of SO_2 in the vicinity of those sites.

A summary of ambient and outdoor (outside of residences) SO_2 concentrations is provided in Table B.1 (Appendix B) from studies (1995 until January 2010) that focus on North America and

that emphasize either seasonal data or comparisons of urban and rural concentrations. Mean concentrations ranged up to a 24 hour average of 11.3 ppb.

4.2 Environmental Fate

Sulphur dioxide is rapidly oxidized to sulphur trioxide (SO_3) and sulphuric acid (H_2SO_4) and its anion, sulphate (SO_4^{2-}), upon atmospheric release. This may occur photochemically or catalytically. Catalytic oxidation plays a large role in the atmospheric chemistry of SO_2 and may involve oxidation reactions: on the surface of particles, such as carbon, metals (resulting in “dry deposition”); with hydrocarbons; as well with gases such as elemental oxygen (O), oxygen (O_2), ozone (O_3), nitric oxide (NO), nitrite (NO_2^-), nitrate (NO_3), dinitrogen pentoxide (N_2O_5), and the hydroxyl radical ($^{\bullet}OH$) (Agency for Toxic Substances and Disease Registry (ATSDR), 1998).

Because of the rapid oxidation of SO_2 there are significant spatial variations in its concentration related to the distance from the source of emissions.

Although SO_3 can also be emitted from the stacks of power plants and factories, it reacts extremely rapidly with water (H_2O) in the stacks or immediately after release into the atmosphere to form H_2SO_4, which mainly condenses onto existing particles when particle loadings are high; it can nucleate to form new particles under lower concentration conditions. Thus, only SO_2 is present in the tropospheric boundary layer at concentrations of concern for human exposures (US EPA, 2008).

5.0 Exposure Assessment

5.1 Sulphur Dioxide Exposure Concentrations

5.1.1 Published Exposure Data

It is important to consider all sources of air exposure to SO_2 when developing exposure parameters, including both indoor and ambient air. Several factors have been identified for evaluating the results of personal exposure studies from outdoor sources. Personal–ambient exposure relationships appear to be very much dependent on ambient conditions (e.g. season and meteorological conditions) and seasonal behaviours (e.g. having open or closed windows; time outdoors); in addition, personal–ambient exposure associations appear to be ventilation-specific as opposed to seasonally-dependent (Sarnat et al., 2000, 2006). This observation may not hold true during winter in cold climates because windows are normally closed (or only open for short periods of time) during winter (Brown et al., 2009).

The fraction of data below the detection limit might be a concern for some studies (Sarnat et al., 2000, 2001, 2005). Correlation coefficients between personal exposure and ambient concentrations would be biased low if data used in their calculation were below detection limits (US EPA, 2008).

General observations from a review of papers discussing the relationship between personal exposure and ambient, outdoor or indoor air concentrations include:

- Personal exposures to SO_2 vary widely depending on location and appear to be most strongly correlated with outdoor exposures (Silverman et al., 1982; Brauer et al., 1989; Hosein et al., 1991; Sarnat et al., 2005).
- Other associations, such as differences in personal exposure by season, are unclear (Sarnat et al., 2001, 2006).
- There is no consistent trend between ambient/outdoor air concentrations of SO_2 and indoor concentrations, except that the indoor concentrations are usually lower. The outdoor/indoor SO_2 exposure concentration ratios are not consistent across studies (ranging from 0.027 to 1.01), making it difficult to model indoor exposures based upon outdoor or ambient concentrations (US EPA, 2008).

When compared against the downward trend in environmental concentrations (see Section 4.1), the information on ambient and personal exposures contained in the papers bulleted above was outdated. Thus the Canadian data reported in these studies present an inadequate assessment of current ambient levels of SO_2, due to marked decreases in air emissions of SO_2 in recent decades. Recent Canadian ambient values for both chronic and acute exposure time periods are presented below. Personal exposures vary based on a number of factors, including activity patterns (e.g. time spent outdoors). Modelling of recent environmental and indoor SO_2 concentrations to acute and chronic exposure doses has been undertaken to further characterize exposures of Canadians; see Section 8.

5.1.2 Canadian Ambient Exposure Monitoring

5.1.2.1 Analysis of NAPS Data

Data from NAPS stations for the year 2011 are presented in Tables 5.1, 5.2 and 5.3; they were analyzed on an all-monitor basis, as well as stratified by urban (residential, industrial, commercial) and rural (undeveloped, forest, agricultural) designations. Only data points with data available for 75% of the averaging time were included. When percentile analysis was done for the 1-h NAPS data from 2011, it became clear that the majority of monitors were not detecting SO_2 (reported as 0.0) on a regular basis. Non-detect recordings were uniform for all stations to the 25th percentile analysis, regardless of location in Canada. This pattern of SO_2 ambient concentrations of generally low levels with intermittent short peaks is reflected by the much higher levels observed with the shorter averaging times. Urban areas had consistently higher levels of SO_2 than rural areas. Residential urban areas were considered the most relevant for the majority of the population and generally had the highest levels, although Industrial areas were, as expected, slightly higher in some cases.

Table 5.1: NAPS SO_2 (ppb) summary information for 2011—hourly averaging time

Hourly averaging time	All sites	Urban	Urban–Residen-tial	Urban–Industrial	Urban–Com-mercial	Rural	Rural–Undevel-oped	Rural–Forest	Rural–Agricul-ture
n	879505	765391	470899	86583	207909	114114	16905	16210	80999
mean	1.5	1.7	1.8	1.3	1.5	0.5	0.2	0.7	0.6
SD	5.5	5.9	6.2	6.9	4.4	1.6	0.7	2.4	1.5
min	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
p1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
p5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
p10	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
p25	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
p50	0.0	0.0	0.0	0.0	1.0	0.0	0.0	0.0	0.0
p75	1.0	1.0	1.0	1.0	1.0	1.0	0.0	1.0	1.0
p90	3.0	3.0	3.0	2.0	3.0	1.0	1.0	1.0	2.0
p95	6.0	6.0	8.0	4.0	5.0	2.0	1.0	2.0	3.0
p99	27.0	30.0	33.0	15.0	21.0	6.0	3.0	11.0	6.0
max	388.0	388.0	**314.0**	388.0	206.0	70.0	12.0	58.0	70.0

Table 5.2: NAPS SO_2 (ppb) summary information for 2011—daily averaging time

Daily averaging time	All sites	Urban	Urban–Residen-tial	Urban–Industrial	Urban–Com-mercial	Rural	Rural–Undevel-oped	Rural–Forest	Rural–Agricul-ture
n	37523	32593	20112	3706	8775	4930	716	700	3514
mean	1.5	1.7	1.8	1.3	1.5	0.5	0.2	0.7	0.6
stddev	3.8	4.0	4.5	3.4	3.0	0.9	0.5	1.4	0.8
min	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
p1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
p5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
p10	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
p25	0.0	0.1	0.0	0.2	0.1	0.0	0.0	0.0	0.0
p50	0.6	0.7	0.6	0.7	0.7	0.2	0.0	0.1	0.3
p75	1.3	1.4	1.4	1.4	1.3	0.7	0.2	0.8	0.8
p90	3.1	3.4	3.9	2.5	3.2	1.5	0.5	1.9	1.5
p95	5.9	6.7	7.8	3.9	6.0	2.1	0.9	3.1	2.1
p99	21.0	22.8	27.5	12.7	15.4	4.3	2.5	7.1	3.9
max	88.0	88.0	**56.0**	88.0	52.3	11.2	5.7	11.2	10.0

Table 5.3: NAPS SO_2 (ppb) summary information for 2011—annual averaging time

Annual averaging time	All sites	Urban	Urban–Residen-tial	Urban–Industrial	Urban–Com-mercial	Rural	Rural–Undevel-oped	Rural–Forest	Rural–Agricul-ture
n	102	88	54	10	24	14	2	2	10
mean	1.3	1.5	1.5	1.4	1.4	0.5	0.2	0.7	0.6
stddev	1.6	1.7	1.7	1.2	1.8	0.4	0.1	0.8	0.3
min	0.0	0.0	0.0	0.4	0.2	0.1	0.1	0.1	0.3
p1	0.1	0.0	0.0	0.4	0.2	0.1	0.1	0.1	0.3
p5	0.1	0.2	0.1	0.4	0.2	0.1	0.1	0.1	0.3
p10	0.2	0.2	0.2	0.6	0.3	0.1	0.1	0.1	0.3
p25	0.4	0.4	0.4	0.8	0.4	0.3	0.1	0.1	0.3
p50	0.8	0.9	0.9	1.1	0.8	0.5	0.2	0.7	0.5
p75	1.4	1.5	1.8	1.2	1.4	0.6	0.3	1.2	0.6
p90	3.3	3.5	3.4	2.9	3.5	1.1	0.3	1.2	1.1
p95	4.7	5.2	5.3	4.5	5.2	1.2	0.3	1.2	1.1
p99	7.9	8.6	8.6	4.5	7.9	1.2	0.3	1.2	1.1
max	8.6	8.6	**8.6**	4.5	7.9	1.2	0.3	1.2	1.1

5.1.2.2 Analysis of Health Canada Exposure Data

Sulphur dioxide air concentration data generated by ambient Airpointer monitors in Sault Saint Marie, ON, Montreal, QC, and Halifax, NS, during the years 2009 to 2011 demonstrate the complexity in analysis of SO_2 levels in ambient air. These data were generated by the Exposure Assessment Section of the Air Health Effects Assessment Division, Health Canada, which measured ambient air in these communities for three to five months.

Both the Airpointer monitor and NAPS monitors use a pulsed fluorescence gas analyzer developed by Thermo Scientific to measure SO_2. Comparison between the Airpointer and NAPS data shows the data are in good agreement. Moreover, these Airpointer data complement NAPS data because they are more sensitive for SO_2 analysis, providing a minute-by-minute analysis that captures short-term emission increases and the volatility of SO_2 better than the integrated monitors, which average concentration over a given time frame (e.g. 1-h averaging time).

Overall, the Airpointer air quality readings (Table 5.4) at all locations showed air concentrations of less than 12 ppb up to the 75th percentile exposure for all averaging times, With the exception of the Bonney neighbourhood of Sault Ste. Marie, which is near an industrial site and which exceeded 12 ppb exposure at all averaging times in the 90th percentile exposure, ambient air concentrations did not exceed 12 ppb until the 95th percentile measurements or greater, and the maximum exposure concentrations after the 99th percentile were found at shorter averaging times. These data indicate that SO_2 levels are typically measured very close to the limit of detection, but that there are acute spikes in concentration, particularly in areas where industry influences air quality measures for SO_2. The frequency and intensity of the concentration spike is likely related to the source of the SO_2 emissions, and is expected to vary by location.

Table 5.4: Airpointer data percentile analysis by monitoring site

					Percentiles (ppb)										
Location	Averaging Period	No. of measurements	Mean (SO_2 ppb)	Std. Dev.	Min.	1st	5th	10th	25th	50th	75th	90th	95th	99th	max
Halifax 1012	24 hours	360	1.6	1.6	0	0	0.1	0.3	0.6	1.1	1.9	3.6	4.8	8.2	11.4
	60 minutes	8348	1.6	3.1	0	0	0	0.1	0.4	0.7	1.5	3.6	6.4	15.2	55.6
	30 minutes	16862	1.6	3.4	0	0	0	0.1	0.4	0.7	1.5	3.6	6.4	16.1	91.4
	10 minutes	50991	1.6	3.5	0	0	0	0	0.4	0.7	1.4	3.6	6.4	16.3	127.1
	1 minute	512061	1.6	3.6	0	0	0	0	0.4	0.7	1.4	3.6	6.4	16.5	240.6
Halifax 2044	24 hours	361	0.5	0.6	0	0	0	0	0.1	0.3	0.6	1.1	1.6	3.2	4.8
	60 minutes	8276	0.5	1.1	0	0	0	0	0	0.1	0.4	1.1	1.9	5.1	29
	30 minutes	16559	0.5	1.2	0	0	0	0	0	0.1	0.4	1.1	1.9	5.5	38.1
	10 minutes	50444	0.5	1.2	0	0	0	0	0	0.1	0.4	1.1	1.9	5.6	40.2
	1 minute	508450	0.5	1.3	0	0	0	0	0	0.1	0.4	1.1	1.9	5.6	48.7
Halifax 2045	24 hours	359	0.8	1.0	0	0	0	0.1	0.2	0.4	1.1	2.1	2.7	4.4	8
	60 minutes	8248	0.8	2.1	0	0	0	0	0	0.2	0.7	1.9	3.6	9.5	69.6
	30 minutes	16498	0.8	2.2	0	0	0	0	0	0.2	0.7	1.9	3.6	10.2	81.1
	10 minutes	50244	0.8	2.3	0	0	0	0	0	0.2	0.7	1.8	3.6	10.9	116.5
	1 minute	506190	0.8	2.4	0	0	0	0	0	0.2	0.7	1.8	3.6	11.2	122.2
Montreal, Chenier	24 hours	136	2.5	3.8	0	0	0.1	0.1	0.3	0.9	2.9	7.9	10.3	18.3	22.6
	60 minutes	3155	2.5	5.7	0	0	0	0	0.1	0.5	1.7	6.4	12.8	30.9	63.5
	30 minutes	6457	2.4	5.9	0	0	0	0	0.1	0.5	1.7	6.3	13	32.6	74.6
	10 minutes	19376	2.4	6.2	0	0	0	0	0.1	0.5	1.6	6.1	12.4	34	87.8
	1 minute	194045	2.4	6.3	0	0	0	0	0.1	0.5	1.6	5.9	12.3	34.6	107.5
Montreal, St.Eglise	24 hours	68	1.1	1.1	0	0	0.1	0.1	0.2	0.7	1.6	3.1	3.3	5.3	5.3
	60 minutes	1589	1.1	2.2	0	0	0	0	0.1	0.4	1.1	2.9	5	11.4	29.5
	30 minutes	3181	1.1	2.3	0	0	0	0	0.1	0.4	1.1	2.9	5.3	11.6	33.5
	10 minutes	9688	1.1	2.4	0	0	0	0	0.1	0.4	1	3	5.2	12.2	51.5
	1 minute	96977	1.1	2.4	0	0	0	0	0.1	0.4	1	2.9	5.3	12.2	54
Montreal, St. Octave	24 hours	97	2.9	2.3	0.2	0.2	0.4	0.4	1.2	2.4	3.9	6.2	7.5	14	14
	60 minutes	2227	2.9	4.3	0	0	0	0	0.4	1.5	3.6	7.2	11	21.7	44.4
	30 minutes	4555	2.9	4.7	0	0	0	0	0.3	1.3	3.4	7.3	11.9	24.5	46.8
	10 minutes	13663	2.9	5.2	0	0	0	0	0.3	1.1	3.3	7.3	12.3	25.8	66.6
	1 minute	136406	2.9	5.9	0	0	0	0	0.3	1.1	3.1	7.1	12.1	29.1	154.6
Sault Ste Marie, Bonney	24 hours	80	6.2	7.7	0	0	0	0	0.2	3.0	3	19.8	23.9	30.9	30.9
	60 minutes	1935	6.4	13.4	0	0	0	0	0	0.5	0.5	22.9	36.5	60.7	119.9
	30 minutes	3958	6.5	14.2	0	0	0	0	0	0.5	0.5	23.4	37.2	68.9	147.2
	10 minutes	11795	6.4	15.2	0	0	0	0	0	0.5	0.5	22.2	37.3	71.5	322.1
	1 minute	118232	6.5	16.5	0	0	0	0	0	0.5	0.5	20.6	36.9	77.7	498.5
Sault Ste. Marie, College	24 hours	93	1	1.3	0	0	0.1	0.1	0.2	0.5	0.5	2.7	3.8	7.5	7.5
	60 minutes	2148	1	3.2	0	0	0	0	0.1	0.2	0.2	1.4	3.6	17.2	41.6
	30 minutes	4393	1	3.3	0	0	0	0	0.1	0.2	0.2	1.3	3.4	18.9	47.4
	10 minutes	13181	1	3.4	0	0	0	0	0	0.2	0.2	1.3	3	19.3	54.9
	1 minute	131539	1	3.5	0	0	0	0	0	0.1	0.2	1.3	3	19.5	80.5

6.0 Sulphur Dioxide Dosimetry and Toxicokinetics

Dosimetry refers to the determination of the amount of SO_2 or its reaction products reaching and persisting at specific sites (in this case, in the respiratory tract) after exposure. Dosimetric information is important for understanding inhalation toxicity, including the extrapolation of effects found in toxicological studies of laboratory animals to those observed in humans, and for relating effects in healthy individuals to those in susceptible individuals.

For dosimetric purposes the respiratory tract can be divided into three sections: extrathoracic, tracheobronchial, and alveolar. The extrathoracic region is the area through which air first passes during inhalation and includes airways within nasal and oral passages to the larynx. In contrast to most experimental animals used in inhalation studies, which are obligatory nose-breathers, humans are oro-nasal breathers, able to breathe either through the nose, the mouth, or both airways simultaneously. Air enters through the extrathoracic region, and passes through the tracheobronchial section of the respiratory tract via the trachea. The trachea bisects into two bronchi, which subsequently branch into smaller segments until the terminal bronchiolar region. The gas-exchange section at the end of the terminal bronchioles is referred to as the alveolar region, which is specifically composed of respiratory bronchioles, alveolar ducts, alveolar sacs and alveoli. All of the conducting airways, with the exception of the trachea and portions of the main stem bronchi, are surrounded by parenchymal tissue, while blood and lymphatic vessels irrigate alveolar structures (US EPA, 2004; Wang, 2005).

6.1 Particle Dosimetry

Sulphur dioxide can form particles, as described in Section 4.2.2. Retention of particles (particulates) within the respiratory tract is governed by the balance between deposition and clearance processes. Deposition of inhaled particles in the respiratory tract is mainly influenced by the physical and chemical properties of the particles, and the morphology and physiological status of the respiratory tract. After deposition onto the surfaces of the respiratory tract, particles are subjected to either absorptive or non-absorptive particulate clearance processes. These processes may result in their removal or translocation of particles from airway surfaces, as well as their removal from the respiratory tract itself. Clearance of deposited particles depends upon the initial site of deposition and upon the physicochemical properties of the particles, both of which affect the disposition of the particles to specific translocation pathways.

Sulphur particles are routinely classified as a component of PM. They typically fall within the range of particulates less than 2.5 micrometers aerodynamic diameter ($PM_{2.5}$; fine particles), and evidence supports sulphur particles forming a large part of the ultrafine pollutant particle fractions (Jeong et al., 2004). Fine particles, including sulphur particles, were evaluated by Health Canada as part of the *Canadian Smog Science Assessment* document (Government of Canada, 2012). For the purposes of this assessment, only the gaseous SO_2 was considered; for information on the health effects of PM, please refer to the *Canadian Smog Science Assessment* document.

6.2 Gas Dosimetry

Similarly to particle dosimetry, gas dosimetry must consider the physiology and morphology of the respiratory tract, as well as breathing patterns. Physicochemical properties of SO_2 relevant to respiratory tract uptake include its solubility and diffusivity in the fluid of epithelial cells, as well as its reaction rate with other components of epithelial fluid.

The amount of SO_2 absorbed from the gas phase to the aqueous phase is directly proportional to the partial pressure or concentration of SO_2 in the gas phase. Henry's Law constant provides information on the solubility of SO_2 in liquids at equilibrium, and the value (0.048 (mol/L) air/(mol/L) water at 37°C and 1 atm pressure) is inversely proportional to the gas solubility (US EPA, 2008). Sulphur dioxide gas is very water-soluble and will be absorbed rapidly, with at least 99% of the gas absorbed (US EPA, 2008).

The site where SO_2 is absorbed is dependent upon whether the individual exposed is at rest or is undergoing physical exertion. Sulphur dioxide is predominately absorbed in the nasal passages of both humans and laboratory animals under resting conditions; but under conditions of physical exertion (greater than mild exertion), SO_2 absorption shifts from the extrathoracic regions to the tracheobronchial regions (US EPA, 2008). This bi-modal dosimetry pattern occurs because humans shift from nasal breathing to oro-nasal breathing and experience increased ventilation rates as their level of physical exertion increases.

6.3 Interspecies Variation

Species can differ from each other in fundamental aspects of physiology and anatomy (e.g. metabolism, airway branching, hormonal regulation) that may limit extrapolation from laboratory animals to humans (US EPA, 2008). Many data on SO_2 effects originate from laboratory experiments in animals exposed either through inhalation or intratracheal instillation. Extrapolating findings from laboratory animals to humans exposed under similar scenarios requires a good understanding of the similarities and differences in dosimetry across diverse species. Comparing the results of dosimetric studies in animals to those in humans necessitates that the following be considered: 1) differences in laboratory exposure protocols and dosimetry calculation, 2) anatomical and physiological differences between human and animal lungs, and 3) incorporation of the above in interspecies model extrapolation. A detailed description of these differences can be found in the *Canadian Smog Science Assessment* document (Government of Canada, 2012). With respect to absorption kinetics, it appears that for both laboratory animals and humans, under conditions of rest, the absorption rate is close to 99% in the extrathoracic areas (US EPA, 2008).

6.3.1 The Ovalbumin Sensitization Model of Asthma in Animals

Several papers have been published evaluating the applicability of animal models to asthmatic responses in humans. To date, no animals are known to have a naturally occurring asthmatic phenotype (Kucharewicz et al., 2008). In humans, the asthmatic phenotype is characterized by chronic airway inflammation, and immediate or late (or both) asthmatic responses after exposure to an asthmatic trigger (Pauluhn and Mohr, 2005; Kucharewicz et al., 2008). A representative allergic asthma model has been developed whereby an animal, usually a rodent, is sensitized by a chemical agent—often ovalbumin (OVA), but also house dust mite or *Ascaris* antigens—on one or multiple occasions to simulate either an acute or chronic asthmatic

response (Whitehead et al., 2003; Pauluhn and Mohr, 2005; Kucharewicz et al., 2008). After sensitization, the animals are challenged with the substance of interest; if the asthmatic response is being tested the animal should be challenged with OVA at the time of exposure to the chemical of interest (Bissonnette, 2012). If airway hyperresponsiveness (AHR) is being evaluated, the animal should be challenged with OVA 24 h prior to exposure to the chemical of interest (Bissonnette, 2012). These results are generally compared against both positive and negative control groups (positive control—rodents challenged with OVA only; negative control—rodents not exposed to anything).

Overall, interpretation of OVA-sensitized rodent models of asthma requires sensitivity to variables such as the OVA challenge method used, the rodent strain evaluated, and the length of time the OVA challenge has persisted with respect to the endpoint evaluated. For example, a challenge when evaluating asthmatic-type responses in allergic-sensitized animals arises because the OVA model of allergic sensitization can be modified in many ways, and the type of sensitization used is important to evaluation of results. Additionally, species and strain differences in response to OVA sensitization and development of the allergic phenotype are known (Kucharewicz et al., 2008; Zhu and Gilmour, 2009). The OVA sensitization followed by an OVA challenge produces a significant increase in total immunoglobulin-E (IgE) and histological changes in the airway (Pauluhn and Mohr, 2005) that are often consistent with human asthma pathology; however, some changes are not consistent with the human asthmatic phenotype (e.g. pulmonary parenchymal inflammation), and these factors should be considered when extrapolating to human exposure scenarios.

6.3.1.1 The Rat Model of Asthma

The allergic sensitization model most commonly used to extrapolate human asthmatic responses is the OVA-induced asthmatic phenotype in the rat (Kucharewicz et al., 2008). After OVA sensitization, rats exhibit features of airway allergy and allergic asthma that can be equated to human responses: specifically, immediate and late asthmatic responses after an allergen challenge; responses after non-specific challenge with methacholine, acetylcholine or serotonin; IgE production; and inflammatory responses (Kucharewicz et al., 2008). As a model of airway remodelling, OVA-sensitized rats must be evaluated carefully. After allergen sensitization, a rat requires at least three OVA challenges before it is possible to see airway remodelling presented as an increase in airway smooth muscle (caused by hyperplasia, proliferation and the inhibition of apoptosis) (Palmans et al., 2000; Kucharewicz et al., 2008).

The review by Kucharewicz et al. (2008) indicates that rat models of asthma are focused mainly on evaluating inflammatory processes related to human asthma. To that end, there are significant differences between rat strains (e.g. Brown Norway, Wistar, Sprague Dawley, and Fisher or Lewis rats) outlined in the literature (Kucharewicz et al., 2008). Additionally, Kucharewicz et al. noted that OVA-sensitized animal models of asthma are suitable for evaluating acute inflammatory events but not chronic events, due to adaptive responses.

6.4 Toxicokinetics of Sulphur Dioxide Exposure

The term toxicokinetics describes the rate at which a chemical enters the body and what happens to the chemical once it is in the body.

6.4.1 Route of Exposure

Humans can be exposed to SO_2 through inhalation, dermal and oral exposures. Ocular effects following gaseous exposure have also been described. However, the most relevant exposure pathway to humans is through inhalation, since SO_2 is a gas under standard conditions. Following inhalation of SO_2, the respiratory tract could be exposed to a variety of components, including SO_2 alone, hydrogen ions (H^+), H_2SO_4 or SO_3^{2-} and SO_4^{2-}, which may be in combination with the ammonium ion or a metal cation. A further complication is the fact that a number of these components may be in particulate form or absorbed to particulates, which may vary in chemical composition (UK Department of Health, 1992).

6.4.2 Absorption

Inhaled SO_2 is very water soluble. It is rapidly solubilized in the upper respiratory tract and can then be absorbed across nasal mucosa and the mucosal cells of the trachea (ATSDR, 1998; Arts et al., 2006; van Thriel et al., 2010). Sulphur dioxide is minimally absorbed by mucosa of the lower respiratory tract due to limited exposure. Lower respiratory tract exposure is increased with increased ventilation associated with a transition from nasal to oro-nasal breathing at a mean minute ventilation of 30 L/mm (ATSDR, 1998).

The fraction of SO_2 gas that desorbs from the respiratory tract is unclear. The ATSDR (1998) referenced a study showing that desorption fractions of SO_2 from mucous membranes of humans were as high as 15%; however, desorption to this level is unlikely given the solubility of the gas. Additionally, this finding was not supported by a controlled exposure study using dogs, which found that the concentration of SO_2 in exhaled gas was low, representing 1% of the exposure level (ATSDR, 1998). For the purposes of this risk assessment, an absorption rate in humans of 99%, as serum sulphite, will be used.

Gaseous SO_2 may also solubilize to sulphurous acid (H_2SO_3) in the tear solution of the eye (van Thriel et al., 2010).

6.4.3 Distribution

Once absorbed across mucosal cells, SO_2 is hydrolyzed to SO_3^{2-}, the sulphur trioxide radical ($^{\bullet}SO_3^{2-}$), with equilibrium products of HSO_3^- and H^+, which are taken up by the blood and distributed throughout the body (Gunnison et al., 1981; ATSDR, 1998). The equilibrium dissociation ratio for HSO_3^- and SO_3^{2-} is 1:3 M/M, in neutral fluid and plasma of mammals (Shapiro, 1977). In mice, inhalation of SO_2 resulted in increased SO_3 content in the brain, heart and lung, in a dose-dependent manner. For each doubling of SO_2 concentration, organ concentrations of SO_3^{2-}, expressed as μg/mg protein, increased from 1.1 to 1.5 times (Meng et al., 2005a).

6.4.4 Metabolism

Reported metabolic pathways for SO_3^{2-} in the blood include: 1) enzymatic oxidation to SO_4^{2-} by sulphite oxidase (SOX); 2) two-step enzymatic oxidation by peroxidases (e.g., horseradish peroxidase, prostaglandin hydroperoxidase); 3) formation of disulphide bonds with proteins to form S-sulphonate ($R\text{-}S\text{-}SO_3^-$); 4) reaction with amino acids (e.g. binding cysteine to form S-sulphocysteine); 5) transformation to thiosulphate ($S_2O_3^{2-}$); and 6) auto-oxidation to SO_4^{2-} in the presence of metals (Crawhall, 1985; Constantin et al., 1996; ATSDR, 1998; Komarnisky et al., 2003; US EPA, 2008). Of these, the most commonly reported pathways for SO_3^{2-} metabolism are by SOX found in the mitochondria (highest levels in the liver, kidney and heart) and the

formation of disulphide bonds with proteins (R) to generate R-S-SO_3^-. Of interest to this discussion is that the ATDSR (1998) reported that plasma levels of R-S-SO_3^- correlate positively with concentrations of SO_2 in the air in studies using humans exposed to SO_2 by inhalation. The metabolism of S-sulphonates is unknown, but it is hypothesized that they will be reduced by glutathione reductase and the SO_3^{2-} molecule will be oxidized by SOX to SO_4^{2-}.

Sulphite oxidase is necessary for sulphur-containing amino acid catabolism. It oxidizes SO_3^{2-} to SO_4^{2-}, which is the major excretory form of sulphur in urine (ATSDR, 1998; Komarnisky et al., 2003). Sulphite oxidase is ubiquitous in human tissues; its activity varies depending on the tissue being evaluated and with age (Constantin et al., 1996).

6.4.4.1 Half-life

The World Health Organization's INCHEM database (WHO INCHEM) was the only source for half-life data for derivatives of SO_2 in humans or animal models, and it referenced studies performed by Gunnison in the 1970s. Various endpoints were reported by INCHEM, with an estimated SO_3^{2-} half-life in humans of 15 min (based upon 10 min in the Rhesus monkey [i.v. administration; doses of 0.3–0.6 mmol/kg-bw]) and a plasma S-sulphonate half-life of 4 and 8 d in the rat and rhesus monkey, respectively. One study referenced showed plasma S-sulphonate levels in humans increased by 1.1 ± 0.16 nmol/ml for each increment of 1 ppm in exposure level.

6.4.5 Elimination

The primary route of elimination has been identified as urinary excretion, primarily as SO_4^{2-} (ATSDR, 2011). At this time, it is unclear whether SO_2 is released from pulmonary capillaries during expiration.

7.0 Health Effects Assessment

This section presents the health-related literature on SO_2 from epidemiological, controlled exposure, toxicological and *in vitro* studies over the years 2007–2011, as well as a brief summary of the US EPA (2008) findings.

7.1 Odour Detection

El-Dars et al. (2004) published an odour threshold for SO_2 at 0.5 ppm. This value was substantiated by van Thriel et al. (2010) in their laboratory study, whereby the lowest exposure concentration of 0.5 ppm was associated with odour annoyance. Other groups reported odour threshold ranges for SO_2 from 0.3 to 1 ppm (ATSDR, 2011; Indian Institute of Science, 2011). The published odour threshold of 0.5 ppm is greater than the air quality criteria or standards regulated by Canadian provinces and territories, as well as by international bodies and governments.

7.2 Irritation

A review by Arts et al. (2006) of studies of groups of 6 to 37 healthy volunteers exposed to concentrations of between 0.2 and 23 ppm SO_2, with exposures lasting from minutes up to several hours and carried out with or without physical exercise, identified irritant effects to the upper airway and the eye at exposure levels of 1 ppm and higher in combination with exercise. Asthmatic volunteers reacted similarly to healthy individuals but showed these reactions at slightly lower levels. Lung function changes were also observed at levels of 1 ppm and higher, although these effects were again almost exclusively associated with exercise (Arts et al., 2006). Exercise results in increased ventilation parameters, which in turn results in lower respiratory tract perfusion and more exposure to the gas when compared against exposure in individuals at rest.

Exposure of workers in occupational settings to SO_2 concentrations greater than 6 ppm has been reported to produce instantaneous mucous membrane irritation. Symptoms included ocular irritation, lacrimation, rhinorrhea, cough, shortness of breath, chest tightness or discomfort and a choking sensation (Arts et al., 2006).

7.3 Respiratory Morbidity

7.3.1 Summary of 2008 US EPA Integrated Science Assessment

7.3.1.1 Short-term Exposure and Respiratory Morbidity

7.3.1.1.1 Airway inflammation

The US EPA (2008) reported that there was insufficient controlled human exposure and epidemiologic evidence to conclude that exposure to SO_2 at current ambient concentrations is associated with airway inflammation. Toxicological studies in guinea pigs, however, indicated that repeated exposures to SO_2 at concentrations as low as 0.1 ppm may exacerbate inflammatory responses in allergic animals (Riedel et al., 1988; Park et al., 2001).

7.3.1.1.2 Respiratory morbidity in adults (asthma)

The US EPA (2008) concluded that there is a causal relationship between respiratory morbidity and short-term exposure to SO_2. The strongest evidence for this causal relationship came from controlled human exposure studies reporting respiratory symptoms and decreased lung function following peak exposures to SO_2 of 5–10 min duration. These effects have been observed consistently across studies involving asthmatics exercising at mild to moderate intensity (Sheppard et al., 1981; Bethel et al., 1985; Linn et al., 1987, 1988, 1990). Statistically significant decreases in lung function accompanied by respiratory symptoms (e.g. wheeze and chest tightness) were clearly demonstrated following exposure to 0.4–0.6 ppm SO_2. Some studies have also reported moderate to large decrements in respiratory endpoints of asthmatic subjects (5–30%) at exposures of 0.2–0.3 ppm, but these results were not statistically significant.

The US EPA (2008) adopted guidance from the American Thoracic Society (ATS) on what constitutes an adverse health effect of air pollution (ATS, 2000), and concluded that an air pollution-induced shift in the population distribution of a given health endpoint should be considered adverse, even if the shift does not result in immediate occurrence of illness in any one individual in that population. The ATS (2000) also recommended that transient loss in lung function with accompanying respiratory symptoms attributable to air pollution be considered an adverse health effect. Taking this into account, the US EPA (2008) found that in the asthmatic subpopulation, mainly represented by otherwise healthy asthmatics, both the magnitude of decrements in lung function and the percentage of individuals affected were consistently related to increased SO_2 exposure at concentrations between 0.2 and 1.0 ppm (Linn et al., 1983, 1984, 1987, 1988, 1990; Bethel et al., 1985; Horstman et al., 1986). Sulphur dioxide-induced decrements in lung function (measured as increased specific airway resistance (sR_{aw}), decreased forced expiratory volume in 1 second (FEV_1) and peak expiratory flow rate (PEFR)) have frequently been associated with increases in respiratory symptoms among asthmatics (Balmes et al., 1987; Linn et al., 1983, 1987, 1988, 1990; Gong Jr. et al., 1995).

One of the key studies discussed by the US EPA (2008) was by Horstman et al. (1986). In this study, asthmatic subjects were exposed to five dose groups of SO_2 at concentrations ranging from 0 to 2 ppm for 10 min under exercising conditions (ventilation rate = 42 L/min). The authors reported that for 22% of the subjects, the concentration of SO_2 needed to produce a doubling of sR_{aw} compared to clean air exposure ($PC(SO_2)$), was <0.5 ppm. Two subjects experienced moderate decrements in lung function following exposure to SO_2 at concentrations ≤0.3 ppm. For approximately 15% of the subjects, the $PC(SO_2)$ was >2 ppm, with approximately 35% of asthmatic subjects experiencing a doubling in sR_{aw} versus clean air at ≤0.6 ppm SO_2 .

More recently, a controlled human exposure study of unmedicated SO_2-sensitive asthmatics exposed to increasing SO_2 concentrations (0, 0.5, and 1.0 ppm) over 10 min with varying levels of exercise (Gong Jr. et al., 1995) found that respiratory symptoms (shortness of breath, wheeze, and chest tightness) increased in a concentration-dependent manner. The investigators also reported that increasing SO_2 concentration had a greater effect on sR_{aw} and FEV_1 changes than increasing exercise level; specifically, exposure to 0.5 ppm SO_2 during light exercise evoked a more severe symptomatic response than heavy exercise in clean air. Similarly, Trenga et al. (1999) reported significant correlations between decreased FEV_1 and increased respiratory symptoms following 10-min SO_2 exposures (0.5 ppm) via mouthpiece.

Interestingly, the severity of individual asthma was not a predictor of individual sensitivity to SO_2.

In a related study, Linn et al. (1990) found that in medication-dependent moderate asthmatics, their normal treatment method (e.g. use of a long-acting bronchodilator) did not prevent airway responses to SO_2 and exercise. They did, however, find that SO_2-induced bronchoconstriction was significantly reduced when normal medication was supplemented with administration of a short-acting beta agonist immediately preceding exposure.

A large body of evidence supporting the US EPA determination of causality comes from epidemiologic studies reporting associations with respiratory symptoms, emergency department (ED) visits, and hospital admissions (see below) following short-term SO_2 exposures. A number of Canadian studies including a multi-city study were identified. In general, the epidemiologic studies examining adults did not provide strong evidence for an association between short-term exposure to ambient SO_2 and lung function, mainly because of a strong correlation between SO_2 and various co-pollutants in most studies, and the lack of evidence evaluating potential confounding by co-pollutants, which limited interpretation of these data.

7.3.1.1.3 Respiratory morbidity in children

The National Cooperative Inner-City Asthma Study reported that morning respiratory symptoms were found to be most strongly associated with 1- to 2-d lags in SO_2 concentration (median 3-h average ranged from 17 ppb to 37 ppb) (Mortimer et al., 2002); the associations remained robust in multi-pollutant models with O_3 and NO_2. In multi-pollutant models with PM_{10} the SO_2 effect was reduced, and became non-significant; however, the EPA indicated that this might be due to reduced statistical power or collinearity from multi-pollutant adjustment, which included O_3 and NO_2 (US EPA, 2008). Similarly, the Childhood Asthma Management Program study reported an association between SO_2 (median 24-h average concentrations of from 2.2 to 7.4 ppb) and increased risk of asthma symptoms at all lag periods, though the 3-d moving average was statistically significant (Schildcrout et al., 2006). The adverse effect to asthmatics appeared to be slightly larger in two-pollutant models with CO or NO_2, particularly at lag 2-d; however, effect estimates did not change appreciably when evaluating PM_{10} as a co-pollutant (Schildcrout et al., 2006). Once again, the Harvard Six Cities Study (Schwartz et al., 1994) analysis reported that SO_2 concentrations were associated with cough incidence and lower respiratory tract symptoms following exposure to 4.1 ppb SO_2 (median 24-h average concentration).

In co-pollutant analyses, PM_{10} was found to attenuate the SO_2 effect (Schwartz et al., 1994), which led to the conclusion that if the PM_{10} fraction is made of fine sulphate particles the PM_{10} association may be stronger than the SO_2 association. This study also investigated the SO_2 concentration–response function, reporting a non-linear relationship between SO_2 concentrations and respiratory symptoms. Although a trend toward increased lower respiratory tract symptoms with increasing SO_2 concentrations was observed at concentrations as low as 10 ppb, no statistically significant increase in the incidence was reported until the SO_2 concentration exceeded a 24-h average of 22 ppb (Schwartz et al., 1994). The last multi-city analysis that contributed to the US EPA's 2008 discussion was the Pollution Effects on Asthmatic Children in Europe (PEACE) study. It evaluated the effects of acute exposure to various pollutants, including SO_2, on the respiratory health of children with chronic respiratory symptoms over the winter of 1993/1994 (Roemer et al., 1998). The researchers found no

associations between SO_2 exposure and respiratory symptoms or bronchodilator use under any lag periods considered.

There is limited epidemiologic evidence indicating that atopic children and adults may be at increased risk for SO_2-induced respiratory symptoms (van der Zee et al., 1999, 2000; Boezen et al., 1999, 2005). For example, alternate analyses of longer time periods under the PEACE study observed statistically significant associations between SO_2 exposure and respiratory symptoms in children (van der Zee et al., 1999; Boezen et al., 1999). Particularly, the Boezen et al. 1999 analysis presented a strong case for effects because of the use of clinical endpoints such as AHR and atopy in children living in the Netherlands. Their analysis showed that in children with relatively high serum total IgE either with or without AHR, the prevalence of lower respiratory tract symptoms increased with increasing SO_2 concentration. For children with AHR and relatively high serum total IgE, the odds ratio (OR) for the prevalence of lower respiratory tract symptoms, for each 10 ppb increase in SO_2 concentration, was 1.70 with a 5-d moving average. For children without AHR but with relatively high serum total IgE, the OR was 1.82 with a 5-d moving average (Boezen et al., 1999).

Numerous epidemiologic studies have observed associations between short-term (≥ 1 h, generally 24-h average) exposure to SO_2 and adverse respiratory health effects in children. The associations between ambient SO_2 concentrations and several respiratory outcomes were generally consistent, with the large majority of studies showing positive associations. Multi-city studies, as well as several single-city studies, generated statistically significant findings for children. The effects on lung inflammation and AHR related to short-term exposure to SO_2 at levels as low as 0.1 ppm found in animal toxicological studies support the biological plausibility for the epidemiologic associations (Riedel et al., 1988; Park et al., 2001).

7.3.1.1.4 Hospital visits

Ambient SO_2 concentrations and ED visits and hospitalizations for all respiratory causes were for the most part consistent and robust for children and older adults (≥65 years), and for asthmatics (US EPA, 2008). These findings are generally strong when additional co-pollutants are included in the model. These associations are supported by panel studies that observed SO_2-related increases in asthma and other respiratory symptoms in children, as well as by controlled human exposure and animal toxicological studies that found a positive relationship between SO_2 exposure and various respiratory outcomes.

SO_2, Asthma, and ED Visits: Central effect estimates reported by the US EPA for asthma and ED visits range from -10% to 40% excess risk in ED visits and hospitalizations for asthma per 10 ppb increase in 24-h average SO_2 (Jaffe et al., 2003; Wilson et al., 2005; Ito et al., 2007; US EPA, 2008). Most of the effect estimates are positive (suggesting an association with SO_2 and ED visits and hospitalizations for asthma), though few were statistically significant at the 95% confidence level when results were stratified for children. Overall, studies reported by the US EPA (2008) regarding ED visits and hospitalizations provide evidence to support an association between ambient SO_2 levels and ED visits and hospitalizations for asthma.

SO_2, chronic obstructive pulmonary disease and ED Visits: Data on chronic obstructive pulmonary disease (COPD) and ED visits were very limited. The US EPA (2008) concluded that inconsistent evidence did not support a relationship between ambient SO_2 levels and ED visits and hospitalizations for COPD.

Respiratory diseases other than asthma or COPD and ED visits: Only a few studies were available to evaluate respiratory health outcomes other than asthma and COPD, and these results were mixed. Limited evidence indicates an association between ambient SO_2 levels and ED visits for upper and lower respiratory tract diseases (Moolgavkar et al., 1997; Lin et al., 1999, 2005; Atkinson et al., 1999; Hajat et al., 2002; Concejão Martins et al., 2002; Michaud et al., 2004; Peel et al., 2005; Barnett et al., 2005; Farhat et al., 2005; Villeneuve et al., 2006); however, it was difficult for the US EPA to draw conclusions about the effects of SO_2 on these diseases because of heterogeneity in the diseases evaluated and the limited data for each disease endpoint.

7.3.1.1.5 Other considerations

Experimental results from laboratory animals support the epidemiologic observations; studies in animals sensitized with OVA antigen demonstrate that repeated exposure to near-ambient SO_2 levels (as low as 0.1 ppm in guinea pigs) can exacerbate allergic responses, including airway inflammation and AHR (Riedel et al., 1988; Park et al., 2001). Additionally, two recent controlled human exposure studies, which demonstrated an increase in airway response to an inhaled allergen in asthmatic subjects following exposures to a combination of 0.2 ppm SO_2 and 0.4 ppm NO_2, support the epidemiological evidence that SO_2 exposures may lead to AHR in atopic children and asthmatic adults (Devalia et al., 1994; Rusznak et al., 1996).

Results from intervention studies have shown that improvements in air quality, in particular large decreases in SO_2 concentrations, were associated with improvements in respiratory symptoms and lung function (Peters et al., 1996; Keleş et al., 1999; Heinrich et al., 2002; Frye et al., 2003). The study by Peters et al. (1996) evaluated the effects of regulatory changes made in Hong Kong in 1990, which required all power plants and road vehicles to use fuel oil with a sulphur content of ≤0.5% by weight. The intervention study showed that these changes resulted in rapid improvements in air quality—with up to 80% reduction in SO_2 concentration and up to 38% reduction in SO_4^{2-} concentrations. When comparing polluted and unpolluted districts, these pollutant reductions were associated with a decline in reported symptoms of cough, sore throat, phlegm, and wheezing (Peters et al., 1996). Another set of studies (Heinrich et al., 2002; Frye et al., 2003) found that reductions in air pollutant levels, including 90% decreases in SO_2 concentration and 60% decreases in total suspended particles (TSP) were related to decreases in adverse respiratory outcomes. In addition, Frye et al. (2003) concluded that corresponding increases in lung function parameters of forced vital capacity (FVC) and FEV_1 per 5 ppb decrease in annual mean SO_2 concentration might indicate that persistent poor respiratory function outcomes are reversible with improvements to air quality. However, SO_2 is usually found in conjunction with other pollutants (TSP, PM_{10}, metals), and therefore it was difficult for the US EPA to ascribe the improvements in lung function and respiratory symptoms to SO_2 alone.

Animal toxicology studies that expanded on the intervention studies but were conducted at higher concentrations (≥1 mg/m^3 PM and ≤1 ppm SO_2) suggested that SO_2 effects may be potentiated by co-exposure to PM (US EPA, 2008). However, the relevance of these results to normal ambient exposures is unclear because the reported improvements in respiratory health may be jointly attributed to declines in both SO_2 and PM. The US EPA (2008) concluded that, considered in conjunction with the larger body of evidence from epidemiologic, controlled human exposure, and animal toxicological studies, intervention studies are supportive of SO_2-related effects on respiratory morbidity.

7.3.1.2 Long-term Exposure and Respiratory Morbidity

The US EPA (2008) reported that the overall epidemiologic evidence for respiratory effects of long-term exposure to SO_2 was inadequate to infer a causal relationship. Studies examining the effects of long-term exposure to SO_2 on asthma, bronchitis, and respiratory symptoms (Dockery et al., 1996; Studnicka et al., 1997; Hirsch et al., 1999; Ramadour et al., 2000; Herbarth et al., 2001; Pikhart et al., 2001; Goss et al., 2004; Hwang et al., 2005; Pénard-Morand et al., 2005) reported positive associations in children; however, the variety of outcomes examined and the inconsistencies in the observed results made it difficult to conclusively determine the effect of long-term exposure of SO_2 on respiratory symptoms.

The US EPA reported only a few animal toxicology studies examining the effect of long-term exposure to SO_2 on lung function. Results from these studies do not provide strong biological reasons for respiratory morbidity resulting from long-term ambient exposure to SO_2 . The studies reviewed by the US EPA reported no effects on physiological lung function at SO_2 concentrations ≤5 ppm in rabbits and dogs (Scanlon et al., 1987; Douglas et al., 1994); however, one study found decreased residual volume at 1 ppm SO_2 in rats (Smith et al., 1989). In addition, no morphological changes were found in guinea pigs exposed to 1 ppm SO_2 in a subacute study (Conner et al., 1985), or in rats exposed sub-chronically to 5 ppm SO_2 (Wolff et al., 1989). While mild, bronchiolar epithelial hyperplasia was reported in rats exposed for 4 months to 1 ppm SO_2 (Smith et al., 1989), this change was not observed following 8 months' exposure. Animal toxicology studies also provide no evidence for decrements in lung host defence at or near levels of SO_2 expected under ambient conditions (US EPA, 2008).

Overall, the available evidence from the epidemiologic and animal toxicological studies is inadequate to infer that respiratory effects occur from long-term exposure to SO_2 at ambient concentrations.

7.3.2 Evaluation of Respiratory Morbidity from Exposure to SO_2: 2007–2011

7.3.2.1 Acute Exposure

7.3.2.1.1 Pulmonary inflammation and oxidative stress

Toxicological evaluation in animals: Recent toxicological studies have demonstrated that changes to airway and pulmonary morphology could be induced by inflammation after exposure to high concentrations of SO_2. In one study evaluating the effects of SO_2 to pulmonary morphology, female Brown Norway rats were exposed to either 150 ppm or 300 ppm SO_2 for 2.5 or 5 h/d, for 5 d/week over a 2-week period (Arts et al., 2010). The authors reported that a dosing regimen of 300 ppm over 2.5 h/d was the relevant exposure scenario for which inflammatory changes could be seen at the bronchial and bronchioli level, but at which no effects to body weight (or other signs of distress) were observed. Whole body and liver, kidney, and lung weights and histopathological results were compared to unexposed control animals. Results indicated that there was significant epithelial cell degeneration and hyperplasia, oedema, and granulocyte-related inflammation along the nasal passage. Interestingly, they reported that proximal effects were more severe in the 1-d exposed animals than in the longer exposure scenarios. Distal effects were unrelated to exposure duration. Epithelial hyperplasia and metaplasia were also observed in the larynx, trachea, and the bronchiolar/bronchial

squamous epithelial cells. Changes to goblet cell numbers and goblet cell hyperplasia were reported for the larger and smaller bronchioli, respectively (Arts et al., 2010).

Cai et al. (2008) exposed female BALB/c mice to 50 ppm SO_2 through whole-body chamber exposure. Exposures lasted for 60 min on d 7, 9, and 11 of the experiment. They reported a statistically significant seven-fold increase of bronchioalveolar lavage fluid (BALF) total leukocytes as compared to control. They also reported that 78% of all leukocytes in the BALF were neutrophils, indicating acute neutrophilic inflammation, which the authors concluded could result in chronic allergic airway inflammation and subepithelial fibrosis. Eosinophil counts were also significantly increased, although the differential ratio of eosinophils remained the same as in controls. Mice exposed to SO_2 also experienced a loss of cilia, epithelial sloughing, bronchial swelling and peribronchial infiltration of neutrophils (Cai et al., 2008). Exposure to SO_2 prior to challenge with OVA caused exaggerated BALF eosinophilia, and facilitated and enhanced subepithelial fibrosis with more significant elevation of BALF endothelin-1 (ET-1) and transforming growth factor (TGF-β1) levels as compared to pre-exposure concentrations.

McLeod et al. (2007) reported similar results, whereby the BALF neutrophil and eosinophil counts were 138.2 and 5.2 times greater in SO_2-exposed (1000 ppm for 3 h/d for 4 d) Harley guinea pigs than in the control groups. The increased inflammatory cell counts and number of capsaicin-induced coughs were attenuated by treatment with the anti-inflammatory drug dexamethasone. Respiratory frequency and minute ventilation were decreased and enhanced pause was increased with SO_2 exposure, indicating bronchoconstriction. Cough responses but not bronchoconstriction were inhibited by dexamethasone. There was a marked cellular extravasation surrounding the airways and goblet cell metaplasia, indicating inflammation. There was also evidence of neurogenic inflammation (McLeod et al., 2007).

In summary, several recent studies in laboratory animals identified effects related to pulmonary inflammation and oxidative stress, including at the lowest level tested of 50 ppm.

Human exposure studies: A repeated-measures crossover human study, whereby 16 healthy humans (median age: 25.5 years) were exposed to 0, 0.5, 1, and 2 ppm SO_2 for 4 h, evaluated the irritant effects of SO_2 exposure. Endpoints such as exhaled breath condensate (EBC) and biomarkers of inflammation in nasal lavage fluid (NALF) and fractional exhaled nitric oxide (FeNO) were evaluated before and after SO_2 exposure (Raulf-Heimsoth et al., 2010). The biomarkers of inflammation evaluated were: EBC (leukotriene B4, prostaglandin E2, 8-isoprostaglandin F2α) and NALF (Substance P, interleukin-8 (IL-8) and brain-derived neurotrophic factor (BDNF)) (Raulf-Heimsoth et al., 2010). Their results show that 4-h exposure to up to 2 ppm SO_2 did not induce significant changes in the FeNO, nor in the composition of EBC and NALF biomarkers when compared with case-controlled pre-samples.

An analysis by Liu et al. (2009b) examined, among other endpoints, oxidative stress and airway inflammation biomarker in 182 asthmatic children 9–14 years of age. They found that interquartile range (IQR) increases in 3-d average SO_2 of 5.4 ppb were associated with increases in thiobarbituric acid reactive substances (TBARS), an oxidative stress marker. In contrast, no association between SO_2 and other markers of oxidative stress (8-isoprostane) or airway inflammation (FeNO or IL-6) was observed. For TBARS, including two pollutants in the models did not change the results.

A US panel study of 119 asthmatic participants (divided into three groups of inhaled corticosteroid) who inhaled long-acting β2-adrenergic agonist or placebo identified no association between ambient SO_2 levels and FeNO, which is a biomarker of airway inflammation (Qian et al., 2009a).

To summarize, in recent studies one biomarker of oxidative stress (TBARS) increased with an IQR change of 5.4 ppb, while a number of other biomarkers of oxidative stress and/or inflammation showed no changes at levels of up to 2 ppm.

7.3.2.1.2 Respiratory morbidity

The epidemiological and controlled human exposure literature presented in this section provides a brief description of the study design, location and endpoints discussed. A summary of the effects due to co-pollutants and of multi-pollutant analyses is given briefly, and only where they were evaluated by the study authors.

Controlled human exposure studies: A study of 16 healthy human volunteers (van Thriel et al., 2010) evaluated endpoints of odour annoyance, sensory irritation and pulmonary effects following exposure to SO_2. The subjects were exposed to SO_2 over a 4-h period and twice underwent light exercise for 15 min during each exposure session. Sulphur dioxide exposures of 0.5, 1, and 2 ppm were investigated and compared to pre-exposure measures. Results showed that eye blink frequency, nasal airflow, and lung function were not affected by SO_2 exposure. Regarding subjectively measured chemosensory sensations, only odour annoyance ratings increased in a concentration-dependent manner (see Section 7.1).

In their review of controlled human exposure studies including groups of 6 to 62 asthmatic volunteers exposed to SO_2 at levels of from 0.1 to 8 ppm for short-term durations, Johns and Linn (2011) noted that in the wide range of exposure concentrations, asthmatics were reported to experience bronchoconstriction and respiratory effects after short-term exposures to SO_2 at concentrations as low as 0.4 ppm, while healthy subjects only showed respiratory effects at concentrations as low as 1 ppm.

Using data from five previous human studies of short-term exposures of asthmatics, subjects were classified as “responders” or “non-responders” with “responder” being defined as a ≥100% increase in sR_{aw} or a ≥15% decrease in FEV_1 at the highest exposure concentration tested, which was either 0.6 or 1 ppm. There were apparent differences in the slope of the concentration–response curve between responders and non-responders at concentrations of ≤0.5 ppm SO_2. Responders had significant increases in sR_{aw} at concentrations of 0.4 ppm and decreases in FEV_1 at 0.3 ppm, while non-responders did not show significant effects at concentrations of <0.6 ppm (Johns et al., 2010).

In summary, healthy volunteers did not show respiratory effects at levels of up to 2 ppm in a recent study, while a published review of the literature identified effects in healthy subjects starting at 1 ppm and in asthmatic subjects starting at 0.4 ppm. An analysis of previous laboratory exposure studies identified a subgroup of responders among asthmatics who displayed increased sR_{aw} and decreased FEV_1 at levels of 0.4 and 0.3 ppm, respectively.

Epidemiology in healthy adults: Using a cross-sectional study within a cohort of 2,102 healthy Korean subjects, Son et al. (2010) reported a significant negative association between SO_2 and the percentage of predicted FVC. The mean 24-h average SO_2 concentration was 8.6 ppb. No

associations between the percentage of predicted FEV_1 and SO_2 were observed. The pollutants PM_{10}, O_3, NO_2 and CO were also evaluated. Ozone was associated with decreases in FEV_1 and FVC.

Steinvil et al. (2009), in a panel study of 2,380 healthy Israeli adults, reported a statistically significant negative correlation between SO_2 (30-min average = 2.8 ppb) and both FEV_1 and FVC (lags 3–6 d; 7-d moving average) per IQR change in SO_2 concentration. The FEV_1/FVC ratio was not affected because of concurrent decrements in FEV_1 and FVC. In addition, SO_2 emerged as the most potent air pollutant affecting short-term lung function parameters in comparison to $PM_{10,}$ CO, NO_2 and O_3.

In summary, two newer studies identified decreases in FVC with increasing SO_2 exposures; however, inconsistent results were identified for effects on FEV_1.

Epidemiology in adults with respiratory diseases: In a panel study of 121 asthmatic patients in Thailand aged 13–78 (Wiwatanadate and Liwsrisakun, 2011) the effects of SO_2 on PEFR and asthma symptoms were evaluated. The major air pollution sources in this study were open burning and forest fires. The investigators reported that at exposure concentrations of 1.73 ppb, SO_2 was associated with increases in both evening PEFR and daily average PEFR at lag 4 d. Exposure to air pollutants in this study was not associated with asthma symptoms. Co-pollutants of $PM_{2.5}$, PM_{10}, CO, NO_2 and O_3 were evaluated, and positive associations were reported in single-pollutant models and various PEFR outcomes (particularly evening PEFR and ΔPEFR). In multi-pollutant models, weak correlations were reported for SO_2, these co-pollutants, and PEFR outcomes (Wiwatanadate and Liwsrisakun, 2011).

Conversely, in a 2-year panel study of 40 adults living in Italy with moderate-to-severe chronic asthma, Canova et al. (2010) observed that increments of 3.82 ppb SO_2 were associated with decrements in PEFR, most notably evening PEFR, over all lag periods. The trend never achieved significance. Measures of FEV_1 did not vary significantly. The mean 24-h average SO_2 concentration was 1.36 ppb (3.57 $\mu g/m^3$). No effects were reported for exposure to PM_{10} or NO_2 in single- or multi-pollutant models.

A cohort study conducted in Spain from 1999 to 2001 (Feo Brito et al., 2007) compared the effects of short-term exposure to SO_2 and pollen levels on daily asthmatic symptoms in pollen-allergic asthmatic patients. Patients lived in either a highly industrialized or a non-industrialized city. The 137 study participants recorded the intensity of their symptoms, their use of medication, and their PEFR measurements. The mean 24-h average SO_2 concentrations for the two cities were 39.8 and 2.4 ppb, respectively. In the industrialized city, the risk of asthma symptoms showed a significant increase of 4% for each IQR increase in SO_2 concentration at lag 1 d. The IQR increases in SO_2 concentration were not statistically associated to the number of symptoms in the non-industrialized city, indicating that pollen-sensitive asthmatics present more symptoms of seasonal asthma in industrialized communities. Co-pollutants of PM_{10}, NO_2, and O_3 were evaluated, and significant increases in asthma symptoms were reported for PM_{10} and NO_2 in the high-pollution area.

A US panel study of 152 asthmatic participants, divided into 3 groups of inhaled corticosteroid, inhaled long-acting β2-adrenergic agonist, or placebo, identified a negative association between ambient SO_2 levels and peak expiratory flow (PEF) in the group taking inhaled corticosteroid,

but a positive association in the group taking the long-acting β2-adrenergic agonist (Qian et al., 2009b).

To summarize, the newer studies in adults with asthma identified inconsistent results for SO_2-related changes in PEFR and asthma symptoms and no association with changes in FEV_1.

Epidemiology in healthy children: A meta-analysis of 11 cross-sectional studies evaluated 10,394 children aged 7–14 from seven Chinese cities, assessing correlations between lung function (as FEV_1, FVC, and maximal mid-expiratory flow (MMEF)) and exposure to ambient air pollutants (Liu and Zhang, 2009). The reported mean SO_2 concentrations ranged between 4.96 and 225.95 ppb. Co-pollutants of TSP and nitrogen oxides (NO_x) were also evaluated. A significant negative correlation was reported for FVC and FEV_1 with increasing SO_2 concentration; effects at the lower concentration range were more pronounced. The authors also reported that SO_2 had more severe respiratory morbidity effects in girls than in boys. No significant correlation between SO_2 concentration and MMEF was observed. Significant negative correlations were also reported between exposure to TSP and FVC and FEV_1, and between exposure to NO_x and MMEF (Liu and Zhang, 2009).

Moon et al. (2009) in a study of 696 primary school children showed that in industrialized and highly populated Korean cities, the incidence of upper respiratory symptoms (e.g. runny nose, sneezing) increased significantly (by 3.2% at lag 0 d) with each 2.96 ppb increase in SO_2. The authors observed that exposure to SO_2 increased the incidence of children's allergic symptoms, including irritated eyes and itching skin. No correlations between SO_2 and the other pollutants investigated ($PM_{10,}$ O_3, NO_2 and CO) were found. The authors reported that CO affected respiratory and allergic symptoms in children; that NO_2 (elevated) increased the incidence of upper respiratory symptoms, and that O_3 significantly decreased respiratory symptoms.

In summary, one newer study and one meta-analysis of studies of healthy children in Asia identified decreased FVC and FEV_1, no change in MMEF, and increased upper respiratory and allergy symptoms as being associated with SO_2.

Epidemiology in children with respiratory diseases: A study evaluating the effects of various air pollutants on a cohort of 31 asthmatic children (aged 4–11) in Thailand was undertaken for just under 1 year (Wiwatanadate and Trakultivakorn, 2010). The authors investigated the effects of SO_2 (mean daily concentration = 1.73 ppb (data reported for 70% of study days)) on PEFR. Sulphur dioxide exposure was significantly associated with decreased coefficients for evening PEFR (-2.12), daily average PEFR (-0.73), and ΔPEFR (-0.73). No significant association was observed for morning PEFR, but the trend was toward a negative coefficient. The association between PEFR and SO_2 remained even in a two-pollutant model with O_3; however, SO_2 was weakly correlated with all co-pollutants ($PM_{2.5}$, PM_{10}, CO, O_3, and NO_2) evaluated.

Similarly, O'Connor et al. (2008) examined 861 asthmatic children aged 5–12 from the US Inner-City Asthma Study (ICAS). Respiratory endpoints of FEV_1 and PEFR were evaluated over a 2-week period four times over a 2-year period. Asthma symptoms were evaluated every 2 months over the same time frame. The extrapolated mean concentration SO_2 (24-h average) was ~6 ppb. The authors reported that decreases in FEV_1 and PEFR were significantly related to the 5-d average SO_2 concentration but not to the 1-d average concentration. Additionally, in a single-pollutant analysis, when comparing effects at the 90th percentile exposure vs. the 10th percentile exposure (SO_2 change = 12.4 ppb) they found that SO_2 exposure was significantly

related to reductions in predicted FEV_1 and PEFR of -1.60% and -2.14%, respectively (O'Connor et al., 2008). Asthma symptoms and missed school days were not significantly associated with SO_2 exposures, though a positive trend was demonstrated. Pollutants of NO_2 and $PM_{2.5}$ were also evaluated. In single-pollutant models, higher NO_2 and $PM_{2.5}$ concentrations were associated with significantly lowered pulmonary function and asthma-related missed school days. Higher pollutant levels were independently associated with reduced lung function in the three-pollutant model (O'Connor et al., 2008).

A Canadian panel study of 182 asthmatic 9- to 14-year-olds evaluated the effects of air pollutant exposure on respiratory morbidity over a 1-month period. The mean 24-h SO_2 concentration was 6 ppb, and co-pollutants of $PM_{2.5}$, O_3, and NO_2 were evaluated (Dales et al., 2009). The authors reported a significant association between decreased FEV_1 during the daytime and daytime SO_2 concentrations. In contrast, no significant associations between SO_2 and the percentage of predicted evening or morning FEV_1 were observed. Adverse effects associated with SO_2 exposures were weakly correlated with all co-pollutants examined. The researchers also reported an OR for chest tightness of 1.30 for days with a mean SO_2 concentration in the greatest quartile (≥8.8 ppb) vs. the lowest quartile (<2.3 ppb) (Dales et al., 2009). An alternate analysis of the same data (other endpoints discussed above (Liu et al., 2009b)) examined the effects of SO_2 on forced expiratory flow (25–75%) ($FEF_{25–75\%}$) of FVC. They found that IQR increases in 3-d average SO_2 concentration of 5.4 ppb resulted in 3.1% decreases in $FEF_{25–75\%}$ of FVC.

In summary, several recent studies of asthmatic children identified decreased PEFR and FEV_1 associated with SO_2, while effects on asthma symptoms or school attendance were not observed.

7.3.2.1.3 Hospital visits for respiratory diseases

Given the volume of information in this section an attempt has been made to organize the section by age (adult vs. children), study type, disease being evaluated, and location (North American, Australian, European, Asian). An analysis of effects due to co-pollutants and of multi-pollutant analyses is provided briefly, and only where evaluated by the study authors.

Hospital visits in adults: Several studies have evaluated the effect of SO_2 on ED visits for asthma in adults. Stieb et al. (2009), in a seven-city time-series study, investigated the associations between ED visits for asthma and air pollution. The mean 24-h average SO_2 concentration across the seven Canadian cities ranged from 2.6 to 10.0 ppb. Associations between hospital visits for asthma, COPD, and respiratory infections were investigated for SO_2 and co-pollutants (CO, NO_2, O_3, PM_{10}, and $PM_{2.5}$). Percentages of ED visits for asthma were negatively related to increases to SO_2 concentration of 5.1 ppb (at lags 0, 1 or 2 d); these associations were not statistically significant. Similar trends (negative percentage increase, not statistically significant) were reported for COPD and other respiratory infections. Moderate to high correlations were observed between pollutants, except O_3, which was often negatively correlated to other pollutants (especially during cold seasons) (Stieb et al., 2009).

A time-stratified case-crossover study examined 57,912 ED visits for asthma between 1992 and 2002 in Edmonton, AB, and did not identify an association between ED visits and ambient SO_2 levels at lags 0 to 3 d or cumulative 3-d or 5-d mean exposure estimates. Positive associations were observed with other pollutants (NO_2, CO) (Villeneuve et al., 2007).

A time-series evaluation of 6,447 patients transported to hospital for asthma symptoms in 2005 was undertaken by Abe et al. (2009) in Tokyo, Japan. The researchers evaluated children (those under 15 years of age) separately from adults. Pollutants SO_2, NO, NO_x, suspended particulate matter (SPM) and CO were assessed. The mean 24-h average SO_2 concentration reported was 5.3 ppb. The authors did not observe significant associations between the daily number of ED visits by ambulance for asthma and ambient SO_2 concentrations in adults. Nor were associations identified for any other pollutants examined. Of note was the observation that cooler temperatures were associated with more emergency transport for asthma exacerbations in adults.

In Toronto, ON, Burra et al. (2009) assessed how variations in socioeconomic status (SES) affect the number of ambulatory physician consultations for asthma following exposure to air pollution. Estimates of adjusted risk were performed using generalized additive model (GAM) and generalized linear model (GLM) methods for each IQR increase in SO_2 over several lag periods (1-d to 5-d). The mean daily one hour maximum ambient concentration of SO_2 from 1992 to 2001 was 9.7 ppb and the maximum was 62 ppb. The authors reported that for both high and low income brackets, SO_2 was significantly related to increases in adjusted relative risk (RR) of physician visits for asthma exacerbation at lag 1 d (RR = 1.022 and 1.021 for males and females in the low SES group; RR = 1.017 and 1.015 for males and females in the high SES group, respectively). An IQR increase of 7 ppb in SO_2 was associated with a visit rate of 6.09/10,000 in the low SES group and 2.21/10,000 in the high SES group. When comparing the highest SES against the lowest SES groups at lag 1 d, the risk was significantly increased for the lower SES group, but only marginally so (RR = 1.005). Results were similar for NO_2, $PM_{2.5}$, but O_3 was found to reduce risk of asthma visits in all quartiles evaluated. The study authors noted that multiple-pollutant models would help to elucidate which pollutant(s) are associated most strongly with adverse health outcomes (Burra et al., 2009).

Similarly, in a case-crossover study, Kim et al. (2007) evaluated the influence of SES on ED visits for asthma symptoms using data from 92,535 patients in 2002. Pollutants evaluated were PM, CO, SO_2, NO_2 and O_3. The reported ambient SO_2 concentration was 4.7 ppb as a daily average. Results indicated that the estimated RRs of asthma-related ED visits were significantly increased for SO_2 exposures at lags 3 and 4 d, when all SES groups were considered together. When ED visits for asthma were compared across SES groups at the individual and regional levels, the effects did not vary significantly between quintiles of SES, indicating that SES was not a significant modifying factor for asthma-related ED visits in Korea. Of all the pollutants evaluated, NO_2 showed the strongest associations with asthma in the low-income communities when compared against communities with higher SES.

With respect to other adverse respiratory outcomes, Tramuto et al. (2011), in an Italian case-crossover study from 2004 to 2007, evaluated 48,519 ED visits for endpoints of acute respiratory symptoms: dyspnoea/shortness of breath, cough, asthma, and pneumonia. The reported mean 24-h average SO_2 concentration was 1.3 ppb (3.4 $\mu g/m^3$), with high collinearity among pollutants (especially with NO_2). Results of single-pollutant models indicated a positive relationship between ED visits for respiratory causes and SO_2 in all seasons (OR = 1.044) and warm seasons (OR = 1.068), but not for cold seasons, per 3.82 ppb (10 $\mu g/m^3$) increase in SO_2. When stratified by age, the results were significant for the combined sexes and for males aged 75–84 at lag 0 d (Tramuto et al., 2011), in both all-season and warm-season analyses. Similar trends were observed for other pollutants evaluated, with significant positive associations being

reported for PM_{10}, NO_2, and CO, especially among females. A positive association was observed in the cold season only for PM_{10}.

Similarly, an evaluation of the effects of ambient air pollution on respiratory health endpoints, including hospital admissions in Romania for asthma (approximately 453 cases) and chronic bronchitis (approximately 257 cases), was performed by Leitte et al. (2009). Pollutants TSP, SO_2 and NO_2 were evaluated. The mean 24-h average concentration of SO_2 was 1.79 ppb (4.68 $\mu g/m^3$) with a maximum of 4 ppb. Statistically significant 15% (lag 2 d) or 9% (lag 7 d) increases in RR of hospitalization for chronic bronchitis were reported for each 0.38 ppb (1 $\mu g/m^3$) increase in SO_2 concentration. In multi-pollutant analysis, the effect of SO_2 at lag 2 d remained significant (RR = 13%). No threshold for hospitalization for chronic bronchitis and SO_2 exposure was found at lag 2 d. Results for a 10 $\mu g/m^3$ increase in TSP showed increased percentage risks of hospital admission for chronic bronchitis at lags 1 and 4 d, whereas no significant adverse effects on COPD or asthma were found for all pollutants. NO_2 was not associated with chronic bronchitis (Leitte et al., 2009).

Migliaretti et al. (2007), in a case-control study of 4,645 cases based in Turin, Italy, reported that there was an increased risk of ED visits for chronic bronchitis, emphysema and other COPDs of 2.20% per 3.82 ppb increase in exposure to SO_2. The mean SO_2 concentration for all patients evaluated was 4.94 ppb (12.93 $\mu g/m^3$). Elderly adults (>65 years of age) were found to be more sensitive to these adverse effects than younger adults (15–64 years of age), with a significant risk increase of 2.4% vs. 1.6% (non-significant), respectively. Using analyses of ORs, the authors also showed that the effect of SO_2 remained significant in a bi-pollutant model with TSP. Single-pollutant models for TSP and CO showed increased percentages of hospital visits for both pollutants, with CO having the largest effect. The effects of CO were only observed among the elderly.

In a time-series study, Peacock et al. (2011) evaluated the effects of exposure to SO_2 on COPD exacerbations, respiratory symptoms and lung function in 94 COPD patients in London, England. The mean 24-h SO_2 concentration was 7.5 ppb, with an IQR of 6.1 ppb. The authors reported that changes to SO_2 concentrations, either by 1 ppb increases or by IQR, were not significantly associated with hospital admissions for COPD. Results for PM_{10} per IQR change in pollutant concentration were associated with significant percentage increases in ORs for dyspnoea, even after adjustment for other pollutants. Similarly, for each IQR increase in PM_{10}, NO_2 or black smoke, ORs increased for declines in peak flow rate (Peacock et al., 2011).

Milutinović et al. (2009) examined the risk of exposure to SO_2 in urban air and 4,572 ED admissions for COPD in Serbia. The GLM with Poisson regression was fitted to the data, and showed that no effect was found for SO_2 (mean concentration of 5.97 ppb (15.64 $\mu g/m^3$)) with or without controlling for black smoke (BS); an association was made with COPD admissions and BS exposure.

In Beijing, China, Leitte et al. (2011) studied the association between air pollutant exposure and ED visits for respiratory causes (specifically: upper respiratory infection, pneumonia, acute bronchitis and other diseases of the respiratory tract, including chronic lower respiratory disease) in 15,981 ED visits from 2004 to 2006. The reported mean ambient concentration of SO_2 was 33.21 ppb (87.0 $\mu g/m^3$). No significant association was noted for ED visits for respiratory disease with an IQR of 38.17 ppb (100 $\mu g/m^3$) increment in SO_2 concentration at lag

0 d and lag 5 d. The authors reported that NO_2 was the most efficient predictor of ED visits for respiratory causes.

In Shanghai, China, associations between ambient SO_2 levels over the years 2005–2007 and hospital admissions for respiratory disease were not identified. SO_2 levels during the study ranged from 8 to 235 $\mu g/m^3$. Associations were also not identified for the other pollutants examined (NO_2, PM_{10}) (Chen et al., 2010).

A significant association was reported between exposure to SO_2 and hospitalization for respiratory disease in a study based out of Delhi, India. The mean 24-h average SO_2 concentration was 3.27 ppb (Jayaraman, 2008). The authors found a significantly increased RR (1.082) for a 3.82 ppb increase in SO_2 concentration and hospital admission for respiratory diseases using a single-pollutant model at lag 1 d. Though the risk remained above one, significance was lost in multi-pollutant analyses after controlling for CO, NO_2, O_3, SPM and respirable suspended particulate matter (RSPM).

In Kahosiung, Taiwan, Cheng et al. (2007) examined the association between hospital admissions for pneumonia and air pollution among 82,587 people from 1996 to 2004. The mean 24-h average SO_2 concentration was 9.32 ppb. Under the single-pollutant model, pneumonia admissions were significantly associated with each 5.5 ppb IQR increase in SO_2 concentration. This was observed on both warm and cool days (of note, a cool day is any day below 25°C), with ORs of 1.03 and 1.18, respectively. The observed effects of SO_2 on pneumonia admissions were not maintained in the presence of co-pollutants PM_{10}, CO, or NO_2, but were maintained in the presence of O_3.

Similarly, in Taipei, Taiwan, Chiu et al. (2009) examined the association between hospital admissions for pneumonia and air pollution among 152,594 subjects from 1996 to 2004. The mean 24-h average SO_2 concentration was 4.27 ppb. Results were stratified by temperature for warm and cool days, respectively. The effects were statistically significantly elevated on warm days and significantly lower on cool days, with ORs of 1.06 and 0.94, respectively. In this study, a cool day was defined as colder than 23°C. The statistically significant increase in hospitalization for pneumonia following SO_2 exposure, as estimated in a single-pollutant model at a temperature of 23°C, was only maintained in the presence of O_3. The significant decrease in hospitalization observed for cooler days was maintained for all pollutants evaluated (PM_{10}, CO, O_3 and NO_2).

Another study in Taipei examined out-patient visits and ED visits for asthma between 2000 and 2002. A 10% increase in SO_2 concentration was associated with significant mean 0.27% and 0.19% increases in outpatient visits using multi-pollutant models at the 0-d and 1-d lag times. An increase in asthma ED visits at the 2-d lag time was significant in the single-pollutant model, but not in the multi-pollutant model. Results were stratified by age for the 0-d lag time, and SO_2 associations with outpatient visits were significant for all age groups except the aged 0–15 group in multi-pollutant models (Chan et al., 2009).

Yang et al. (2007) identified an association between Taipei hospital admissions for asthma and SO_2 levels between 1996 and 2003; however, the positive association was not maintained in multi-pollutant models.

Bell et al. (2008a) did not find an association between SO_2 and Taipei hospital admissions for pneumonia or asthma over the years 1995–2002, during which SO_2 levels ranged from 0.2 to 26.9 ppb.

Wong et al. (2010a) evaluated the confounding effects of influenza on estimates of Hong Kong hospital admissions for all respiratory diseases that were associated with air pollution. Mean 24-h average SO_2 was 6.79 ppb (17.8 $\mu g/m^3$). For almost all endpoints and time frames, there was no effect observed (see study tables 19, 21). The researchers found that influenza resulted in an increased percentage of excess risk (0.64%) of hospitalization for COPD per 3.82 ppb increase in average concentration of SO_2 at lag 0–1 d (corresponding to the 2-d moving average of the current and previous day's concentrations (see study Table 21 for additional details).

In summary, recent studies on hospital visits for adults display inconsistent results, with negative, positive and no associations reported between SO_2 levels and hospital visits due to asthma or acute respiratory symptoms. Associations between SO_2 levels and visits for COPD were not observed in recent studies.

Hospital visits in children: In a time-stratified case-crossover study in Sydney, Australia, from 1997 to 2001, Jalaludin et al. (2008) evaluated the risk of ambient air pollutant exposure on ED visits for asthma in children. The mean 24-h ambient air concentration of SO_2 was 1.07 ppb with a maximum of 4.1 ppb. The authors reported an increase in ED visits for asthmatic children (age 1–14, n = 1826) for each IQR increase of 0.8 ppb SO_2 at lag 0–1 d (vs. 0, 1, 2, and 3 d); stratification by age showed that SO_2 exposure increased ED visits for asthma for ages 1–4 and 5–9, specifically. Effects of SO_2 appear to result in a higher percentage change in ED visits for asthma in cool months (1.3%) than in warm months (0.5%, not statistically significant), which the authors attributed to confounding from respiratory virus exacerbation of asthma. No significant seasonal associations were observed when results were stratified by age. When evaluating the effect of co-pollutants, attenuation of effect was observed for $PM_{2.5}$, PM_{10}, and CO, while NO_2 and O_3 increased ED visits for asthma in children.

In Athens, Greece, Samoli et al. (2011) examined the association between air pollution and both ED visits and acute asthma symptoms among 3,601 asthmatic children aged 0–14, from 2001 to 2004. The mean SO_2 concentration was 6.41 ppb (16.8 $\mu g/m^3$). Exposure to SO_2 was associated with annual increases in daily asthma admissions of 5.98% (for a 3.82 ppb SO_2 increase) and 7.84% (for an IQR increase in SO_2 of 4.96 ppb (13.0 $\mu g/m^3$)) at lag 0 d. In two-pollutant model analyses, the effect was significant when controlling for NO_2 (7.60%) and O_3 (5.97%), but did not remain significant after controlling for PM_{10}, despite the elevated risk (4.76%). The more severe significant percentage increases in ED visits for asthma symptoms following SO_2 exposure were reported in the spring (11.06% for the 3.82 ppb increase; 12.23% per IQR increase), but high percentage increases were observed for all seasons.

In Taiwan, Yeh et al. (2011) examined the association between seasonal changes in air pollution and asthma hospitalization in children younger than 18 from 2001 to 2002 using regression models. The annual mean SO_2 concentration was 3.83 ppb. Regression analysis of all age groups showed a weak, but statistically significant correlation between seasonal SO_2 exposure and asthma admissions. The correlations for co-pollutants PM_{10} and O_3 were also weak and did not exceed 0.384. Stratification by age showed that primary-school children (aged

6–12) had the highest correlation, followed by preschool children (aged 2–5). No association was found for adolescents (aged 13–18).

Conversely, several studies reported no association between SO_2 exposure and asthma symptoms. In an Italian study using data from 2001 to 2002, Bedeschi et al. (2007) investigated the association between ED visits and air pollution among asthmatic children. Over 1,050 ED visits for children were included in the study, of which 797 visits were for respiratory disorders and 254 were asthma-related visits. The median age of the children evaluated was 2 years. The mean 24-h average SO_2 concentration was 3.55 ppb (9.30 $\mu g/m^3$). No significant associations were found between ED visits for respiratory disorders and daily levels of SO_2. Associations with 10 $\mu g/m^3$ increases in pollutants PM_{10}, TSP and NO_2 were reported.

As noted earlier, a time-series evaluation of 6,447 patients transported to hospital for asthma symptoms in 2005 was undertaken by Abe et al. (2009). They evaluated children (those under 15 years of age) separately from adults. The mean 24-h average reported for Tokyo, Japan, was 5.3 ppb. They authors did not observe significant associations between the daily number of ED visits by ambulance for asthma and ambient SO_2 concentrations in children. No significant effect correlations were presented for other pollutants evaluated (NO, NO_x, SPM, and CO).

With respect to the effect of SO_2 on other respiratory symptoms, a French study by Ségala et al. (2008) examined the association between ED visits and hospitalizations for severe bronchiolitis caused by respiratory syncytial virus (RSV) and air pollution in 50,857 Parisian children younger than 3 years of age. The study took place between 1997 and 2001, and both GAM and case-crossover analyses were performed. The reported mean 24-h average SO_2 concentration was 4.01 ppb (10.50 $\mu g/m^3$). The case-crossover analyses showed that SO_2 was positively associated with medical consultation and hospitalization; an increase of 3.82 ppb SO_2 (10 $\mu g/m^3$) was associated with increased ORs of 1.08 and 1.10 for consultations and hospitalizations for bronchiolitis, respectively, at lag 0–1 d. At lag 0–4 d, the ORs were increased to 1.12 for both consultations and hospitalizations. Similar results were obtained for the GAM model, which adjusted for seasonality, day of the week, and meteorological variables, with ORs of 1.06 for consultation and 1.11 for hospitalization at lag 0–4 d. The authors also reported a strong correlation between SO_2 and the other pollutants (PM_{10}, BS, and NO_2).

In an evaluation of younger children, Orazzo et al. (2009), in an Italian multi-city study, investigated the associations between air pollution exposures and ED visits for wheezing symptoms and gastroenteric disorders in children 0–2 years of age. The mean 24-h average SO_2 concentration (all seasons) ranged from 2.10 ppb (5.5 $\mu g/m^3$) to 8.1 ppb (21.1 $\mu g/m^3$). Exposure to SO_2 was associated with ED visits for wheeze at all lag periods covered (significant from lag 0–3 d until lag 0–6 d) with the percentage increase in risk of wheeze augmenting with lag period. At lag 0–6 d, the increased risk of wheeze was 3.4% for an IQR increase of 3.05 ppb in SO_2 (8.0 $\mu g/m^3$). No association was reported between SO_2 exposure and gastrointestinal disorders. The authors concluded that CO and SO_2 were most strongly associated with wheeze, and positive associations were also reported for PM_{10} and NO_2. When data were stratified by season, the associations were stronger in summer for wheezing and in winter for gastroenteric disorders.

In a more general analysis, Lam et al. (2007) examined the association between ED visits and air pollution among children younger than 6 years of age from 2001 to 2002 in an Australian

study. The mean 24-h average SO_2 concentration was 0.35 ppm. No significant association between SO_2 and ED visits for child respiratory problems was observed; associations were reported for O_3, $PM_{2.5}$ and PM_{10}.

In summary, recent studies on hospital visits of children display inconsistent results, with positive or no associations being reported between SO_2 levels and hospital visits due to asthma. Several positive associations were attenuated when multi-pollutant modelling was undertaken.

7.3.2.2 Long-term Exposure

7.3.2.2.1 Epidemiology in adults

In an analysis of four cross-sectional surveys from the UK, Forbes et al. (2009a) evaluated the relationships of FEV_1 and FVC to chronic SO_2 exposure by 42,975 white adults above 16 years of age. Confounding factors, such as smoking, social class, region and season were considered. The annual median SO_2 concentrations from 1995 to 2001 ranged from 1.45 to 3.74 ppb (3.8–9.8 $\mu g/m^3$). Results indicated that a 3.82 ppb (10 $\mu g/m^3$) increase in SO_2 exposure was associated with lower FEV_1; this effect was more pronounced in men than in women. When stratified by age group, the authors found that decrements in FEV_1 were more pronounced for those ≥45 years of age. Smoking status was also found to affect FEV_1 in those exposed to SO_2. The association between SO_2 exposure and FEV_1/FVC ratio showed a significant decrease in the model adjusted for age, sex and their two-way interactions for all survey years combined. No correlation between SO_2 and the co-pollutants evaluated (PM_{10}, NO_2, and O_3) was reported.

A Canadian case-control study by Neupane et al. (2010) examined the effects of air pollution on 345 pneumonia patients and 494 controls aged 65 and older from July 2003 to April 2005. Health data were collected by personal interview, and subject addresses were matched with air pollutant data to facilitate regression analyses. The annual mean concentration of SO_2 was reported at 4.7 ppb or 5.80 ppb, using either bicubic spline regression or inverse distance weighting functions, respectively. The authors found that exposures to ambient SO_2 were not associated with hospitalization for community-acquired pneumonia, but that long-term exposures to NO_2 and $PM_{2.5}$ were associated with hospitalization for this disease.

A British cohort study by Wood et al. (2010) examined 399 patients with PiZZ genotype (e.g. with α-1-antitrypsin deficiency (AATD)) from 1997 to 2006. People with AATD typically exhibit faster declines in lung function than subjects with non-PiZZ-related COPD. The authors examined the associations between lung function declines (as FEV_1 and gas-transfer coefficient (KCO)) and exposure to ambient air pollutants. The mean concentration of ambient SO_2 per year of decline (per year a patient was in the cohort) was 1.57 ppb (4.12 $\mu g/m^3$). Non-significant decreases in both FEV_1 and KCO was observed for each 0.38 ppb (1 $\mu g/m^3$) increase in SO_2 exposure.

Residents of Miyakejima Island in Japan participated in a health checkup just before returning to the island in 2004, after evacuation due to volcanic activity in 2000, and 407 residents also participated in a checkup in 2006, after 2 years of exposure to an average of 0.03 ppm SO_2. The island was divided into areas with increasing average SO_2 concentrations of 0.019, 0.026, 0.032 and 0.045 ppm; however, no significant differences were observed among the four areas

in terms of lung function tests, including FVC and FEV_1 measurements. No deterioration of lung function was detected in residents between 2004 and 2006 (Iwasawa et al., 2009).

In summary, recent studies in adults identified inconsistent results for changes to FEV_1 and no significant changes to FVC, pneumonia hospitalizations or KCO that were related to long-term exposures to SO_2.

7.3.2.2.2 Epidemiology in children

In Spain, using the standardized asthma survey protocol set out under the International Study of Asthma and Allergies in Children (ISAAC), a cross-sectional study of 20,455 schoolchildren aged between 6 and 7 was undertaken to analyze the relationship between air pollutants and the prevalence of recent symptoms of asthma, allergic rhinitis, and atopic eczema from 2002 to 2003 (Arnedo-Pena et al., 2009). The annual 24-h average SO_2 concentration was reported to be 4.73 ppb (12.4 $\mu g/m^3$). When comparing exposure at the lowest quartile (L1 = <3.89 ppb (<10.2 $\mu g/m^3$)) against the higher quartile exposures (L2 = 3.89 – <6.37 ppb (10.2–16.7 μgm^3)); L3 = >6.37 ppb (>16.7 $\mu g/m^3$)) the authors reported that adjusted ORs were significant for severe asthma (L2 = 1.29; L3 = 1.32), nocturnal dry cough (L2 = 1.50; L3 = 1.17), rhinitis (L2 = 1.40; L3 = 1.56) and rhinoconjunctivitis (L2 = 1.49; L3 = 1.70). No increases in the OR for wheeze were reported; the OR for atopic eczema increased, but not significantly. Co-pollutants of CO, NO_2 and TSP were evaluated; a relatively strong correlation was found between SO_2 and CO. The annual average concentration for CO was associated with higher prevalence of rhinitis, rhinoconjunctivitis, and eczema, while annual average concentrations of NO_2 and TSP were inversely associated with nocturnal dry cough (Arnedo-Pena et al., 2009).

In a cross-sectional study of 72,279 children aged 3–17 from the US National Health Interview Survey (NHIS), Parker et al. (2009) examined the associations between chronic air pollution exposures and respiratory allergy or hay fever symptoms among children from 1999 to 2005. Of the children included in the study, 19.2% reported hay fever, respiratory allergy or both conditions within the previous 12 months. The measured annual median SO_2 concentration was 3.90 ppb; the IQR was 2.35–5.5 ppb. The authors reported an unadjusted OR of 1.05 for associations between 3 ppb SO_2 annual average exposure and respiratory allergy or hay fever among children; the ORs became non-significant in the models adjusted for year, poverty, race, family structure, insurance, caregiver, age, educational status of adults, urban status, region and median income of county. When evaluating the subset of data for which exposure data were available within 20 miles of the childrens' homes, the ORs became non-significant in both single- and multi-pollutant analyses.

Shima et al. (2007) investigated 2,094 children 6–12 years of age in a prospective cohort study in Japan; they monitored the serum concentrations of C-reactive protein (CRP) and respiratory symptoms of wheeze, dyspnoea, and asthma. The annual mean SO_2 concentration from 1998 to 2000 ranged between 4.3 and 6.3 ppb. The 90^{th} percentile serum CRP measures were associated with increased ORs for SO_2 exposure (1.45) and wheeze (1.85) but not with asthma. However, SO_2 showed very high correlation with SPM and NO_2; therefore it is difficult to draw any conclusions on whether SO_2 had an independent effect on serum CRP concentration.

Lastly, in 2007, Hwang and Lee (2010) performed a cross-sectional study of 5,049 Taiwanese children 12–14 years of age, with or without asthma. The association between air pollutants and the prevalence of bronchitis, chronic phlegm, chronic cough and bronchitic symptoms was

evaluated in single- and multi-pollutant analyses. The 3-year annual mean SO_2 concentration was 4.33 ppb, with an IQR of 1.31 ppb. No association between SO_2 and the respiratory symptoms evaluated was found for the single- or multi-pollutant models. A relatively strong correlation was found between $PM_{2.5}$ and SO_2 concentrations. Using the same modelling, significant effects were observed for NO_2 and CO for bronchoconstriction and O_3 for phlegm.

To summarize, several recent studies of children identified inconsistent results, with positive or no associations being identified between SO_2 levels and the occurrence of asthma, wheeze, bronchitis or allergic symptoms.

7.4 Cardiovascular Morbidity

7.4.1 Summary of 2008 US EPA Integrated Science Assessment

7.4.1.1 Short-term Exposure and Cardiovascular Morbidity

Several studies have observed positive associations between ambient SO_2 concentrations and ED visits or hospital admissions for cardiovascular disease (CVD) (e.g. all CVD, cardiac disease, cerebrovascular disease) particularly among individuals ≥65 years of age, but results are not consistent across studies (US EPA, 2008). Unfortunately, the US EPA reported that only a limited number of studies assessed potential confounding by co-pollutants, despite moderate to strong correlations between SO_2 and various co-pollutants in most studies.

The US EPA (2008) concluded that despite some positive findings, evidence from controlled human exposure and epidemiologic studies of heart rate variability (HRV) in healthy individuals as well as those with asthma or CVD was inconsistent (Gold et al., 2000, 2003; Tunnicliffe et al., 2001; Liao et al., 2004; Park et al., 2005; Routledge et al., 2006). They concluded that these inconsistencies did not support an effect of SO_2 on the autonomic nervous system; though there was some evidence of systemic effects on HRV at levels as low as 0.2 ppm (Tunnicliffe et al., 2001). In patients with angina, no HRV effect was observed upon SO_2 exposure (0.2 ppm); however, the authors noted that this may be because of the use of medication to control angina (Routledge et al., 2006). This medication (beta-blockers) is known to increase indices of vagus-nerve-mediated cardiac control, which would negate anticipated effects of SO_2. One epidemiologic study of SO_2 relating to cardiac repolarization was reported (Henneberger et al., 2005); it showed an association between SO_2 and QT interval duration. The QT interval represents the time for both ventricular depolarization and repolarization to occur; thus, it roughly estimates the duration of an average ventricular nervous action potential. Specifically, Henneberger et al. (2005) reported that for ambient exposures to 2 ppb SO_2 (as a mean 24-h average) 24 h before the electrocardiogram was administered, QT interval duration was affected, which indicates that SO_2 affected cardiac repolarization. In co-pollutant analyses, the authors reported that stronger associations were observed for PM indices than for SO_2 (Henneberger et al., 2005). *In vitro* (Nie and Meng, 2005a, 2006) studies suggested a potential role for L-type calcium currents in cardiac injury related to SO_2 exposures, but the relevance of these studies to ambient exposures was unknown. Epidemiologic evidence from studies of the effect of SO_2 on implantable cardioverter-defibrillator (ICD)-recorded arrhythmias was inconsistent.

Studies of blood pressure and blood markers of cardiovascular risk failed to provide consistent evidence to support a role for SO_2 in the development of CVD; in addition, the only human

epidemiological data for SO_2 effects on blood pressure was rendered non-significant after co-pollutant analysis (Ibald-Mulli et al., 2001; de Paula Santos et al., 2005). Although some studies of hospital admissions and ED visits for CVD reported positive and statistically significant associations with SO_2, findings were inconsistent when reviewed as a whole (US EPA, 2008). Many researchers were unable to distinguish the effect of SO_2 from correlated co-pollutants, while others reported attenuation of the SO_2 effect when they switched to two-pollutant models. Similarly, analysis of biomarkers of cardiac risk (fibrinogen, white blood cell count, factor VIII-C coagulant activity and von Willebrand factor) were insufficient to determine whether there was an effect of SO_2 on blood markers of cardiac risk (US EPA, 2008).

7.4.1.2 Long-term Exposure and Cardiovascular Morbidity

Cardiovascular effects were observed in animal studies using rodents exposed to SO_2 by inhalation. The animal toxicological studies showed oxidative damage in the form of tissue oxidation and glutathione depletion in rodent hearts after exposure to at least 5 ppm SO_2. The Women's Health Initiative cohort study (Miller et al., 2007) was summarized as it pertained to SO_2 exposure, and the results indicated that in single-pollutant models, SO_2 showed a positive association with cardiovascular events in women (hazard ratio = 1.07). In multi-pollutant models with all pollutants ($PM_{2.5}$, PM_{10}, CO, SO_2, NO_2, O_3), the association with SO_2 became stronger (1.13). Correlations between pollutants were not described, and the extent of confounding could not be determined; however, $PM_{2.5}$ was the best predictor of cardiovascular events. The US EPA (2008) did not draw any conclusions on the effect of long-term exposure to SO_2 and cardiovascular health due to limited data.

7.4.2 Evaluation of Cardiovascular Morbidity from Exposure to SO_2: 2007–2011

The epidemiological literature presented in this section provides a brief description of the study design, location and endpoints discussed. Effects due to co-pollutants and multi-pollutant analyses are mentioned briefly and only where they were evaluated by the study authors.

7.4.2.1 Short-term Exposures

7.4.2.1.1 Epidemiology in adults

In a Canadian evaluation of 31 older patients (aged 50–85) living in Montreal with congestive heart failure (CHF), Goldberg et al. (2008) investigated whether oxygen saturation and pulse rate were associated with air pollution. The investigators measured patients' oxygen saturation, pulse rate, weight and temperature over a 2-month period; subjects recorded their daily measures every morning. Sulphur dioxide was significantly associated with lowered oxygen saturation (lag 1 d and 3-d mean) and increased pulse rate (lag 1 d and 3-d mean) with an IQR increase of 3.28 ppb (8.6 $\mu g/m^3$). After adjusting for the effects of weather, the effect of an IQR increase of 3.28 ppb SO_2 on oxygen saturation and pulse rate remained unchanged, though significance was only maintained at lag 1 d. Co-pollutants CO, $PM_{2.5}$, NO_2 and O_3 were evaluated and were found to have no effect on oxygen saturation or pulse rate. No multi-pollutant analyses were performed.

Wellenius et al. (2007) measured circulating levels of B-type natriuretic peptide (BNP) in 28 patients in Boston, MA, aged 33–88 with CHF and impaired systolic function. BNP is produced principally by heart ventricles in response to increased wall stress and is used as an indicator of CHF. The study did not report a significant association between SO_2 (mean 24-h average of 4.8

ppb) and BNP levels at any of the lags examined (lag 0 d, lag 1–3 d). The authors concluded that the within-person variability in BNP levels in this population renders this biomarker relatively useless for air pollution assessments (Wellenius et al., 2007).

In a cross-sectional Korean study, Choi et al. (2007) examined the relationship between exposure to air pollution and blood pressure in 10,459 healthy adults from 2001 to 2003. The reported 24-h average SO_2 mean concentration was 5.1 ppb in warm months (July–September) and 6.9 ppb in cold months (October–December); the variation in SO_2 concentration by season was not significantly different. The adjusted model accounted for age, sex, body mass index, cholesterol level, diabetic factors, smoking and alcohol consumption, as well as temperature, relative humidity and barometric pressure. The results of the adjusted model indicated that there were significant weak correlations between SO_2 and blood pressure changes. Specifically, during the warm season, SO_2 exposure was weakly correlated to diastolic blood pressure at lag 1 d; during the cold season SO_2 exposure was weakly correlated to systolic blood pressure at lag 1 d and to diastolic blood pressure at lag 2 d. The authors also reported that only in warm months were PM_{10} and NO_2 concentrations associated with measures of blood pressure, while O_3 concentrations were associated with these measures in cold weather. No multi-pollutant analyses were performed.

Briet et al. (2007) investigated the impact of air pollutants on endothelial function in 40 healthy white male subjects in Paris, France. They focused upon the effect of air pollutants on flow-mediated dilation, which is a measure of endothelium-dependent regulation of vascular tone at focal sites in the circulatory system; specifically, flow-mediated dilation is when the blood vessel dilates in response to increased blood flow (Kelm, 2002). The Briet team's subjects were studied twice at 2-week intervals. The 5-d mean SO_2 concentration was 4.58 ppb (12 $\mu g/m^3$). The researchers adjusted for sodium and potassium levels in the diet, susceptible genotypes and subject factors. For all pollutants evaluated, increased pollutant concentration was associated with decreased endothelial function, but the strongest associations were found for SO_2. The investigators found that flow-mediated dilation was negatively correlated with mean SO_2 concentrations at lag 0 d. Co-pollutants (NO and CO) were not well correlated to SO_2 effects; at lag 0 d, SO_2 accounted for 23% of the variance in flow-mediated dilation (Briet et al., 2007). In their multivariate analysis, the authors reported that changes to SO_2 concentration explained 10% of the variance in amplitude of flow-mediated dilation (significant interquartile percentage decreases of approximately 2% were shown). These baseline correlations were reinforced in their analysis of changes in SO_2 concentration after a 2-week interval, whereby increases in SO_2 concentration accounted for 19% of the variance of endothelial function. These results, taken together, indicated that SO_2 was associated with decreased flow-mediated dilation in healthy humans, likely due to changes in endothelial function rather than an effect on smooth muscle relaxation. No correlation was found for SO_2 and small artery reactive hyperaemia or hyperaemic/ischemic mean flow ratio. It was found that PM_{10}, $PM_{2.5}$ and NO_2 were significantly and positively correlated with reactive hyperaemia.

Anderson et al. (2010) conducted a panel study in London, England, of 705 patients aged 56–71 with implanted ICDs to treat tachycardia. The authors examined the effect of air pollutants (SO_2, SO_4^{2-}, PM_{10}, $PM_{2.5}$ and O_3) on tachycardia only on occasions in which the ICD was activated (delivered treatment) and performed statistical analyses equivalent to a fixed-stratum case-crossover evaluation. The mean 24-h average SO_2 concentration was 1.03 ppb (2.71 $\mu g/m^3$) (IQR 0.76 (2.00 $\mu g/m^3$)). Increased but non-statistically significant ORs were reported for

ICD activation and 3.82 ppb (10 μg/m^3) increases in SO_2 concentration at lag 0–1 d and lag 0–5 d. Sulphur dioxide did not highly correlate with any other pollutant. Of note in this study was that particle SO_4^{2-} was the only pollutant significantly associated with ICD activation over the time periods analyzed.

To summarize, recent studies show increased blood pressure and pulse rate and decreased oxygen saturation and flow-mediated dilation to be associated with increased SO_2 levels. Multi-pollutant modelling was not done in several of the studies. No significant associations were observed between SO_2 levels and tachycardia in patients with defibrillators or small artery reactive hyperaemia in healthy individuals.

7.4.2.1.2 Hospital visits and cardiac conditions

Stieb et al. (2009), in a multi-city study, investigated the associations between ED visits for cardiac conditions (angina, MI, heart failure, dysrhythmia/conduction disturbance) and air pollution. Pollutants evaluated were CO, NO_2, O_3, PM_{10}, $PM_{2.5}$ and SO_2 in single-pollutant models. The mean 24-h average SO_2 concentration across the seven Canadian cities studied ranged from 2.6 to 10.0 ppb. The investigators found that ED visits for angina and MI were significantly increased (2.1%) with each 5.1 ppb increase in SO_2 concentration of (lag 1 d). A negative association between SO_2 and cardiac arrhythmia (-2.6%) was observed at lag 2 d. No trends or associations were found for heart failure and SO_2 exposure. Of the other pollutants evaluated, increases in angina and MI were observed for CO (2.1% at lag 0 d) and NO_2 (2.6% at lag 0 d; 2.7% at lag 1 d), but O_3 was negatively associated with this endpoint (-3.0% at lag 1 d). Ozone was also associated with increased respiratory visits for asthma (3.2% at lag 2 d). Associations with COPD were significantly negative for CO (-3.3% at lag 1 d) and NO_2 (-3/4% at lag 1 d). Significant positive associations between heart failure and all pollutants except for SO_2 were observed (Stieb et al., 2009).

In a case-crossover study based in Taipei, Taiwan, Yang (2008) evaluated the association between air pollution concentrations and hospitalization for CHF from 1996 to 2004. The mean ambient concentration of SO_2 was 4.27 ppb. The authors reported that exposure to SO_2 did not influence hospital admissions under either the single- or multi-pollutant models on either hot or cool (<20°C) days. Significant associations were, however, reported between other pollutants evaluated (PM_{10}, NO_2, CO and O_3) and CHF on warm days in single and multi-pollutant models (Yang, 2008).

A time-series analysis conducted in Taipei, Taiwan, did not identify an association between hospital admissions for ischemic heart disease (IHD) or cerebrovascular disease and SO_2 exposure over the years 1995–2002, during which SO_2 levels ranged from 0.2 to 26.9 ppb (Bell et al., 2008a).

A time-series analysis conducted in São Paulo, Brazil (Santos et al., 2008), reported a link between daily SO_2 concentrations from 1998 to 1999 and non-significant increases in ED visits for cardiac arrhythmia at lag 0 d to lag 6 d. The mean 24-h average SO_2 concentration was 5.74 ppb (15.05 μg/m^3). Strong, significant correlations were reported for SO_2 and the co-pollutants CO, NO_2 and O_3.

In a recent time-stratified case-crossover study, Rich et al. (2010) explored whether both transmural and non-transmural MIs were associated with acute exposure to SO_2. The 2-year investigation involved residents of New Jersey, USA, aged 18 years or more, who had been

admitted to hospital for a first MI. The reported IQR 24-h average SO_2 concentration was 4.1 ppb. Transmural MIs were not found to be significantly associated with a 4.1 ppb increase in mean SO_2 at lag 1 d in both single- and bi-pollutant models with $PM_{2.5}$ (Rich et al., 2010).

At the same SO_2 exposure concentration (mean 24-h average = 4.36 ppb), a recent Taiwanese case-crossover study (Hsieh et al., 2010) found that SO_2 was not significantly associated with increased MI hospital admissions from 1996 to 2006 on warm or cool days, with a cool day being defined as a temperature less than 23°C. Significant associations were, however, reported between other pollutants evaluated (PM_{10}, NO_2, CO and O_3) and MIs on warm days; and multi-pollutant models with NO_2 and O_3 showed significant effects in combination with the other pollutants on warm days (Hsieh et al., 2010).

Silverman et al. (2010), in a study of the people of New York City, NY, did not report a significant association, as RR, between SO_2 (24-h average SO_2 concentration of 6.3 ppb) and hospital admissions for cardiac arrest over the time period 2002–2006.

Similarly, an Australian study (Dennekamp et al., 2010) examined out-of-hospital cardiac arrest incidence from 2003 to 2006. The mean 24-h average SO_2 concentration was 5.1 ppb. There was no significant percentage change to cardiac arrests per 0.76 ppb IQR increase in SO_2 concentration.

Using a time-series approach, Pereira Filho et al. (2008) examined the risk of cardiovascular ED visits (as hypertension and "cardiac ischemic disease") in Type II diabetics exposed to air pollution in Brazil. The mean 24-h concentration of SO_2 was 5.27 ppb (13.8 $\mu g/m^3$), with an IQR of 3.06 ppb (8.02 $\mu g/m^3$). The authors, in their regression analysis, reported a significant weak correlation between SO_2 and ED visits for CVD in diabetics at lag 1 d and as 2- and 3-d moving averages with an IQR increase of 8.02 $\mu g/m^3$ SO_2. A similar trend was seen in the control, non-diabetic subjects, with a significant weak correlation between SO_2 exposure at lag 0 d, and under all moving averages (2-, 3-, and 4-d). However, SO_2 was significantly correlated with all other co-pollutants examined (O_3, NO_2, CO and PM_{10}) (Pereira Filho et al., 2008).

In a study based out of Edmonton, AB, Szyszkowicz (2008) evaluated 10,881 ED visits for acute ischemic stroke against air pollution from 1992 to 2002. The mean daily average SO_2 concentration was 2.6 ppb, with an IQR of 2.3 ppb. The authors reported an increased percentage change in RR for ED visits for stroke in relation to an IQR increase in SO_2 concentration. These findings were age-related. In those 20–64 years of age, a 10.3% increase in risk was observed in the cold seasons at lag 1 d. In those aged 65–100, a 4.4% increase in risk was observed during the cold months (lag 1 d), along with a 6% increase when stratified for women over the same lag period. Similarly, a 4.6% increase in stroke was reported for females aged ≥65 during all seasons at lag 1 d. In men over 65 years of age, a 9.1% increased risk for stroke was reported in the warm months only (Szyszkowicz, 2008). In other pollutant analyses, both NO_2 and O_3 (but not CO) were found to increase hospital visits to a similar or greater degree than SO_2; multi-pollutant analyses were not performed.

In contrast, as part of the Public Health and Air Pollution in Asia (PAPA) analysis, Wong et al. (2010a) evaluated the effect of SO_2 exposure on hospital admissions for CVD in Hong Kong. The mean 24-h average SO_2 concentration was 6.8 ppb. The investigators reported that the percentage excess risk for heart disease admissions increased in all ages (0.98%), particularly in those ≥65 (1.25%), and also increased for IHD admissions (0.93%) with each 3.82 ppb (10

μg/m^3) increment in SO_2 (see Table 18 in reference). The percentage excess risk was not significant for stroke. Influenza did not influence these associations. For information on other pollutants considered in this paper, please refer to the original document (Wong et al., 2010a), which provides extensive analysis.

In a time-series study, Dales et al. (2010) evaluated the association between air pollution and venous thromboembolic disease (e.g. venous thrombosis, deep vein thrombosis, and pulmonary embolism) in the general Chilean population between 2001 and 2005. The ambient 24-h average daily mean SO_2 concentrations ranged from 5.76 to 11.32 ppb, and the authors evaluated effects based upon regional IQR increases. Using pooled estimates, results from the single-pollutant models showed a significant increase in the RR of venous thrombosis (1.06) and pulmonary embolism (1.05) for each 5.85 ppb increase in SO_2 concentration. Pooled estimates for other pollutants evaluated (O_3, $PM_{2.5}$ and NO_2) resulted in similar ORs of hospitalization for venous diseases (range: 1.05–1.08) and pulmonary embolism (range: 1.05–1.10). In multi-pollutant analyses, the RRs of venous thrombosis and pulmonary embolism from SO_2 exposure were both reduced, at 1.01 and 1.02, respectively. The RR values for persons older than 64 were higher than the values for those under 64 (Dales et al., 2010).

Ito et al. (2011) evaluated the risk of cardiovascular ED hospitalization for New York City, NY, from 2000 to 2006. Cross-correlations and Poisson time-series models evaluated outcomes of cardiovascular mortality, including hypertensive disease, MI, IHD, dysrhythmia, heart failure and stroke in persons older than 40 years of age. The reported 24-h average concentrations of SO_2 were 7.4 ppb (annual mean); 3.9 ppb (summer mean) and 10.8 ppb (winter mean). Co-pollutants of $PM_{2.5}$, (CO, elemental and organic carbon, SO_4^{2-}, NO_2, NO_3), and various metals were evaluated. Data were adjusted for temporal trends, the day of the week, same-day analysis, and delayed temperature effects. Results indicated that there was a ~1.2% increased excess risk for SO_2 exposure and hospitalization for CVD at lag 0 d. These trends were presented figuratively, and showed a ~1.2% excess risk for both the cold season and the yearly analysis with each IQR increase of 6 ppb SO_2. A ~2% excess risk was indicated for the warm season. Results were mixed for the other pollutants; however, $PM_{2.5}$ and NO_2 showed consistent, significantly increased percentage excess risks of cardiovascular hospitalization over the whole year and when stratified by season, particularly in the warm season. Organic and elemental carbon had increased percentage excess risks at lag 0 d in all evaluations, and SO_4 showed a similar trend; however, it was not always significant (Ito et al., 2011).

In an evaluation of ED visits for CVD, a time-stratified case-crossover study was undertaken in Beijing, China, from 2004 to 2006 (Guo et al., 2009). The mean concentration of SO_2 was 18.82 ppb (49.32 μg/m^3). Co-pollutants of $PM_{2.5}$ and NO_2 were considered in multi-pollutant analyses of effects. Pearson correlation analysis showed that SO_2 was significantly positively correlated with NO_2 and $PM_{2.5}$ but negatively correlated with temperature and relative humidity measures. Results indicated that in single-pollutant analyses SO_2 was significantly associated with hospital ED visits at lags 0, 1 and 2 d (ORs: 1.014, 1.012 and 1.011, respectively). The other pollutants evaluated, $PM_{2.5}$ and NO_2, were only associated with ED visits at lag 0 d (ORs: 1.005 and 1.014, respectively). In multi-pollutant analyses SO_2 was significantly associated with ED visits for CVD (OR: 1.013) with NO_2 (but not $PM_{2.5}$, or both co-pollutants) (Guo et al., 2009).

In Shanghai, China, associations between ambient SO_2 levels over the years 2005–2007 and hospital admissions for all causes and CVD were identified at lag d 5 in single-pollutant models

in a time-series study. SO_2 levels during the study ranged from 8 to 235 $\mu g/m^3$. Associations were also identified for the other pollutants examined (NO_2, PM_{10}). In multi-pollutant models, the association with SO_2 was maintained with adjustment for PM_{10}, but became non-significant after adjustment for NO_2 (Chen et al., 2010).

In summary, though several recent studies indicate that increased ED visits for CVD are associated with increased SO_2 levels; inconsistent results (positive or no association with increased SO_2 levels) were identified for specific subsets of CVD (e.g. MIs) or stroke, and in a majority of the studies, other co-occuring pollutants demonstrated equal or stronger associations.

7.4.2.2 Long-term Exposures

To investigate the effect of long-term air pollution on changes to blood pressure, blood lipids, blood sugar and blood biomarkers of inflammation (e.g. interleukin-6 and neutrophil concentration), Chuang et al. (2011) conducted a secondary analysis of data obtained from the Taiwanese Social Environment and Biomarkers of Aging study using GAM statistical methods. The mean annual average SO_2 concentration was 4.94 ppb. The authors reported no association between exposure to SO_2 and any endpoints measured for each 3.18 ppb IQR increase in annual ambient SO_2 levels. Other pollutants evaluated (PM_{10}, $PM_{2.5}$, O_3, NO_2 and CO) showed positive associations with most of the endpoints examined.

In a cohort study evaluating the association between air pollution and early vascular damage, Lenters et al. (2010) examined 750 young adults who were engaged in the Atherosclerosis Risk in Young Adults study. Exposure data for the year 2000 were estimated from land-use regression models and mapped to the participant locations in the Netherlands. Outcomes of carotid artery intima-media thickness, aortic pulse wave velocity (a measure of systemic arterial stiffness) and the augmentation index (a surrogate measure of systemic arterial stiffness) were evaluated. The mean SO_2 concentration was 1.30 ppb (3.4 $\mu g/m^3$). Only the outcome of pulse wave velocity was significantly increased, with a 5.26% change for each 1.91 ppb (5 $\mu g/m^3$) increase in SO_2 concentration. No associations were reported between SO_2 and carotid artery intima-media thickness and augmentation index.

To summarize, recent studies of long-term exposures to SO_2 identified an increase in aortic pulse wave velocity associated with increased SO_2 levels. No associations were observed with blood pressure, blood lipids, blood sugars, biomarkers of inflammation, carotid artery intima-media thickness or augmentation index.

7.5 Mortality

7.5.1 Summary of 2008 US EPA Integrated Science Assessment

7.5.1.1 Short-term Exposures

The US EPA (2008) concluded that epidemiologic evidence on the effect of short-term exposure to SO_2 on non-accidental all-cause mortality and cardiopulmonary mortality is suggestive of a causal relationship at ambient concentrations. Consistently positive associations were reported between SO_2 and mortality in the epidemiologic literature; however, the observed associations were not robust enough to be maintained after adjustment for co-pollutants.

The US EPA's assessment cited risk estimates for all-cause SO_2 mortality in single-pollutant models from multi-city studies and meta-analyses that ranged from 0.6% (in the National Morbidity Mortality Air Pollution Study (NMMAPS) to 4.1% (in the Italian eight-city study) per 10 ppb increase in 24-h average SO_2 concentration (US EPA, 2008). Given the large confidence band in the Italian study, the US EPA noted that a more stable range may be from 0.6% to 2%. The SO_2 effect estimates for the NMMAPS research (Samet et al., 2000; Dominici et al., 2003) and a Canadian 12-city study (Burnett et al., 2004) are quite comparable (0.6% and 0.7%, respectively), despite differences in the modelling approach. There was significant heterogeneity of estimates within the multi-city studies and meta-analyses; this was attributed to several factors, including differences in model specifications, averaging/lag time, SO_2 levels, and effect-modifying factors (US EPA, 2008). The effect estimates for more specific mortality categories may be larger. Only the Air Pollution and Health: A European Approach (APHEA) study examined possible sources of heterogeneity for SO_2-related mortality (Katsouyanni et al., 1997; Samoli et al., 2003). The only variable that could explain the heterogeneity of city-specific effect estimates for SO_2 was the geographic separation (western versus central eastern European cities), but even after adjusting for geography, heterogeneity in the SO_2 effect estimates remained within the western cities. The intervention study from Hong Kong (Hedley et al., 2002) supported the idea that a reduction in SO_2 levels resulted in a reduction in death counts, but this study did not preclude the possibility that the causal agent was something other than SO_2 that is associated with SO_2 sources.

7.5.1.2 Long-term Exposures

The US EPA (2008) concluded that the available epidemiologic evidence on the effect on mortality of long-term exposure to SO_2 is inadequate to infer a causal relationship at this time. As with earlier US EPA assessments, an association can be made between long-term exposure to SO_2 and mortality (e.g. Imai et al., 1986), but concerns remain about whether the observed association was due to SO_2 alone. In more recent longitudinal cohort studies, the results from two US epidemiologic studies (Dockery et al., 1993; Krewski et al., 2000) revealed an association between long-term exposures to SO_2 or sulphur-containing particulate air pollution and mortality. Specifically, the study by Krewski et al. (2000) reported an increased RR of 1.05 for both total mortality and mortality from cardiopulmonary events with each 5 ppb rise in SO_2 concentration; however, they indicated that the dataset was highly correlated to $PM_{2.5}$, SO_4^{2-} and NO_2 co-pollutants. Similar results and confounding were reported in several analyses of the American Cancer Society (ACS) cohort (Pope III et al., 1995, 2002; Jerrett et al., 2003) and an evaluation by Elliott et al. (2007) of smaller cohorts in Great Britain. In ACS reanalyses, SO_2 was reported to result in an increased RR of 1.06 per 5 ppb increase in the annual average concentration of SO_2 (reported mean SO_2 concentrations ranged from 7.18 to 11.24 ppb) (Jerrett et al., 2003). To address the influence of spatial patterns that may confound associations between SO_2 and mortality, Krewski et al. (2000) conducted extensive two-stage regression modelling, which found that the association between SO_2 and mortality was persistent (but reduced) after adjusting for SO_4^{2-}, $PM_{2.5}$, and other variables. The US EPA (2008) suggested that because SO_2 effect estimates were largely insensitive to adjustment for spatial correlation, the association between SO_2 and mortality may be confounded by PM, but noted that the associations could not be accounted for by $PM_{2.5}$ or SO_4^{2-} alone.

Several other US and European cohort studies did not observe an association between SO_2 exposures and mortality (Abbey et al., 1999; Lipfert et al., 2000, 2006a, 2006b; Nafstad et al., 2004; Filleul et al., 2005), instead reporting that traffic density was the most significant predictor

of mortality (Nafstad et al., 2004; Lipfert et al., 2006a, 2006b). The lack of consistency across studies, the inability to distinguish potential confounding by co-pollutants, and uncertainties regarding the geographic scale of analysis limit the interpretation of a causal relationship.

Data representing all-cause mortality RR estimates associated with long-term exposure to SO_2 from the US and European cohort studies showed that the overall range of RRs spans 0.97 to 1.07 per 5 ppb increase in the annual (or longer period) average SO_2. The analyses of the Harvard Six Cities (Dockery et al., 1993) and the ACS (Krewski et al., 2000) cohort data observed increased RRs (range: 1.02 to 1.07) for each 5 ppb increase in SO_2 concentration. These data show slightly elevated risks of mortality following long-term SO_2 exposures. Educational status appears to be an important effect modifier of air pollution effects in both studies. The Harvard Six Cities data (Dockery et al., 1993) have a small number of exposure estimates, but the study cities were carefully chosen to represent a range of air pollutant exposures. Conversely, the ACS cohort (Pope III et al., 1995, 2002; Jerrett et al., 2003) had far more subjects, but the population evaluated was more highly educated than is representative of the US population. Therefore, the overall effect estimate for the ACS cohort may underestimate the RR for the more general population. Several other US and European studies did not observe an association between long-term exposure to SO_2 and mortality.

In addition to educational status, the geographic scale of analysis appears to influence SO_2 effect estimates and exposure error. In a reanalysis of the ACS data, the county-level analysis showed a smaller SO_2 effect estimate than the metropolitan statistical area-level analysis (Krewski et al., 2000). For SO_4^{2-}, the environmental degradation product of SO_2, the opposite pattern was found. Thus, the US EPA (2008) concluded that the impact of the geographic scale of analysis may depend on the spatial distribution of air pollutants. A cross-sectional analysis in Great Britain using small-scale electoral wards observed an effect estimate similar to the lower end of the range of effect estimates for all-cause mortality from US cohort studies (Elliott et al., 2007). Unfortunately, it was not clear if the effect estimates from this cross-sectional study were directly comparable to those from cohort studies.

Another important issue that contributed to the non-causal determination by the US EPA was that longitudinal cohort studies could not resolve the possibility of confounding and/or interaction among PM indices and SO_2. Therefore these interactions could not be ruled out.

7.5.2 Evaluation of Mortality from Exposure to SO_2: 2007–2011

The epidemiological literature presented in this section provides a brief description of the study design, location and endpoints discussed. Effects due to co-pollutants and multi-pollutant analyses are indicated briefly and only where they were evaluated by the study authors.

7.5.2.1 Short-term Exposure

Several epidemiology papers have been published from 2007 to 2011 evaluating the association between SO_2 and mortality. All the papers presented are time-series epidemiology studies, with the exception of two time-series meta-analyses (the PAPA studies). This section will focus on results of all-cause mortality, respiratory mortality and cardiovascular mortality, specifically. If other significant mortality endpoints were noted in the papers, they will be identified for information purposes.

One US study was identified: Ito et al. (2011) evaluated population mortality data for New York City, NY, from 2000 to 2006. Cross-correlations and Poisson time-series models assessed

outcomes of cardiovascular mortality, including hypertensive disease, MI, IHD, dysrhythmia, heart failure and stroke in persons above 40 years of age. The reported 24-h average concentration of SO_2 was 7.4 ppb (annual mean); 3.9 ppb (summer mean) and 10.8 ppb (winter mean). Co-pollutants $PM_{2.5}$, CO, elemental and organic carbon, SO_4^{2-}, NO_2, NO_3, and various metals were evaluated. Data adjusted for temporal trends, the day of the week, same-day analysis, and delayed temperature effects indicated that there was no increased percentage excess risk for SO_2 exposures. Other pollutants showed varied effects, most notably that $PM_{2.5}$ increased mortality estimates at lag 1 d for all seasons and when stratified by warm or cool season (Ito et al., 2011).

A study by Hu et al. (2008) in Sydney, Australia, evaluated the effect of temperature and air pollutants on total mortality in summer. The authors found that the relative risk of all-cause mortality was increased by 22.3% with each 1 ppb (0.10 pphm) rise in SO_2 (lag 0 d). Lags 1, 2 and 3 d were evaluated using Poisson regression with GAM over the study period (1996–2004). The reported mean concentration of SO_2 (24-h averaging time) was 1 ppb. Co-pollutants O_3, NO_2, and PM_{10} were evaluated. The investigators also reported a 7.8% increase in risk of mortality when the temperature reached 32°C and a 12.1% increase when the mean daily concentration of SO_2 exceeded 3.15 ppb (0.315 pphm). Both NO_2 and O_3 were associated with significant decreases in RR of all-cause mortality per unit increase at lag 0 d (Hu et al., 2008); other pollutants had no significant effect on this endpoint.

A series of European studies have been identified that evaluate the risk of SO_2 exposure on mortality estimates. One study (Berglind et al., 2009) assessed the risk of mortality to survivors of an earlier MI following exposure to SO_2 in five European capitals (Augsburg, Germany; Barcelona, Spain; Helsinki, Finland; Rome, Italy; and Stockholm, Sweden). Poisson regression and GAM allowed for consideration of several lag periods (lags 0, 1, 2, 3, 0–1, 0–4, 0–14 d) from 1992 to 2002. The average 24-h concentration of SO_2 reported in the capital cities ranged from 1 ppb (2.61 $\mu g/m^3$, in Stockholm) to 4.20 ppb (11 $\mu g/m^3$, in Barcelona). Co-pollutants of particulate number count, PM_{10}, NO_2, O_3 and CO were considered. Pooled results from the four cities showed that there was no clear association between SO_2 and daily mortality among survivors of MIs for each 0.76 ppb increase in SO_2 concentration. There was, however, a trend toward an increased percentage change in daily deaths as the lag period increased: lag 0–1 d, 0.09% (95% CI -2.23 to 2.46); lag 0–4 d, 1.60% (95% CI -1.28 to 4.57); and lag 0–14 d, 8.06% (95% CI 4.38–11.9). As for other pollutants, exposure to PM_{10} (all lags evaluated), CO (lag 0–4 d; lag 0–14 d), and NO_2 (lag 0–4 d) was also associated with mortality, while no association between O_3 exposure and mortality was found (Berglind et al., 2009).

A similar study of 14 cities in the Katowice conurbation of Poland was undertaken from 2001 to 2002. It found a significant association between SO_2 exposures (24-h mean: 13.44 ppb (35.2 $\mu g/m^3$)) and both all-cause mortality and cardiovascular mortality using single-pollutant regression models (Kowalska et al., 2007). For all-cause mortality, lag 1 d and the 3-d moving average showed significance in regression coefficients for all age groups in the cohort. For cardiovascular mortality, the highest significance was achieved for the subpopulation of people aged ≥65 at lag 1 d and lag 1–3 d. No association was made between SO_2 exposures and respiratory mortality for any age group or time frame. Co-pollutants PM_{10} and NO_x were considered in single-pollutant analyses. The authors reported that PM_{10} was associated with all-cause mortality in all age groups at lag 1 d, and in those aged ≥65 lag 1–3 d; NO_x was

associated with all-cause mortality in those under 65 at lag 1 d, and over 65 at lag 1–3 d (Kowalska et al., 2007).

In a comparable analysis Kowalska et al. (2008) evaluated the same urban areas of Katowice, Poland, in 1994–1995 against 2001–2002. The investigators found that in individuals exposed to higher mean concentrations of SO_2 (24-h mean 21.76 ppb (57 $\mu g/m^3$)) from 1994 to 1995, higher regression coefficients for both cardiorespiratory and total mortality outcomes were observed. Of greater interest to this discussion, however, was that this paper provided RR estimates for 3.82 ppb increases in SO_2 over background concentrations. The authors reported that for each unit increase in SO_2 concentration, the RR for all-cause and cardiorespiratory mortality increased. These results were more significant for the 3-d moving average (total mortality 1994–1995 = 2.3%; 2001–2002 = 1.2%; cardiorespiratory mortality 1994–1995 = 2.4%; 2001–2002 = 1.9%) than for the 24-h concentration (total mortality 1994–1995 = 1.6%; 2001–2002 = 0.5%; cardiorespiratory mortality 1994–1995 = 1.7%; 2001–2002 = 1.0%). Of note, the reported RR for the mortality endpoints was much lower for the 2001–2002 analysis than for the 1994–1995 data.

Neuberger et al. (2007) reported no significant associations between mortality and SO_2 concentrations in their assessment of various indices of all-cause, cardiovascular, and respiratory mortality. The study, from 2000 to 2004 in Vienna, Austria, found a mean 24-h average concentration of SO_2 of 1.91 ppb (5 $\mu g/m^3$). The authors reported no evidence of confounding by co-pollutants TSP, O_3, NO_2, PM_{10} and $PM_{2.5}$, although TSP, NO_2, PM_{10} and $PM_{2.5}$ were associated with all mortality endpoints.

An evaluation of acute effects (lag 0 d) on cardiovascular mortality following exposures to SO_2 (mean 24-h average 5.61 ppb (14.69 $\mu g/m^3$) in Niš, Serbia, from 2001 to 2005 (Stanković et al., 2007) found that for each 3.82 ppb increase in SO_2 concentration the ORs of cardiovascular mortality were increased, but these results were not significant. The only co-pollutant evaluated was BS, and it was significantly correlated with SO_2. No associations were found between BS and cardiovascular mortality (Stanković et al., 2007).

A Latin-American study by Cakmak et al. (2011) investigated the effects of SO_2 on elderly persons living in five Chilean cities from 1997 to 2007. The reported 24-h averages ranged from 8.47 ppb (Las Condes) to 14.5 ppb (Independencia). Results for pooled risk ratios for all-cause mortality showed an increased risk of 1.089 per IQR increase of SO_2. The IQRs were presented for each city, and ranged from 5.76 ppb (in Las Condes) to 10.4 ppb (in El Bosque). Stratified results, by age, showed increased risk as the population ages (aged <64: RR = 1.053 (95% CI 1.029–1.077) to aged ≥85: RR = 1.089 (95% CI 1.047–1.133)) with the difference in risk estimate between those aged <64 and those ≥85 being statistically significant. The co-pollutants CO, NO_2, O_3, PM_{10}, $PM_{2.5}$, and elemental and organic carbon were evaluated. Mortality risk estimates were similar to those of SO_2 for these pollutants. The authors also reported that indices of low SES, namely education and income, increased the risk of mortality per IQR increase of SO_2.

Eleven papers from Asian countries, including two meta-analyses, were assessed as part of the PAPA study. Only the results for SO_2 will be presented due to the complexity and length of this dataset.

The meta-analyses by Wong et al. (2010b) and Kan et al. (2010) evaluated the risk of increased mortality from exposure to SO_2 using results from several Asian time-series studies undertaken between 1996 and 2004 in four cities: Bangkok, Thailand; and Hong Kong, Shanghai and Wuhan, China. Estimates of risk for all-cause, respiratory, and cardiovascular mortality were calculated using weighted random-effects models. The reported 24-h average concentrations of SO_2 ranged from 5.04 ppb (13.2 $\mu g/m^3$, in Bangkok) to 16.79 ppb (44 $\mu g/m^3$, in Shanghai). Co-pollutants PM_{10}, NO_2 and O_3 were assessed. Their meta-analysis showed that the combined random effects risk estimates, as excess risk of mortality per 3.82 ppb (10 $\mu g/m^3$) increase in average concentration at lag 0–1 d were: all-cause mortality, 1.00%; respiratory, 1.47%; and cardiovascular, 1.09%. No significant associations were identified. Additionally, Kan et al. (2008, 2010) evaluated the effects of SO_2 exposure on all-cause, respiratory, and cardiovascular mortality in a time-series study carried out from 2001 to 2004 in Shanghai, China. Poisson analysis using GLM and lag 0–1 d found that the percentage change in mortality following a 3.82 ppb increase in exposure resulted in non-significant results for all-cause, cardiovascular, and respiratory mortality, with only respiratory mortality showing an overall trend toward increased incidence (1.37%). Stratification by specific subcategories of mortality found that a 3.82 ppb increase in SO_2 was associated with increased mortality estimates from heart disease (1.31%), COPD (1.24%), and acute respiratory infection (2.99%). Risk estimates adjusted for PM_{10} showed significant effects of SO_2 on daily mortality following a 3.82 ppb increase in exposure. Adjustment for sex and age resulted in women and those aged 5–44 being identified as more susceptible to effects from SO_2 exposures, though the values showed considerable variation.

Additional extensive PAPA analysis by Qian et al. (2010) in Wuhan, China, evaluated the effects of all-cause, cardiovascular, and respiratory mortality following exposures to mean (24-h average) SO_2 concentrations of 14.96 ppb (39.2 $\mu g/m^3$) from 2001 to 2004. Lags 0, 1, 0–1 and 0–4 d were considered, along with the co-pollutants O_3, NO_2, and PM_{10}. Statistically significant associations, reported as percentage change, were found with mortality from all-cause (1.20%), cardiovascular (1.47%), and respiratory (2.10%) endpoints following 3.82 ppb increases in SO_2 (lag 0–1 d). Stratification by stroke, cardiac, cardiopulmonary, and non-cardiopulmonary mortality gave similar results. In multi-pollutant models, estimated effects were stronger for SO_2 alone than when co-pollutants were evaluated, which indicated that some confounding was occurring.

Analysis of the PAPA cohort by Wong et al. (2010a) in Hong Kong, China, from 1996 to 2002 evaluated the risk of all-cause, respiratory, and cardiovascular mortality using Poisson regression analysis with GLM. The reported mean 24-h average SO_2 concentration was 6.79 ppb (17.8 $\mu g/m^3$), and the authors specifically examined the confounding effects of influenza infection on mortality outcomes following air pollution exposures. The risk of mortality, reported as percentage excess risk, increased for all-cause (1.23%), respiratory (1.31%), and cardiovascular mortality (1.23%) in those exposed to SO_2. These estimates for all-cause and cardiovascular mortality were higher for those ≥65 years of age, when compared against the general population. Adjustment for influenza status did not change the outcome for the general mortality estimates. Stratified analysis by specific respiratory endpoint showed significant increases in mortality estimates for cardiac disease (2.72%) and lower respiratory tract infection (2.21%) for all ages. The authors also reported that influenza (intensity, epidemic or predominance status) was a confounding factor in the association between SO_2 and death

outcomes for stroke and COPD, and that SO_2 exposure confounded mortality estimates for co-pollutants such as PM_{10} and NO_2.

A further PAPA evaluation using a time-series Taiwanese cohort (Vichit-Vadakan et al., 2010) assessed several mortality outcomes from 1997 to 2003 (lags 0, 1, 2, 3, 4, 0–1, and 0–4 d). Using Poisson regression analysis and GLM, they reported a significant increase in excess risk for respiratory mortality in children <1 year (50.2%) with an IQR (2.10 ppb) increment in SO_2 concentration. All-cause mortality, general mortality, and cardiovascular mortality did not show significant increases with rising SO_2 concentrations. The average SO_2 concentration was reported as 5.04 ppb (13.2 $\mu g/m^3$), and the co-pollutants PM_{10}, NO_2, O_3 and NO were evaluated.

A time-series study evaluating effects of SO_2 on all-cause, respiratory or cardiovascular mortality in Central Taiwan (Liang et al., 2009) showed significant increases in RR of mortality using single-pollutant regression models. All-cause mortality (RR = 1.043, (95% CI 1.018–1.098)) and cardiovascular mortality (RR = 1.087, (95% CI 1.025–1.151)) were increased in winter when the 75th percentile exposures were compared against the 25th percentile exposures; respiratory mortality showed trends toward increased risk, but no significance, in both multi-pollutant and single-pollutant models. No significant increases in risk were reported for other seasons or in multi-pollutant models. The reported mean 24-h average concentration of SO_2 was 1.84 ppb (4.81 $\mu g/m^3$) in winter.

Ou et al. (2008) in a time-series study based in Hong Kong, China, evaluated the effect of SO_2 exposure on all-cause mortality using Poisson regression analysis and GAM. The reported 24-h average concentration of SO_2 was 5.06 ppb (13.26 $\mu g/m^3$) and the co-pollutants PM_{10}, NO_2 and O_3 were assessed. Lags of 0, 1, 2, and 3 d were considered in the model. The results indicated that there was an increased risk of mortality with a 3.82 ppb increment in SO_2 concentration among those with lower SES. For example, the percentage risk estimate was increased for those living in public rental housing in China (2.53%), blue collar workers (3.73%), and uneducated individuals (no formal education) (3.33%). Those with private houses, those who were never employed, those who were employed in white-collar jobs, and those with even primary-level education had negative percentage mortality risk estimates, indicating that in China there are significant socioeconomic differences.

In a time-series analysis based in Hong Kong, China, from 1996 to 2002, Wong et al. (2008a) found that there were significant associations between SO_2 and all-cause and cardiovascular mortality. These associations were only seen in areas with middle or high social deprivation index. The reported mean 24-h average SO_2 concentration was 6.79 ppb (17.8 $\mu g/m^3$), and the highest percentage excess risk per 3.82 ppb increase in SO_2 concentration was reported to be 0.68% for all-cause mortality (lag 0 d), 1.03% for cardiovascular mortality (lag 0 d), and 1.06% for respiratory mortality (lag 0 d). Excess risks at other lag times (lag 1, 2, 3, or 4 d) were decreased compared to lag 0 d.

A previous analysis of the PAPA datasets by Wong et al. (2008b) evaluated the risk of all-cause, cardiovascular or respiratory mortality on populations in Bangkok, Thailand, as well as Hong Kong, Shanghai, and Wuhan, China. The investigators reported significant excess risks for all-cause mortality: 1.61% (Bangkok), 0.87% (Hong Kong), 0.95% (Shanghai), and 1.19% (Wuhan) with each 3.82 ppb increase in average concentration of SO_2 (lag 0–1 d). Respiratory

mortality excess risk estimates for each 3.82 ppb increase in average concentration of SO_2 (lag 0–1 d) were 1.28% (Hong Kong), 1.37% (Shanghai), and 2.11% (Wuhan). Cardiovascular mortality excess risk estimates for similar increments and lags were 1.19% (Hong Kong), 0.91% (Shanghai), and 1.47% (Wuhan). Excess risk estimates were not significant for SO_2 and cardiovascular or respiratory mortality in Bangkok. The reported 24-h averages for each city were 5.04 ppb (13.2 $\mu g/m^3$), 6.79 ppb (17.8 $\mu g/m^3$), 17.06 ppb (44.7 $\mu g/m^3$) and 14.96 ppb (39.23 $\mu g/m^3$) in Bangkok, Hong Kong, Shanghai and Wuhan, respectively. The co-pollutants PM_{10}, NO_2 and O_3 were evaluated.

A study in Korea between 2000 and 2004, when daily mean values of SO_2 were 5.21 ppb, identified positive, statistically significant increases of non-accidental deaths with an interquartile increase of 3.06 ppb SO_2 in single-pollutant models at lag 1 d, when the model included Asian dust days (2.5% (95% CI 1.7–3.3)) and when Asian dust days were excluded (2.7% (95% CI 1.8–3.5)). Positive results were also observed for PM_{10}, CO and NO_2 (Lee et al., 2007).

A study in Delhi, India, undertaken between 2002 and 2004 when daily mean values of SO_2 were 3.4 ppb, found no association between SO_2 and daily all-natural-cause mortality. Positive associations were observed with PM_{10} and NO_2 (Rajarathnam et al., 2011).

In summary, recent short-term exposure studies produced inconsistent results (positive or no association with SO_2 levels) regarding links between all-cause, cardiovascular, or respiratory mortality and SO_2 levels. Several studies identified confounding by other pollutants.

7.5.2.2 Long-term Exposure

Five cohort studies evaluating the effect of SO_2 exposure over chronic time frames were identified. This section focuses on results of all-cause mortality, respiratory mortality, and cardiovascular mortality, specifically. If other significant mortality endpoints were noted in the papers, they are identified for information purposes.

A spatial analysis of the ACS cohort led by Krewski et al. (2009) evaluated the association between air pollutants and mortality by linking pollution levels to survival and adjusting for confounding risk factors of ventilation, education, ethnicity, employment status, and other socioeconomic indices. The cohort included about 1.2 million participants aged 30 or older, and the period of study for this report was 1982 to 2000. The mean air concentration of SO_2 used for this analysis was 9.71 ppb, based upon 1980 levels. Results indicated weak, but statistically significant, associations between 5 ppb incremental changes in SO_2 concentration and all-cause mortality (hazard ratio 1.02), cardiopulmonary mortality (hazard ratio 1.02), and IHD (hazard ratio 1.04). This paper provides extensive analyses of other air pollutants on these mortality endpoints—all of which showed increases that were for the most part statistically significant. Please refer to the paper for more information.

An Australian study (Wang et al., 2009) evaluated associations between long-term exposure to SO_2 and cardiorespiratory mortality among residents of Brisbane. The authors controlled for age, sex and calendar year. The reported SO_2 concentration was 5.4 ppb (1-h maximum average concentration), and the co-pollutants O_3 and NO_2 were considered. The reported RR of cardiorespiratory mortality associated with a 1 ppb increment in annual average concentration of SO_2 was 1.047 in both the single-pollutant and multi-pollutant models. The RR posed by SO_2 was higher than those reported for NO_2 or O_3 under both single- and multi-pollutant models.

Katanoda et al. (2011) followed a cohort for 8.7 years, starting from 1983 or 1985, in the Japanese cities of Miyagi, Aichi and Osaka. Participants were aged 40 or older, and the Cox proportional hazards model adjusted for smoking status, pack-years, sex, age, daily consumption of green and yellow vegetables, occupation, and health insurance. The co-pollutants SPM, estimated $PM_{2.5}$, and NO_2 were considered. The mean 24-h average SO_2 concentration ranged from 2.4 to 19.0 ppb (1974–1983) or from 2.3 to 10.6 ppb (1984–1993); only the 10-year averages from 1974 to 1983 were used in the analysis. Mortality from respiratory diseases and pneumonia was significantly associated with a 10-unit increase in SO_2, with reported adjusted hazard ratios of 1.62 and 1.45, respectively, using the appropriate regional 10-year average concentration as a baseline concentration. Though increased incidence of mortality was reported for COPD, results were not significant. The hazard ratios observed for 10-unit increases in the other pollutants were similar to those for SO_2, but in all cases were less strong (Katanoda et al., 2011).

Cao et al. (2011) examined a large cohort of people aged 40 or older in the China National Hypertension Follow-up Survey. The study followed individuals from 31 Chinese cities between 1991 and 2000. The reported average concentration of SO_2 over that time frame (in the 31 cities) was 27.86 ppb (73 $\mu g/m^3$). The increase in cardiovascular, respiratory or all-cause mortality associated with a 3.82 ppb (10 $\mu g/m^3$) increase in SO_2 was reported at 3.2%, 3.2% and 1.8% in the adjusted model (the only model that accounted for appropriate confounders, such as body mass index, physical activity, education, occupation, smoking status, age at starting to smoke, years smoked, cigarettes per day, alcohol intake, and hypertension). The associations of SO_2 with these mortality indices did not change appreciably after adding the co-pollutants TSP or NO_X into the models (Cao et al., 2011).

Zhang et al. (2011), in a retrospective cohort study of people aged between 35 and 103, evaluated associations between SO_2 and cerebrovascular or cardiovascular mortality. The study was based in Shenyang, China, a heavily industrialized city. The mean annual level of SO_2 for the study period (1998–2009) was 24.05 ppb (63 $\mu g/m^3$) and the range was 9.92–40.46 ppb (26–106 $\mu g/m^3$). Co-pollutants PM_{10} and NO_2 were assessed. No associations between SO_2 and the two mortality endpoints were reported. The authors did, however, indicate that any SO_2 effects may have been masked by high pollutant concentrations of NO_2 and PM_{10}, which were both significantly associated with mortality endpoints (Zhang et al., 2011).

To summarize, most of the recent long-term exposure studies identified positive associations between SO_2 levels and all-cause, cardiovascular, and respiratory mortality.

7.6 Carcinogenicity and Genotoxicity

7.6.1 Summary of 2008 US EPA Integrated Science Assessment

The US EPA (2008) reviewed numerous studies examining the genotoxic effects of SO_2. Sulphur dioxide and its metabolite, SO_3^{2-}, were not found to be mutagenic, nor were they found to cause deoxyribonucleic acid (DNA) damage *in vitro*. *In vivo* studies using mice demonstrated increased mouse bone marrow micronucleated polychromatic erythrocytes and DNA damage in cells isolated from various organs in mice exposed to 5–30 ppm SO_2 for 4–7 h/d for 7 d (Meng et al., 2002, 2005b; Ruan et al., 2003). Despite suggesting that inhaled SO_2 can cause systemic effects at high concentration, these studies do not have much significance in evaluating the genotoxic effects of ambient concentrations of SO_2.

Studies in rats exposed to SO_2 concentrations of 0–30 ppm via inhalation for up to 20 months did not identify carcinogenic or co-carcinogenic (benzo-[a]-pyrene, suspended PM, diesel exhaust particle, diethylnitrosamine) activity.

Examination of the toxicological literature and epidemiologic data indicated that SO_2 at high concentrations may cause DNA damage, but that carcinogenesis, co-carcinogenesis or tumour promotion are not evident (Gunnison et al., 1988). Epidemiologic evidence from studies examining associations between long-term exposure to ambient SO_2 and risk of lung cancer incidence and mortality was inconclusive (Nyberg et al., 2000; Nafstad et al., 2003, 2004; Filleul et al., 2005).

7.6.2 Evaluation of Carcinogencity or Genotoxicity from Exposure to SO_2: 2007–2011

A review of the literature from 2007 onward, including laboratory-based studies and epidemiological evaluations for SO_2 exposure and genotoxicity or carcinogenicity, has provided several recent papers about the effects on humans. The literature presented in this section provides a brief description of the study design and endpoints discussed. Effects due to co-pollutants and multi-pollutant analyses are indicated briefly and only where they were evaluated by the study authors.

7.6.2.1 Human Health

Four epidemiologic studies were found that looked at the relationship between SO_2 and lung cancer incidence or mortality.

The Beelen et al. (2008a, 2008b) studies examined the effects of SO_2 exposure on lung cancer incidence in a large cohort of Dutch people from 1986 to 1997. The mean SO_2 concentration in ambient air was measured at 5.23 ppb (13.7 $\mu g/m^3$ (standard deviation: 5.1)), and the co-pollutants BS, $PM_{2.5}$, and NO_2 were considered. In both studies, no increase in RR was found for lung cancer incidence, evaluated as RR increase per 7.63 ppb (20 $\mu g/m^3$) increment in SO_2. Both studies employed Cox proportional hazards models adjusted for smoking, SES area-level, age, and sex; more in-depth case-cohort analysis accounted for age, sex, body mass index, active smoking, passive smoking, education, occupational exposure, marital status, alcohol use, vegetable intake, fruit intake, energy intake, fatty acids intake, folate intake, fish consumption and area-level indicators of SES.

The Asian studies, conversely, found significant associations between SO_2 and lung cancer mortality. The first, by Cao et al. (2011) examined a large cohort of people aged 40 years or older in the China National Hypertension Follow-up Survey. The study looked at individuals from 31 Chinese cities from 1991 to 2000. The reported average concentration of SO_2 over that time frame (in the 31 cities) was 27.86 ppb (73 $\mu g/m^3$). The percentage increase in lung cancer mortality associated with a 10 $\mu g/m^3$ increase in SO_2 was reported at 4.2% in the adjusted model (the only model that accounted for appropriate confounders, such as body mass index, physical activity, education, occupation, smoking status, age at starting to smoke, years smoked, cigarettes per day, alcohol intake, and hypertension) (Cao et al., 2011). The associations of SO_2 with lung cancer mortality did not change much after adding the co-pollutants TSP or NO_X into the adjusted models (adjusted for TSP: 4.1%; adjusted for NO_X: 4.1%) (Cao et al., 2011).

The Katanoda et al. (2011) study followed a cohort for 8.7 years beginning in 1983 or 1985 in the Japanese cities of Miyagi, Aichi and Osaka. Participants were aged 40 or older, and the Cox proportional hazards model adjusted for smoking status, pack-years, sex, age, daily consumption of green and yellow vegetables, occupation, and health insurance. The co-pollutants SPM, estimated $PM_{2.5}$, and NO_2 were considered. The mean 24-h average SO_2 concentration ranged from 2.4 to 19.0 ppb (1974–1983) or from 2.3 to 10.6 ppb (1984–1993) (Katanoda et al., 2011); only the 10-year averages from 1974 to 1983 were used in the analysis. Lung cancer mortality was associated with a 10-unit increase in SO_2, with a reported adjusted hazard ratio of 1.22 for models evaluating patients with no respiratory diseases, and 1.97 for models evaluating all subjects. Results for the other pollutants were similar to SO_2, and significant, for those with no history of respiratory diseases, but the hazard ratios were at least 0.56 lower than the SO_2 results when those with respiratory diseases were included (Katanoda et al., 2011).

One study evaluated the effect of SO_2 on bladder cancer. This matched case-control study by Liu et al. (2009a) evaluated bladder cancer deaths from 1995 to 2005 among people aged 50–69 in Taiwan. The investigators identified 680 cases and matched them with an equal number of controls. Multiple logistic regression analysis was performed, using the group with the lowest exposure as the reference group. Adjustments were made for marital status and the level of urbanization. The concentration of SO_2 was not reported, but the unadjusted OR for bladder cancer mortality associated with SO_2 showed a concentration–response trend, ranging from 1.42 for SO_2 concentrations ranging from 4.39 to 6.09 ppb, to 1.73 for concentrations ranging from 6.49 to 17.87 ppb. Other pollutants (CO, $PM_{10,}$ NO_2, and O_3) were evaluated; of these, the bladder cancer concentration–response trend was also observed for NO_2 and PM_{10} in single-pollutant models. The authors reported that since the trends were most significant for SO_2 and NO_2, a bi-pollutant model would be generated for these pollutants. Trend analysis for these pollutants using the bi-pollutant model showed that the concentration–response trend toward bladder cancer was maintained (Liu et al., 2009a).

In summary, recent studies have identified inconsistent results for associations between SO_2 levels and lung cancer, while one report indicated a concentration–response trend for bladder cancer.

7.6.2.2 Animal Studies

An animal study evaluating NMRI (Naval Medical Research Institute) outbred mice exposed to 1, 3, 10, or 30 ppm SO_2 (whole body exposure) for 4 h/d for 7 d was looking at the presence of micronucleated polychromatic erythrocytes (Ziemann et al., 2010). The presence of micronucleation of these immature erythrocytes would have indicated chromosomal breakage and genotoxic effects (US FDA, 2000). The study found no significant increase in the number of micronucleated polychromatic erythrocytes at 24 h after the last exposure, compared to clean air controls (Ziemann et al., 2010).

Qin and Meng (2010) exposed male Wistar rats to 21.37 ppm (56 mg/m^3) SO_2 for 6 h/d for 7 d; they found significantly increased messenger ribonucleic acid (mRNA) and protein expression levels of c-myc (1.6-fold and 1.8-fold), Ki-ras (2.2-fold and 2.7-fold), and p53 (1.4-fold and 1.7-fold), and reduced expression levels of p16 (0.67-fold and 0.59-fold) and Rb (0.61-fold and 0.86-fold). The authors elected to evaluate c-myc and Ki-ras because they are known to have proto-

oncogene activity; they assessed p53, p16 and Rb because of their role as tumour suppressor genes (Qin and Meng, 2010).

To summarize, recent studies of laboratory animals exposed to SO_2, found that it did not induce micronucelated polychromatic erthyrocytes in mice; however, changes in mRNA and protein expression of proto-oncogenes and tumour suppressor genes were observed in rats.

7.7 Reproductive and Developmental Effects

7.7.1 Summary of 2008 US EPA Integrated Science Assessment

7.7.1.1 Low Birth Weight

Epidemiological studies on birth outcomes have observed positive associations between SO_2 exposure and low birth weight (LBW) (Wang et al., 1997; Bobak, 2000; Ha et al., 2001; Maisonet et al., 2001; Lee et al., 2003; Liu et al., 2003; Yang et al., 2003; Mohorovic, 2004; Gouveia et al., 2004; Lin et al., 2004; Dugandzic et al., 2006; Bell et al., 2007); however, toxicological studies have yet to provide support for these findings. Of the studies showing a link between SO_2 exposure and LBW, one found an association between LBW in Caucasians (but not other ethnicities or races) at SO_2 concentrations of greater than the 25th percentile (concentration not stated; adjusted OR range 1.12–1.18) during the second trimester of pregnancy (Maisonet et al., 2001). Canadian analyses of a large cohort of women in Nova Scotia found that at a mean 24-h average SO_2 concentration of 10 ppb during the first trimester was associated with increased risk of LBW. Specifically, an RR of 1.14 was reported for each 5 ppb increase in SO_2 concentration (Dugandzic et al., 2006), a result similar to that of Liu et al. (2003) who reported that maternal exposure during the first month of pregnancy was associated with 1.11-fold increased risk of LBW at exposure concentrations of 4.9 ppb (mean 24-h average). Limitations to interpretation of these results include inconsistent results across the trimesters of pregnancy and a lack of evidence regarding confounding by co-pollutants (US EPA, 2008). The US EPA drew no conclusions on SO_2 and its potential to cause LBW during pregnancy.

7.7.1.2 Preterm Delivery, Intrauterine Growth Restriction, Birth Defects, Neonatal Hospitalization and Infant Mortality

The limited number of studies addressing preterm delivery, intrauterine growth restriction (IUGR), birth defects, neonatal hospitalizations, and infant mortality (Xu et al., 1995; Bobak, 2000; Sagiv et al., 2005; Leem et al., 2006) resulted in the US EPA (2008) not drawing conclusions regarding the effect of SO_2 on these outcomes. However, there were interesting associations presented by several authors, including Sagiv et al. (2005), who reported that the mean 6-week exposure prior to birth was associated with an RR of 1.05 for preterm birth with each 5 ppb increase in SO_2 concentration. Increases in SO_2 concentration by 5 ppb 3 d before birth were associated with an RR of 1.04, perhaps reflecting a time-sensitivity related to the normal progression of parturition. In Canada, Liu et al. (2003) reported an OR for preterm birth of 1.09 (95% CI 1.01–1.19) for a 5 ppb increase in SO_2. The US EPA (2008) reported that similar results were found for studies of preterm birth conducted in other countries (Xu et al., 1995; Bobak, 2000; Leem et al., 2006). Other studies showed conflicting results for endpoints of IUGR (Liu et al., 2003, 2007) and neonatal death (Pereira et al., 1998; Lipfert et al., 2000; Lin et al., 2004; Gilboa et al., 2005). A study of cardiac birth defects and oral clefts (Gilboa et al.,

2005) found that the OR for isolated ventricular septal defects was 2.16 for maternal exposure to concentrations ≥2.7 ppb SO_2 during weeks 3–8 of pregnancy.

7.7.1.3 Developmental Effects

The US EPA (2008) discussed two studies of developmental effects of SO_2 on neonatal children. The first (Dales et al., 2006) evaluated hospitalizations for respiratory disorders in children less than 4 weeks of age from hospitals in 11 Canadian cities over 15 years (population weighted average, 24-h average SO_2 of 4.3 ppb). A 5.5% excess risk in respiratory hospitalizations was associated with a 10 ppb increase in 24-h average SO_2 concentrations with a 2-d lag. This effect was slightly attenuated after adjusting for co-pollutants (PM_{10}, gases). The influence of ambient SO_2 concentrations on sudden infant death syndrome (SIDS) (Dales et al., 2004) was investigated by a time-series analysis comparing daily rates of SIDS and daily SO_2 concentrations from 12 Canadian cities during a 16-year period. The mean 24-h average SO_2 level across the 12 cities was 5.51 ppb (IQR, 4.92). There was an 18.0% excess risk of SIDS incidence for a 10 ppb increase in 24-h average SO_2 concentration. The authors concluded that the effect of SO_2 was independent of sociodemographic factors, temporal trends, and weather. No specific conclusions were provided for these effects due to the limited number of studies.

Information on developmental effects in older children was not reported.

7.7.2 Evaluation of Reproductive or Developmental Effects from Exposure to SO_2: 2007–2011

A review of the literature from 2007 onward has provided several recent papers about these effects on humans, mainly from epidemiological evaluations of SO_2 exposure and prenatal and neonatal outcomes. The literature presented in this section provides a brief description of the study design, location and endpoints discussed. Effects due to co-pollutants and multi-pollutant analyses are mentioned briefly and only where they were evaluated by the study authors.

7.7.2.1 Birth, Birth Weight, and Preterm Birth

In Canada, a study by Brauer et al. (2008b) evaluated birth outcomes of small for gestational age (SGA), LBW, and preterm birth in a population-based cohort study in Vancouver, BC. The mean exposure was calculated to be 2.02 ppb (5.3 $\mu g/m^3$; range 0.11–6.79 ppb). The authors found no association between maternal exposure to SO_2 and SGA, LBW, or preterm birth; they also concluded that high correlations between NO, NO_2, CO, and SO_2 made differentiating impacts of specific pollutants unattainable (Brauer et al., 2008b).

In the US, Darrow et al. (2009) investigated the effect of air pollutants on preterm birth in a time-series study. A retrospective cohort of just over 475,000 live births was evaluated for the metropolitan Atlanta, GA, area using Poisson GLM analysis. The mean 1-h maximum concentration of SO_2 for the 4-week average (first month of gestation) was 10.5 ppb, with a large range (3.9–22.7 ppb). Results indicated that 1-h maximum SO_2 was associated with reduced risk of preterm birth in the first month of gestation (RR = 0.97) (Darrow et al., 2009). Other pollutants evaluated (PM_{10}, $PM_{2.5}$, NO_2 and O_3) resulted in mostly null results, but daily preterm birth rates were associated with average NO_2 concentrations in the 6 weeks preceding birth, and with average concentrations of $PM_{2.5}$, SO_4^{2-}, or metals in the preceding week (Darrow et al., 2009).

A study by Jalaludin et al. (2007) evaluating the effect of SO_2 on preterm birth in Sydney, Australia, from 1998 to 2000 showed a statistically significant positive association between preterm births and exposure to SO_2 (among those living within 5 km of a monitoring station) 1 month preceding birth (OR = 1.56), 3 months preceding birth (2.33), and in the first trimester (2.31). Conversely, for all births examined (not only for those within 5 km of a monitoring station) a statistically significant decrease in preterm birth was observed for SO_2 exposure during the first month of gestation and the first trimester. Mean daily average SO_2 concentrations ranged from 3.3 to 3.8 ppb, with a yearly average of 3.6 ppb. Analyses were performed using logistic regression, and covariates of maternal age, maternal smoking during pregnancy, indigenous status, SES, gestational age at first antenatal visit, season of conception, and parity were considered. Pollutant levels during late pregnancy for other pollutants evaluated (PM_{10}, $PM_{2.5}$, O_3, NO_2 and CO) had no effect on preterm birth, though these pollutants showed varying influences on risk of preterm birth during early pregnancy (some increased the risk, some decreased it) (Jalaludin et al., 2007).

Jiang et al. (2007) evaluated preterm birth outcomes in Shanghai, China, in 2004. The daily median reported concentration of SO_2 was 19.66 ppb (51.5 $\mu g/m^3$). A statistically significant 11.89% increase in preterm birth per 3.82 ppb increase in SO_2 was reported only for SO_2 exposures lasting for 8 weeks before birth. Results for other pollutants for each 10 $\mu g/m^3$ increase were lower at 4.42%, 5.43% and 4.63% for PM_{10}, NO_2 and O_3, respectively. Exposures lasting for 6 and 4 weeks before birth were not significant (Jiang et al., 2007).

The study by Bell et al. (2008b) evaluated birth weight using case-control design in a study from 1999 to 2002. Gestational exposure to SO_2 was calculated to be a mean of 4.7 ppb. No association between gestational exposures to SO_2 or the other pollutants (PM_{10}, $PM_{2.5}$, CO, and NO_2) and birth weight were found, even when covariates such as infant sex, mother's age, trimester-based exposure, or gestational age at birth were evaluated.

Conversely, a study by Darrow et al. (2011) evaluated birth weight outcomes in metropolitan Atlanta, GA, from 1999 to 2002, and linear regression analysis showed a statistically significant decrease in birth weight (-3.9g) for third trimester SO_2 exposures (mean: 9.5 ppb). Covariate analysis by ethnicity showed that results remained significant within non-Hispanic white (-5.2g) and Hispanic (-5.7g) subpopulations, but not for non-Hispanic black populations. Ambient levels of NO_2, $PM_{2.5}$, elemental carbon, and water-soluble metals (as a component of $PM_{2.5}$) were also associated with reductions in birth weight per IQR increase in pollutant concentrations (Darrow et al., 2011).

A qualitative study evaluating LBW in Brazil in 2001 (Nascimento and Moreira, 2009) supports the results of Darrow and colleagues; the study found that the ORs for LBW were significantly associated with SO_2 in the second and third quartiles. The overall OR, considering exposure during the 90 d prior to birth, showed increased ORs of 1.30 for SO_2 exposures of 204.43 ppb (535.6 $\mu g/m^3$). This ecological, time-series study also found that SO_2 and PM_{10} levels were highly, and positively, intercorrelated. Covariates evaluated included maternal age (all participants were between 20 and 34 years of age), education, prenatal visits, marital status, and vaginal delivery.

Legro et al. (2010) studied live birth rates in the Northeastern US following *in vitro* fertilization (IVF) in 7403 females. The effects evaluated were the ORs of live births per 0.03 ppm increase in SO_2 concentration during: a) events prior to oocyte retrieval, b) oocyte removal to embryo

transfer, c) embryo transfer to pregnancy test, or d) embryo transfer to date of live birth either at the IVF clinic or near the patients' homes. Logistic regression analysis showed no significant effects for a 0.03 ppm increase in SO_2 (daily mean concentration range: 57–63 ppb from monitors near the laboratory or at patients' homes) at any time during the IVF cycle, although outcomes became poorer with increasing SO_2 exposure. Interestingly, the effect of SO_2 was almost significant for intrauterine pregnancy rates, according to the concentration of SO_2 at the IVF clinic during embryo culture. The authors reported that results were similarly non-significant for other pollutants evaluated, with the exception of a 0.02 ppm increase in O_3 from the date of embryo transfer to the pregnancy test (Legro et al., 2010).

In summary, recent studies reported inconsistent results (increase, decrease or no association with SO_2 levels) for preterm births and inconsistent results (decrease or no association with SO_2 levels) for birth weights.

7.7.2.2 Congenital Anomalies

Vrijheid et al. (2011) prepared a meta-analysis of four studies evaluating the risk of cardiac congenital anomalies in children exposed to SO_2 during either weeks 3–8 of gestation (Gilboa et al., 2005; Strickland et al., 2009; Dadvand et al., 2011a) or annually (Dolk et al., 2010). The authors found that SO_2 was related to increased risk of aortic coartication (narrowing of aorta where the ductus arteriosus of the fetus inserts; the ductus arteriosus allows the blood from the right ventricle to bypass the fetal lungs) and tetralogy of Fallot (a congenital heart defect). The risk of coartication of the aorta increased with both continuous exposure (RR = 1.07 (95% CI 1.01–1.13)) and high vs. low exposure (RR = 1.06 (95% CI 0.89–1.27)); the risk of tetralogy of Fallot increased under situations of continuous exposure (RR = 1.03 (95% CI 1.01–1.05)), indicating a concentration–response relationship. Two studies (Rankin et al., 2009 and Dadvand et al., 2011b) were not included in the initial meta-analysis because they used the same study population as Dadvand et al., 2011a. Replacement of Dadvand et al., 2011a with either study gave non-significant results. Other pollutants examined (CO, NO_2, O_3, PM_{10}) showed similar OR trends to SO_2; however, the ORs for PM_{10} on these endpoints did not achieve significance (Vrijheid et al., 2011).

A study in the UK between 1985 and 1990 (Rankin et al., 2009), evaluating cumulative first-trimester exposures (median exposure in controls over the first trimester: 1366.03 ppb (3579 $\mu g/m^3$)) and in cases: 1337.79 ppb (3505 $\mu g/m^3$)) showed a significant negative association between SO_2 exposures and congenital heart disease and patent ductus arteriosus, but the relationship between SO_2 levels and other anomaly subtypes was less clear. Black soot was the only other pollutant evaluated, and results indicated that exposure to black soot increased the OR (1.10) for nervous system anomalies but not for other anomaly subtypes (Rankin et al., 2009).

A study by Dadvand et al. (2011a), based upon a case-control evaluation of populations in Northern England from 1993 to 2003, identified 2,140 cases of congenital heart disease and showed decreased, but non-significant, ORs of developing congenital heart defects and pooled-cases of congenital heart disease, congenital malformations of cardiac septa, tetralogy of Fallot, and ventricular septal defects to be associated with SO_2 exposures. Results for other pollutants indicated that CO and NO were positively associated with several congenital cardiac malformations, but findings for O_3 and PM_{10} were less consistent (Dadvand et al., 2011a).

The same group of authors evaluated congenital heart disease using a case-control study from 1985 to 1996 (Dadvand et al., 2011b). Exposure assessment for SO_2 exposure was performed for weeks 3-8 of pregnancy, the time frame associated with development of congenital heart defects. The predicted mean concentration of SO_2 was expressed as a series of means within the quartile (e.g. it ranged from 15.91 to 17.53 $\mu g/m^3$ in the second quartile); the first quartile was treated as the reference group, with subsequent quartiles being compared against this reference group to estimate the OR and to investigate concentration–response relationships in consecutive quartiles of exposure. In this analysis, the authors found no association between SO_2 exposure for the various quartiles and congenital heart defects. Endpoints evaluated included septal defects of the ventricles and atria, congenital pulmonary valve stenosis, tetralogy of Fallot, and coartication of the aorta. Black smoke was the only other pollutant evaluated, and a weak association was found between exposure to BS and congenital heart malformation when exposure was used as a continuous variable. When exposure was evaluated by IQR, the ORs for congenital malformation after exposure to BS did not show a dose–response relationship (Dadvand et al., 2011b).

Dolk et al. (2010) evaluated congenital anomalies, both chromosomal and non-chromosomal, in children exposed to SO_2 from 1991 to 1999 in England. The reported mean annual average for SO_2 was 3.00 ppb (7.86 $\mu g/m^3$). No significant association between SO_2 exposure and non-chromosomal anomalies was found, but a non-significant excess risk for chromosomal anomalies was detected. For congenital heart diseases, a statistically significant increased RR for tetralogy of Fallot was observed for an increase in SO_2 from the 10^{th} to the 90^{th} percentile of exposure (1.38). Significantly increased risks of congenital heart malformations were also observed for NO_2 and PM_{10} (Dolk et al., 2010).

Hansen et al. (2008) evaluated ultrasound measurements taken in Australia for weeks 13–26 of gestation. Specifically, the team evaluated data for fetal femur length, biparietal diameter, head circumference, and abdominal circumference and compared it against the mean seasonal concentrations of SO_2. The mean daily average concentration of SO_2 for all seasons was 1.19 ppb (IQR, 1.00); the mean daily average concentration for the second month of gestation was 1.5 ppb. Results of analysis indicated that average monthly exposures of SO_2 during the first 4 months of pregnancy had no effect on head circumference and femur length. Sulphur dioxide concentrations were, however, associated with a statistically significant reduction in abdominal circumference (-1.67 mm) and biparietal diameter (-0.68 mm), described by the mean change for an IQR increase in SO_2. Covariates including the long-term trend, season, temperature, gestation, mother's age, SES, and fetal sex were considered. Of the other pollutants evaluated, PM_{10} exposure significantly reduced head circumference, abdominal circumference, and femur length for exposures lasting 91–120 d under the adjusted models, and O_3 significantly reduced abdominal circumference in exposures lasting 31–60 d under the adjusted model. Nitrogen dioxide had no significant effect on these effect outcomes (Hansen et al., 2008).

The risk of cleft lip or cleft palate was evaluated in a case-control study performed by Marshall et al. (2010) in New Jersey, USA, from 1998 to 2003. Exposures to SO_2 (expressed as means) during weeks 5–10 of gestation were calculated to be 5.1 ppb in control groups, 5.3 ppb in cleft lip groups, and 4.8 ppb in groups with cleft palate. Results of the logistic regression analysis did not indicate a statistically significant association between increasing SO_2 exposure over the critical time period and incidence of cleft palate or cleft lip. Data were expressed as adjusted ORs associated with quartiles of average concentration during weeks 3-8 of pregnancy. All

residences within 40 km of the closest air monitoring station were included. The incidence of cleft lip, with or without presentation of cleft palate (i.e. including cleft palate data), showed a weak positive association with SO_2 exposure, including a statistically significant elevated risk at the highest quartile of exposure (>7 ppb: OR = 1.6). Conversely, the incidence of cleft palate was reduced as SO_2 concentration increased, but the results were not statistically significant. Of the other pollutants evaluated (PM_{10}, $PM_{2.5}$, CO, O_3 and NO_2) only O_3 showed any association with the endpoints assessed, specifically with cleft palate only (Marshall et al., 2010).

In summary, a recent meta-analysis identified positive associations between SO_2 and several cardiac congenital anomalies, although individual studies reported inconsistent results (increase, decrease or no association with SO_2 levels) for this endpoint. One study identified an association between SO_2 and changes in ultrasound measurements and another study reported an association with cleft lip.

7.7.2.3 Other

A cohort study by Woodruff et al. (2008) evaluated postnatal infant mortality in the US from 1999 to 2002. In children aged 28 d to 1 year, they found that there was no association between any type of postnatal mortality and SO_2 exposure (range: 2.81–3.42 ppb). Similar results were reported by Son et al. (2008), who examined postnatal infant mortality in Seoul, Korea, from 1999 to 2003. They found that there were non-significant positive associations between SO_2 and infant daily mortality under mean SO_2 concentrations of 5.6 ppb. Woodruff et al. (2008) reported that 10 $\mu g/m^3$ increases of PM_{10} showed an association with higher mortality from respiratory causes, and each 10 ppb increment in O_3 increased the risk of death from SIDS.

Conversely, Hajat et al. (2007), evaluating infant mortality in 10 UK cities in a time-series study using Poisson generalized analysis, obtained different results. Mean daily pollutant concentrations ranged from 4.35 to 8.13 ppb (11.4–21.3 $\mu g/m^3$), and a statistically significant relationship between infant mortality was observed for SO_2. These results only considered acute changes to SO_2 concentrations. A 3.82 ppb (10 $\mu g/m^3$) increase in SO_2 was associated with an increased RR of 1.02 for all infant deaths, including neonatal and post-neonatal deaths. The other pollutants evaluated (CO, NO, NO_2, O_3, and PM_{10}) had no significant or consistent effect on infant deaths (Hajat et al., 2007).

The incidence of asthma diagnosis in children up to age 4 was evaluated by Clark et al. (2010) in southwestern British Columbia from 1999 to 2000, following *in utero* exposures. This population-based nested case-control study showed that asthmatic children had higher mean exposure to SO_2 than did non-asthmatic children. Control populations were exposed, *in utero*, to calculated levels of 1.95 ppb SO_2 (5.11 $\mu g/m^3$) and asthmatic populations were exposed to a mean concentration of 2 ppb SO_2 (5.25 $\mu g/m^3$); similar exposure concentrations persisted over the first year of life (control: mean 1.99 ppb SO_2 (5.22 $\mu g/m^3$); asthmatic: mean 2.05 ppb SO_2 (5.37 $\mu g/m^3$)). Exposure estimates for SO_2 showed elevated risks of asthma diagnosis for both *in utero* and first-year average exposures. Upper quartiles of exposure for SO_2 showed elevated ORs for asthma risk with respect to the lowest quartile of exposure, but the trend across quartiles was not consistently linear. Similarly increased risks of asthma were reported for NO, NO_2, CO, PM_{10}, and black carbon; for $PM_{2.5}$ only *in utero* were the exposures associated with increased risk of asthma; and O_3 was not reported to increase the risk of asthma (Clark et al., 2010).

In the study using Kunming albino mice (Meng and Liu, 2007), male mice were exposed to 0, 10 or 20 ppm (0, 28 or 56 mg/m^3) SO_2 using whole-body exposures (4 h/d for 7 d; killed 18 h after final exposure). Results indicated that ultrastructural morphologies of lungs, livers, spleens, testes, brains, hearts and kidneys were damaged due to SO_2 exposures (Meng and Liu, 2007).

Lee et al. (2011a, 2011b) evaluated maternal CRP protein (inflammatory biomarker) concentrations in a prospective cohort of 1,696 women, before week 22 of gestation in Allegheny County, PA, from 1997 to 2001. They found no association between high CRP concentrations and SO_2 exposure. Covariates of gestational week sampled, maternal body mass index, maternal age, maternal race, maternal education, parity, cigarette smoke exposure, household income, season of sampling, and year entering study were evaluated.

In summary, recent studies reported inconsistent results (increased or no association with SO_2 levels) for infant mortality. One study identified no association with CRP and another study found increased asthma incidence in infants exposed to higher levels of SO_2.

8.0 Relationship Between Endogenous Sulphur Status and the Applied Dose

Little is known about the influence of environmental exposures to SO_2 on normal body burdens of sulphur; nonetheless, it is important from a toxicological perspective to model the potential applied dose (as SO_3^{2-}) to humans that may result from exposure to levels of SO_2 measured in the Canadian environment. By comparing this modelled information against known body burdens of SO_3^{2-} it becomes possible to evaluate whether the adverse effects reported in the literature are toxicologically likely to occur under ambient exposure scenarios in Canada. In other words, by modelling the change to serum sulphite status—a highly regulated molecule—it becomes possible to determine whether the adverse effects in the literature are biologically plausible based upon toxicological understanding of homeostatic disruption.

The following sections detail known information on normal body burden of serum sulphite in humans, and model the effect of acute or chronic environmental exposures on predicted applied dose of serum sulphite in humans. The intent is to compare the predicted applied dose against normal body burdens to determine whether the adverse effects reported in the literature are realistic under normal ambient exposures to the Canadian populations.

8.1 Endogenous Sources

8.1.1 Endogenous Production of SO2

Wang et al. (2011) provided an excellent description of endogenous SO_2 production. Briefly, in mammals, SO_2 can be derived from sulphur-containing amino acids. L-cysteine is oxidized via cysteine deoxygenase to L-cysteine sulphinate, which converts to β-sulphinylpyruvate through transamination by aspartate aminotransferase. It spontaneously decomposes to pyruvate and SO_2. Additional endogenous pathways arise from oxidation of hydrogen sulphide, and include 1) oxidation of hydrogen sulphide by sulphide oxidase to thiosulphate and then conversion to sulphite by thiosulphate sulphurtransferase or glutathione-dependent thiosulphate reductase; and 2) conversion of hydrogen sulphide to sulphite by nicotinamide-adenine dinucleotide phosphate oxidase in neutrophils activated by oxidative stress.

Sulphur dioxide can also originate from sulphur monoxide (SO) by dismutation (a specific type of redox reaction in which SO is simultaneously reduced and oxidized so as to form two different products).

Endogenous SO_2 generation can be regulated by acetylcholine and noradrenalin in vascular tissue (Wang et al., 2011).

8.1.2 Body Burdens of Endogenous SO_2

The reported concentration of SO_2 in humans, measured as serum sulphite, is 4.87 ± 2.49 μM (reference range: 0–10 μM) (Ji et al., 1995), which is equivalent to 15.86 μg/kg-bw (range: 0–

32.68 μg/kg-bw) sulphite in an adult (see example calculation, below). This range was determined from the blood of healthy Americans (34 male and 41 female). No information was presented on potential SO_2 exposures of the reference subjects. It is unknown whether there are age or sex differences in serum sulphite concentration in humans. The importance of interspecies variation in serum sulphite body burdens is similarly unknown, but results from rats indicate that they have higher serum sulphite concentrations ((15.54 ± 1.67 μM in male Wistar rats (Du et al., 2008); and 16.77 ± 8.24 μM in rats (Meng et al., 2009)) when compared against human body burdens.

8.1.2.1 Conversion of Serum Sulphite Concentration: μM to μg/kg-bw

Factors:

Average amount of blood in human adult: 8% of body weight (Barrett et al., 2012)

Average volume of blood in human adult = 5600 mL in 70 kg person (Barrett et al., 2012))

Fraction of blood that is plasma = 55% (Barrett et al., 2012)

NOTE: Serum is the plasma fraction minus its clotting factor proteins. The average plasma protein fraction is 7% (Mescher, 2010).

Molecular mass of sulphite = 80 g/mol

Calculation of average amount of plasma in human adult

= 5.6 L * 0.55

= **3.08 L in 70 kg human adult**

Calculation of average volume of serum in human adult

= [3.08 L plasma - (3.08 L plasma * 0.07)]

= **2.86 L in 70 kg human adult**

Calculation of concentration of serum sulphite in average human adult

= 4.87 μmol/L * 2.86 L

= **13.93 μmol in 70 kg human adult**

Conversion of μmol to g sulphite

= 13.93 μmol * 1 mol/1,000,000 μmol * 80 g/mol

= **1.11×10^{-3} g sulphite in 70 kg human adult**

Conversion to μg/kg-bw sulphite

= 1.11×10^{-3} g * 1,000,000 μg/g /70 kg

= **15.86 μg/kg-bw sulphite in an adult**

Sulphite status is highly regulated to maintain homeostasis in humans (Wang et al., 2011); therefore, it is not surprising that disease status can affect serum sulphite levels in humans. For example, those with acute pneumonia or renal failure have significantly increased serum sulphite concentrations.

8.2 Selection of Exposure Data for Exposure Modelling

Personal exposure models using published Canadian SO_2 air concentrations and NAPS data are provided in Section 8.2.1.1 and Section 8.2.1.2, for chronic and acute exposures, respectively. The results of both the acute and chronic personal exposure models (given as applied dose serum sulphite) have been compared against the reported average adult body burden of serum sulphite, calculated as 15.86 μg/kg-bw. This enables determination of the predicted percentage change to normal body burden serum sulphite in human adults under ambient exposure conditions in Canada.

8.2.1 Approach to Personal Exposure and Applied Dose Modelling

Since data are available for multiple time points, the following approach was undertaken to model the most relevant personal exposure scenarios in order to determine the applied dose of SO_2, as serum sulphite.

For chronic exposures, the maximum annual average from the NAPS sites in 2011 was used to model the applied dose using the Canadian Air Personal Exposure Model (version 2) (CAPEM2). The Canadian Human Activity Pattern Survey (CHAPS) was used to develop models of Canadian time–activity patterns, which were then incorporated by the Air Health Effects Assessment Division of Health Canada to develop the CAPEM2 (model described in detail in Appendix A). Briefly, CAPEM2 estimates personal inhalation exposure using contaminant concentrations, time–activity data from CHAPS, and receptor characteristics to determine human exposure to a chemical, in selected microenvironments (Golder Associates, 2010). Six age groups are defined by the model (<1 year; 1–4 years; 5–11 years; 12–19 years; 20–59 years; ≥60 years), which also considers variables such as body weight, and age- and activity-specific patterns of exposure.

The maximum annual averages were selected from the NAPS data (presented in Table 5.3) to represent the worst-case scenario for both urban and rural exposures. Preliminary data from Health Canada's Urban Transport Exposure Study, which, in part, monitored in-vehicle SO_2 data during summer and winter rush hour periods in Toronto, ON, and Montreal, QC, in 2010 and 2011, found an in-vehicle median of 4.6 ppb. The majority of the measurements were below the detection limit. In Health Canada indoor air studies carried out in Montreal, Halifax and Edmonton, 91% of SO_2 samples taken were below the detection level (on the 24-h averaging time frame). Therefore, it was not possible to determine an indoor–outdoor exposure ratio. In assuming that the exposure was the detection level, we are taking a conservative approach to population-level exposure while acknowledging that there may be some circumstances where people are exposed at above the level of detection.

The exposure values used in CAPEM2 were:

- Ambient annual average (urban areas): 8.6 ppb SO_2
- Ambient annual average (rural areas): 1.2 ppb SO_2
- Indoor exposure (24-h average): 1.2 ppb SO_2
- In-vehicle median: 4.6 ppb SO_2

For acute exposures, the maximum urban residential 24-h and 1-h averages from the NAPS 2011 sites were used (see Tables 5.1 and 5.2), and the maximum 10-min average from the Airpointer data given in Table 5.4 was used to model applied dose using the Chemicals Management Plan (CMP) exposure model. The CMP exposure model uses the physiological parameters outlined in Table 8.3. Several differences exist between the CMP and CAPEM2 models. The CAPEM2 model evaluates the first two age groups as "less than 1 year" and "1-4 years," whereas the CMP model breaks down the first two age groups as "0–0.5 years" and "0.5–4 years." Minor differences in body weight profiles for each age group are also present. The most prevalent difference between the models is the allocation of inhalation rates per age group, whereby CAPEM2 distinguishes between age groups and activity levels (L/min), and the CMP model simply gives a daily intake value (m^3/d). Additionally, the CMP model assumes the same ratio of time spent outdoors to time spent indoors for all age groups. The reason for these discrepancies lies in the intended use of the model: the CAPEM2 was intended for sophisticated chronic inhalation exposures for various Canadian subpopulations; conversely, the CMP model was intended to determine average daily exposure from all routes of exposure, including inhalation routes. Therefore, the CMP model does not employ a sophisticated inhalation breakdown when contrasted against the CAPEM2 model, but despite its advantages, the CAPEM2 model is not suited for acute exposure analyses. The CMP model was selected in lieu of other potential models because it has been validated as an appropriate model for acute exposures and will provide consistency between this assessment and assessments performed by other groups at Health Canada. The values used in the CMP model were:

- Ambient 24-h averaging time (urban–residential): 56 ppb SO_2
- Ambient 1-h averaging time (urban–residential) : 314 ppb SO_2
- Ambient 10-min averaging time (urban–industrial): 322 ppb SO_2
- Indoor exposure (24-h average): 1.2 ppb SO_2

8.2.1.1 Chronic Exposure Modelling (CAPEM2 model)

The maximum chronic exposure dose was calculated for children aged 5–11 (1.24 μg/kg-bw/d), and was based upon the annual average urban exposure value of 8.6 ppb. The highest rural exposure dose was calculated for children 1–4 years of age (0.80 μg/kg-bw/d), based upon the annual average urban exposure value of 1.2 ppb. For the purpose of comparison against reported body burdens of serum sulphite in humans, the adult (20-59 years) maximum value for each averaging time was used for analysis (Table 8.2).

Table 8.1: Exposure dose (μg/kg-bw/d) from chronic exposure analyses

	Intake (μg/kg-bw/d) by age (years)					
Outdoor air exposure	**<1**	**1–4**	**5–11**	**12–19**	**20–59**	**≥60**
Annual avg (urban NAPS stations)	0.31	0.91	1.24	0.41	0.32	0.31
Annual avg (rural NAPS stations)	0.31	0.80	0.62	0.30	0.27	0.25

Based upon the known serum sulphite concentration body burden (15.86 μg/kg-bw), and the assumption that 99% of the exposed SO_2 is metabolized to serum sulphite, the predicted increases in body burden of SO_2, as serum sulphite, are 2% and 1.7% for exposures measured as annual averages for urban or rural NAPS stations, respectively.

Table 8.2: Serum sulphite body burden increase following chronic inhalation

	Analysis for human adult (aged 20–59)			
Outdoor air exposure	**SO_2 intake (μg/kg-bw/day)**	**Serum sulphite (μg/kg-bw/day)**	**Adult body burden of serum sulphite (μg/kg-bw)**	**Increased serum sulphite (%)**
Annual avg (urban NAPS stations)	0.32	0.32	15.86	2.00
Annual avg (rural NAPS stations)	0.27	0.27	15.86	1.69

8.2.1.2 Acute Exposure Modelling

Application of the parameters outlined in Table 8.3 against the Canadian maximum values produced from analyses of acute time points (24-h average; 1-h average; 10-min average; indoor exposure), resulted in applied dose estimates for acute inhalation exposure to SO_2 (Table 8.4).

Table 8.3: Physiological parameters used in acute exposure modelling

		Age (years)					
Physiological	**Units**	**0–0.5**	**0.5–4**	**5–11**	**12–19**	**20–59**	**≥60**
Body weights	Kg-bw	7.5	15.5	31.0	59.4	70.9	72.0
Inhalation rates	M^3/d	2.1	9.3	14.5	15.8	16.2	14.3
Time spent outdoors	d	0.125	0.125	0.125	0.125	0.125	0.125
Time spent indoors	d	0.875	0.875	0.875	0.875	0.875	0.875

Taken from: Health Canada. 1998. Exposure factors for assessing total daily intake of Priority Substances by the general population of Canada. Unpublished report, December 1998. Ottawa (ON): Priority Substances Section, Environmental Health Directorate, Health Canada.

The maximum acute exposure daily dose was calculated for children 0.5–4 years of age, for all averaging times considered. The highest exposure doses were calculated for the 10-min averaging time frame, which was expected due to the 10-min average being associated with the highest exposure concentrations. Note that the 1-h and 10-min values represent overestimates for this model, as the model calculates a daily intake, assuming 3 h/d spent outside. For the purpose of comparison against reported body burdens of serum sulphite in humans, the adult (20-59 years) maximum value for each averaging time was used for analysis (Table 8.5).

Table 8.4: Daily intake (μg/kg-bw/d) from acute inhalation analyses

		Calculated daily intake by age group (μg/kg-bw/d)					
Outdoor air exposures	**Exposure medium**	**0–0.5 y**	**0.5–4 y**	**5–11 y**	**12–19 y**	**20–59 y**	**≥60 y**
Maximum 24-h average (56 ppb (147 μg/m^3)	Outdoor air	5.1	11.0	8.6	4.9	4.2	3.6
	Indoor air*	0.8	1.6	1.3	0.7	0.6	0.5
	Total	5.9	12.7	9.9	5.6	4.8	4.2
Maximum 1-h average (314 ppb (823 μg/m^3)	Outdoor air	28.8	61.7	48.1	27.4	23.5	20.4
	Indoor air*	0.8	1.6	1.3	0.7	0.6	0.5
	Total	29.6	63.4	49.4	28.1	24.1	21.0
Maximum 10-min average (322 ppb (844 μg/m^3)	Outdoor air	29.5	63.3	49.3	28.1	24.1	21.0
	Indoor air*	0.8	1.6	1.3	0.7	0.6	0.5
	Total	30.3	64.9	50.6	28.8	24.7	21.5

* assuming 1.2 ppb (3.14 μg/m^3) indoor exposure

Based upon the known mean serum sulphite concentration body burden (15.86 μg/kg-bw), and the assumption that 99% of the exposed SO_2 is metabolized to serum sulphite, the predicted increases in body burden of SO_2, as serum sulphite, are 30%, 150% and 154% for exposures measured as the maximum 24-h average, 1-h average, and 10-min average, respectively.

Table 8.5: Serum sulphite body burden increase following acute inhalation

	Analysis for human adult (20–59 years of age)			
Outdoor Air Exposure	**SO_2 intake * (μg/kg-bw/d)**	**Serum sulphite (μg/kg-bw/d)**	**Adult body burden serum sulphite (μg/kg-bw)**	**Increase in serum sulphite (%)**
Maximum 24-h average (56 ppb (147 μg/m^3))	4.8	4.8	15.9	30.0
Maximum 1-h average (314 ppb (823 μg/m^3))	24.1	23.9	15.9	150.4
Maximum 10-min average (322 ppb (844 μg/m^3))	24.7	24.5	15.9	154.2

* assuming 1.2 ppb indoor exposure concentration (all environments)

8.3 Relevance of the Modelled Applied Dose

The results obtained in Sections 8.2.1.1 and 8.2.1.2 above cannot be directly applied to any epidemiological or toxicological evaluation of the effects of SO_2; however, they are relevant to interpretation of the observed epidemiological effects. Indirect application of serum sulphite body burden information to the health literature allows consideration of the biological plausibility of the effects. A change to the body burden for a highly regulated molecule such as serum sulphite may be expected to have an effect on the body if it goes outside the normal range (0–32.68 μg/kg-bw; mean: 15.86 μg/kg-bw). From a toxicological perspective, it is anticipated that the effects would be adverse. Given the limitations to the dataset, it is impossible to determine whether the calculated applied dose of serum sulphite would result in body burdens outside the range in any one individual; however, from a population health perspective it could be assumed that this will occur, and that adverse effects would be manifested in the Canadian population with increased exposure. It should be noted that the applied dose modelling included a number of conservative assumptions that may result in an overestimate of the predicted applied doses.

For SO_2 the literature provides evidence for an adverse effect after ambient air exposures, so it is important to consider the models which show that ambient exposures to SO_2 result in higher than normal body burdens and to ascertain whether the systemic effects reported in the literature are plausible. Serum sulphite levels can, at this time, only be considered with respect to systemic effects of SO_2 exposure. Of the effects outlined in Section 7, the systemic acute effects to consider include some cardiac effects and *in utero* effects; both of these appear to be attributable to spikes in exposure rather than chronic exposures. Of note: most lung effects are due to direct action of SO_2 on the pulmonary nervous system and would not be well correlated to systemic effects of increased serum sulphite body burdens, so these effects cannot be justified for consideration using systemic exposure models.

In the case of chronic exposures, which based upon the available literature were arguably only relevant to pregnancy outcomes, the modelled SO_2 exposures from urban or rural environments result in exposure doses ranging from 0.27 to 1.24 μg serum sulphite/kg-bw/d. However, with *in utero* effects in mind, for the purpose of comparison against reported body burdens of serum sulphite in a 70 kg adult, the adult maximum value for each averaging time was used for analyses. Based upon the known average serum sulphite concentration body burden (15.86 μg/kg-bw), and the assumption that 99% of the inhaled SO_2 is metabolized to serum sulphite, the predicted increases in adult body burden serum sulphite were calculated to be 2% and 1.7% for exposures measured as annual averages for urban or rural NAPS stations, respectively.

The maximum acute SO_2 exposure dose, as serum sulphite was calculated for children 0.5–4 years of age, for all averaging times considered. The highest exposure doses were calculated for the 10-min averaging time frame, which was expected, due to the 10-min average being associated with the highest exposure concentrations. However, the only systemic effects associated with SO_2 exposure are related to effects in adults (*in utero* effects and cardiovascular effects). Thus, for the purpose of comparison against reported body burdens of serum sulphite in adults, the adult maximum value for each averaging time was used for analyses. Based upon the known serum sulphite concentration body burden (15.86 μg/kg-bw), and the assumption that 99% of the exposed SO_2 is metabolized to serum sulphite, the predicted increases in body burden of SO_2, as serum sulphite, are 30%, 150% and 154% for exposures measured as the 24-h average, 1-h average, and 10-min average, respectively.

Thus, there is moderate confidence that some effects reported in the literature could be attributed to systemic effects of SO_2 exposure, despite, in most cases, a weak signal compared against the same result for other pollutants. We can therefore explore the biological plausibility of various mechanisms or modes of action with greater confidence that these systemic effects are realistic based upon predicted increases to SO_2 body burdens.

9.0 Proposed Mechanisms and Modes of Action

Based upon the adverse health effects detailed in Section 7, the modelled increases in serum sulphite discussed in Section 8, and both animal toxicology and controlled human exposure data, several known and speculated pathways for the effects observed following SO_2 exposure are proposed below.

9.1 Respiratory Morbidity—Bronchoconstriction and Mucous Production

The most commonly described adverse endpoint following inhalation exposure to SO_2 is respiratory morbidity manifested as bronchoconstriction, which has been observed not only in the controlled human exposure literature, but also in the epidemiological literature. The bronchoconstrictive effect can be potentially explained by three mechanisms: effects to vagus nerve receptors, neurogenic inflammation, and effects to other receptors involved with bronchoconstriction. Of these, the vagus nerve responses are most well characterized; however, they do not fully explain the variation and degree of sensitivity to SO_2 exposure, which is why alternate hypotheses have been presented. Other morbidity endpoints presented in this section include increased mucous production and secretion.

9.1.1 Effects on the Vagus Nerve: C-Receptor Fibres, Acetylcholine, and Muscarinic Receptors

Bronchoconstriction following acute SO_2 exposure results from chemosensitive receptors (vagus nerve afferents; i.e. rapidly activating receptors and sensory C-fibre receptors) in the tracheobronchial tree being activated. In animal models, activation of these receptors stimulates central nervous system reflexes, including bronchoconstriction from smooth muscle contraction, mucous secretion, mucosal vasodilation, cough, and apnea followed by rapid shallow breathing. There are also effects on the cardiovascular system, such as bradycardia and hypotension or hypertension. In some cases, C-fibre activation is theorized to cause secretion of neuropeptides, resulting in neurogenic inflammation, a situation important in animal models of airway inflammatory disease. The relevance of neurogenic inflammation (see Section 9.1.2) to humans remains uncertain because of differences in respiratory tract innervation.

In humans, the mechanisms for SO_2-induced bronchoconstriction are less clear because of differences between asthmatic and non-asthmatic responses. Asthma is characterized by inflammation and airway hyperresponsiveness, which manifests as excessive bronchoconstriction to contractile stimuli (Barnes, 1996; Buels and Fryer, 2012). Mechanisms for asthma in humans are still being elucidated, but evidence since the 1950s has provided insight into the role of parasympathetic nerves, particularly post-ganglionic muscarinic receptors, in asthmatic pathology through vagally-mediated acetylcholine (ACh) release (Barnes, 1996; Buels and Fryer, 2012). There are five muscarinic receptors in humans, and of these, three (M_1, M_2 and M_3) are of importance to pulmonary physiology. Muscarinic M_2 receptors on postganglionic parasympathetic nerves block ACh release. This M_2 receptor

function is inhibited by M_1 receptors in ganglia, which increase ACh release by facilitating neurotransmission. Additionally, in airway smooth muscle, M_2 receptors supplement contraction mediated via M_3 receptors (Barnes, 1996; Buels and Fryer, 2012); therefore the balance between muscarinic receptor expression and activation is of importance. For example, excessive bronchoconstriction and increased mucus secretion in asthma are mediated, at least in part, by ACh released by the vagus nerves onto muscarinic M_3 receptors (Buels and Fryer, 2012).

Interestingly, the mechanism of bronchoconstriction following SO_2 exposure appears to differ between non-asthmatics and asthmatics under some circumstances. In non-asthmatics, bronchoconstriction occurs through cholinergic pathways and ACh release. In asthmatics, however, it appears that bronchoconstriction is the result of both parasympathetic (ACh-mediated) pathways and inflammatory or other pathways. Additionally, it has been reported that SO_2 triggers bronchospasm and also stimulates afferent receptors, leading to a reflex cholinergic bronchoconstriction (Barnes, 1996); consequently, therapeutic options differ between non-asthmatics and asthmatics experiencing bronchoconstriction following SO_2 exposure. In non-asthmatic humans, bronchoconstriction induced by SO_2 can be reduced with anticholinergic drugs. In asthmatics, bronchoconstriction following SO_2 exposure is only partially blocked by anticholinergic agents (Barnes, 1996), which indicates that other pathways may be involved, such as phenotypic differences in receptor expression (discussed below) or cholinergic exacerbation of inflammatory responses. It has been proposed that inflammation (see Section 9.2) contributes to enhanced SO_2 sensitivity in asthmatics because it alters autonomic responses, enhances mediator release, and/or sensitizes vagus nerve afferents.

9.1.2 Hypothesized Pathway: Neurogenic Inflammation

Neurogenic inflammation is a process whereby inflammatory mediators (biologically active peptides) are released from sensory nerves of the airways after irritation occurs, exacerbating the irritant response (Barnes, 1996; Groneberg et al., 2004; De Swert and Joos, 2006). Briefly, inflammatory mediators have been demonstrated to enhance cholinergic neurotransmission in the airways by facilitating ACh release at cholinergic nerve terminals (Groneberg et al., 2004). There is evidence for facilitated cholinergic neurotransmission in sensitized animals exposed to allergen (Barnes, 1996; Groneberg et al., 2004). This mechanism has been demonstrated to exacerbate asthma symptoms in several animal species, particularly rodents (Barnes, 2001; Groneberg et al., 2004). In the case of SO_2, neurogenic inflammation has been demonstrated in rodent species following irritation of vagus nerve C-fibres and transient receptor potential cation channel subfamily V, member 1 (TRPV1) channels in the lung (Barnes, 1992; Meggs, 1993; McLeod et al., 2007).

It has been hypothesized that SO_2 may induce airway bronchoconstriction in humans not only by direct stimulation of sensory respiratory nerve endings, but also by neurogenic processes involving biologically active peptides (e.g. tachykinin neuropeptides, calcitonin gene-related peptides) (Barnes, 1992; Meggs, 1993; Barnes, 1996; Groneberg et al., 2004; De Swert and Joos, 2006). The relevance of neurogenic inflammation to humans remains unclear due to species differences and difficulties in doing these studies in human volunteers (Barnes, 2001).

9.1.3 Hypothesized Pathway: Influence of Other Receptor Subtypes

Though this mechanism has not been considered to a large degree in the literature, it is possible that asthmatics may have phenotypic differences that are the result of differential nerve

receptor expression in the vagal ganglia (as evidenced by differences in response to common anti-cholinergic drugs after SO_2 exposure) (Barnes, 1996; Groneberg et al., 2004).

For example, a study in rabbits showed that exposure to SO_2 at concentrations of 200 ppm for 10 min blocked slowly adapting pulmonary stretch receptors (which left only rapidly adapting and C-fibre receptors active). This resulted in decreased respiratory drive (inappropriate drive to breathe, used as model of dyspnoea) in control rabbits but not in emphysematous rabbits (Dallak et al., 2007).

The literature has indicated that increased TRPA1 (transient receptor potential ankyrin 1) receptor or ASIC (acid sensitive ion channel) expression and/or activity on neurons may result in bronchoconstriction (i.e. an asthmatic response) by non-cholinergic mechanisms. Neurons with ASIC expression have been well characterized for their responses to acid stimuli (Kollarik et al., 2007; Chu et al., 2011). These extensive reviews provide information on how ASICs work. Briefly, ASICs are widely expressed in the nervous system, and play a role in peripheral sensory transduction of acidic stimuli by voltage-independent, cation-gated protein channels activated by elevated protons (lowered pH); specifically, nociception and mechanosensation (pain). There are seven known subunits (ASIC1a, 1b1, 1b2, 2a, 2b, 3, and 4), encoded by four genes, which confer distinct acid transduction properties related to pH thresholds and temporal sensitivity (short-term vs. long-term activation). All ASIC subtypes, with the exception of ASIC4, are expressed in peripheral sensory neurons and non-neuronal tissues like vascular smooth muscle cells. Depending on the subunit composition, and the presence of other channels gated or modulated by acids (e.g. multiple studies show co-expression of ASICS and TRPV1 on the same neuron terminal), ASICS may regulate the biological response to a particular threshold (to a particular change in pH) by calcium-dependent mechanisms. ASICs are the most likely candidate for non-cholinergic asthmatic responses to SO_2 exposure.

Alternatively, TRPA1 neuronal receptors are sensitive to activation by multiple irritant chemicals (including several sulphides and oxidizing agents), and have been shown to induce reactive bronchoconstriction and airway dysfunction syndrome, which is characterized by asthma-like symptoms in response to irritants and by chemical sensitivity (Bessac and Jordt, 2008, 2010). Interestingly, TRPA1 receptor activity is dependent upon covalent interactions between the agonist and receptor, a situation modulated by reduced glutathione (antioxidant) status. This covalent mechanism does not necessarily follow concentration–response kinetics, and Bessac and Jordt (2008) have postulated that this ". . . *may result in robust TRPA1-induced irritation even at low subacute exposure levels, for example during periods of increased photochemical smog exposures, or low level indoor air pollution. Once irreversibly [modified by covalent bonds], channels may remain active for extended periods of time even when the irritant stimulus is removed*." To a lesser degree, TRPV member 4 may play a role; it is known to cause sensory activation upon exposure to acid (Kollarik et al., 2007).

The importance of phenotypic changes in nerve receptors is likely to be related to their spatial expression (e.g. where they occur in the respiratory tract: esophageal area vs. laryngeal area vs. bronchopulmonary areas), and several recent animal studies (Kollarik et al., 2007; Chou et al., 2008) have ascertained that distinct types of sensory nerves and receptors are projected by the nodose and jugular neurons. Additionally, the interaction between co-receptors is likely to be an important factor, further contributing to the complexity of this area of study.

9.1.4 Mucous production

Tachykinins are biologically active peptides indicated in the process of neurogenic inflammation and bronchoconstriction. A discussion of tachykinin release and the potential effect to airway afferent nerve endings as part of neurogenic inflammation has been provided in Section 9.1.2; it supports the conclusion that SO_2 may result in increased tachykinin release into the airway, contributing to bronchoconstriction. Interestingly, evaluation of the role of tachykinins in mucosal secretion—another hallmark of asthma—has demonstrated that local tachykinin administration evoked mucosal secretion; specifically, in the lower tracheobronchial tree, seromucous glands and goblet cells produce mucus (De Swert and Joos, 2006). Substance-P has also been reported to be involved in submucosal secretion of liquid and mucous in excised porcine airways (Trout et al., 2001) and may play a role in SO_2-mediated mucous secretion. Alternatively, a study in rats found that exposures of up to 80 ppm SO_2 did not increase basal or acetylcholine-stimulated secretory activity (Wagner et al., 2006). These data support a potential association between SO_2 exposure and increased mucous production, though more information is required.

Increased mucous is also expected from the upregulation of the MUC5AC gene, an effect that has been reported in sensitized asthmatic rats (Li et al., 2007) and in human bronchial epithelial cells (Li and Meng, 2007) following SO_2 exposure.

9.2 Respiratory Morbidity—Inflammation and Apoptosis

As presented above, bronchoconstriction and respiratory symptoms are the most commonly observed adverse responses to SO_2 inhalation. This section will explore whether inflammatory and apoptotic mechanisms may explain changes to FVC and FEV_1 observed in epidemiological studies evaluating the effect of SO_2 on lung function parameters. The inflammatory pathways discussed are direct tissue inflammation and cell-mediated inflammation, with a third section outlining possible pro-inflammatory changes to the lung following exposure to SO_2.

9.2.1 Direct Tissue Inflammation

Inhalation of SO_2 may induce an inflammatory response in the lung because of heightened oxidative effects due to the formation of reactive oxygen species (ROS). In addition to direct oxidative effects, prolonged, elevated ROS concentrations in lung tissue may result in modulation of pro-inflammatory genes in both healthy and diseased individuals.

For example, under high exposure concentrations Kunming albino mice exposed to 8.40, 21.37 or 42.75 ppm (22, 56 or 112 mg/m^3) SO_2 for 6 h/d over 7 d experienced lipid peroxidation (measured as TBARS, which are formed as a byproduct of lipid peroxidation) and decreased antioxidant status in both their lung and heart tissues (Meng et al., 2003). Glutathione status was reduced in both the heart and lung tissues of both male and female mice. The TBARS measurements were statistically elevated at all exposure concentrations in both sexes and in both lung and heart tissues, indicating lipid peroxidation. Additionally, at the lower exposure concentration, activity of superoxide dismutase and glutathione peroxidase were significantly increased in the lung; conversely, these activity levels were significantly decreased at high concentration. Catalase activity was shown to be consistently decreased in the lung following

SO_2 exposure at all concentrations, but the decrease was only statistically significant for the lungs of male mice at 42.75 ppm SO_2 exposure (Meng et al., 2003).

As a whole, these results, as well as other laboratory analyses (Meng and Liu, 2007; Ergonul et al., 2007; Xie et al., 2007) indicate that SO_2 exposure can cause oxidative damage to the lungs and hearts of mice; however, the relevance of these adverse oxidative effects to humans under conditions of normal ambient exposure is unclear.

9.2.2 Cell-mediated Inflammation

Labbé et al. (1998) in earlier research showed that *in vitro* exposure of neutrophils to sodium sulphite (Na_2SO_3) induced superoxide production via neutrophil oxidative burst mechanisms. The response occurred within 5 min of exposure. The authors also reported that Na_2SO_3 induced gene expression in human neutrophils in a concentration-dependent matter by mRNA analysis, while it did not modulate neutrophil apoptosis nor reverse the effect of granulocyte-macrophage colony stimulating factor on apoptosis. The effects of SO_2 on neutrophilic oxidative bursts and reactive oxidative species reported by Labbé are supported by earlier evidence (Oda et al., 1989; Beck-Speier et al., 1994).

More recent research has supported these cellular observations. Cai et al. (2008) exposed female BALB/c mice to 50 ppm SO_2 through whole-body chamber exposure. Exposures lasted for 60 min on d 7, 9, and 11 of the experiment. The investigators reported a statistically significant seven-fold increase of BALF total leukocytes as compared to control. They reported that 78% of all leukocytes in BALF were neutrophils; there were also significantly increased eosinophil counts, although the differential ratio of eosinophils remained the same as in controls. In addition, mice exposed to SO_2 experienced a loss of cilia, epithelial sloughing, bronchial swelling and peribronchial infiltration of neutrophils. Sulphur dioxide exposure prior to challenge with OVA caused exaggerated BALF eosinophilia, and facilitated and enhanced subepithelial fibrosis with more significant elevation of BALF ET-1 and TGF-β1 levels as compared to pre-exposure concentrations (Cai et al., 2008).

McLeod et al. (2007) reported similar results, whereby the BAL neutrophil and eosinophils counts were 138.2 and 5.2 times greater in SO_2-exposed (1,000 ppm for 3 h/d for 4 d) Harley guinea pigs than in the control groups. The increased inflammatory cell counts and number of coughs were attenuated by treatment with the anti-inflammatory drug dexamethasone. There was a marked cellular extravasion surrounding the airways and goblet cell metaplasia, indicating inflammation. There was also evidence of neurogenic inflammation in the guinea pigs, which may explain the sensitivity of the nodose ganglia (specifically, TRPV1 receptors) to SO_2 exposure. Respiratory frequency and minute ventilation decreased and enhanced pause increased with SO_2 exposure, indicating bronchoconstriction, which was not inhibited by dexamethasone (McLeod et al., 2007).

The relevance of these effects to humans under conditions of normal ambient exposure is unclear.

9.2.3 Pro-Inflammatory and Apoptotic Gene/Protein Expression

The animal toxicology literature has presented findings on airway inflammation and apoptotic responses in the lung following exposure to SO_2. Non-asthmatic rats treated with higher levels (2.7, 5.3 and 10.7 ppm) of SO_2 had concentration-dependent increases in expression of pro-

inflammatory gene tumour necrosis factor-alpha (TNF-α), interleukin 1-beta (IL-1β), induced nitric oxide synthase (iNOS), and intracellular adhesion molecule-1 (ICAM-1) (Yun et al., 2011). Additionally, the influence of SO_2 on expression of cyclooxygenase-2 (COX-2; a pro-inflammatory enzyme) mRNA and protein was evaluated in male Wistar rats following exposures to 2 ppm SO_2 (1 h/d for a week) with or without allergic sensitization (Li et al., 2008). The authors reported that COX-2 mRNA levels in the SO_2- and OVA-treated groups were increased, but not significantly different than, the negative control group. Exposure to OVA and SO_2 in conjunction resulted in statistically significant increases of COX-2 mRNA and protein expression in the lungs and trachea of rats, compared against OVA-positive controls. Therefore the asthmatic phenotype, characterized by OVA exposure, resulted in greater sensitivity to SO_2 exposure as well as in greater and statistically significant increases in both COX-2 mRNA and protein levels measured.

With respect to genes involved with cellular regulation and apoptosis, the results of the three major studies are summarized in Table 9.1.

Table 9.1: Changes to pro- and anti-apoptotic genes or proteins in rats

	Change		Type	Exposure	Species	Notes	Reference
	Gene	**Protein**					
c-myc	↑1.6 fold	↑1.8 fold	Proto-oncogene	20 ppm	Rat	Significant increases/ decreases	Qin and Meng, 2010
Ki-ras	↑2.2 fold	↑2.7 fold					
p53	↑1.4 fold	↑1.7 fold	Tumour suppressor				
p16	↓0.67 fold	↓0.59 fold					
Rb	↓0.61 fold	↓0.86 fold					
Bax	↓	↓	Pro-apoptotic	2 ppm	Rat	Not significantly different compared to negative controls	Xie et al., 2009
P53	↓	↓					
Bcl-2	↑	↑	Anti-apoptotic				
bax	↓0.25 fold		Pro-apoptotic		OVA-challenged rat	OVA positive controls showed similar changes.	
P53	↓0.25 fold						
Bcl-2	↑2 fold	↑>2 fold	Anti-apoptotic				
Caspase-3	↑>2 fold	↑	Apoptosis and necrosis, inflammation	>5 ppm	Rat	Only significant at concentrations >10 ppm; protein increased after 1 week exposure; enzyme activity increased	Bai and Meng, 2010
Caspase-8	↑>2 fold	↑	Mitochondrial death	>21 ppm		Protein increase after 1 week exposure; enzyme activity increased	
Caspase-9	↑1.69 fold	↑		>5 ppm			
	↑2.65 fold			>10 ppm			
	↑4.38 fold			>21 ppm			

Qin and Meng (2010) reported that male rats exposed to 20 ppm SO_2 (6 h/d for 7 d) had significantly increased mRNA and protein expression levels of proto-oncogenes c-myc and Ki-

ras, as well as increased tumour suppressor gene p53. They also reported reduced expression levels of tumour suppressor genes p16 and Rb. The relevance of these changes is unclear at this time, given that both proto-oncogene and tumour suppressor gene and protein expression are increased.

Evaluation of apoptotic events following lower SO_2 exposures (2.7, 5.3 and 10.7 ppm) in male Wistar rats showed a concentration-dependent increase in the ratio of bax/bcl-2, indicating a shift to pro-apoptotic conditions. This observation was supported by another study reporting that higher levels of exposure (10 and 20 ppm) also induce apoptosis (Bai and Meng, 2005). At lower concentrations (2 ppm), an anti-apoptotic environment was reported with increased anti-apoptotic and decreased pro-apoptotic mRNA and protein expression (Xie et al., 2009). This observation was non-significant when compared against negative controls, indicating that at low concentration normal cellular (anti-apoptotic) environments are maintained. In the same study, the lung tissue of rats challenged with OVA, as a model of asthma, had significantly elevated anti-apoptotic mRNA and protein expression and decreases in pro-apoptotic mRNA expression after 2 ppm SO_2 exposures, as compared to negative controls. However, the positive controls (rats exposed to OVA only) showed similar changes to mRNA expression as those observed in the rats challenged by OVA and SO_2, but to lesser degree. Because of this it is impossible to rule out the possibility that the apoptotic response using the mouse model of asthma was due to allergic sensitization from OVA exposure, and not to the SO_2 exposure alone. Accordingly, the Xie et al. (2009) paper provides no evidence of an effect of SO_2 on the lung with respect to apoptotic responses.

Evidence of a concentration-dependent switch from an anti-apoptotic cell environment to a pro-apoptotic cell environment is, however, provided by a study evaluating upregulation of expression and activity of caspase proteases (Bai and Meng, 2010). Caspases are cysteine-dependent aspartate-directed proteases involved with cellular apoptosis, necrosis and inflammation; Caspase-8 and caspase-9 are involved in death-receptor and mitochondrial death pathways, respectively. Male Wistar rats exposed to 5.34, 10.69, or 21.37 ppm SO_2 for 6 h/d for 7 d showed increased caspase-3 mRNA levels; the increase, just greater than two-fold, was significant at the two higher concentrations. Caspase-8 mRNA expression was significantly increased only at 21.37 ppm, but strong concentration-dependent increases in caspase-9 mRNA levels were observed. A related increase in caspase-3, -8, and -9 protein expression was observed 1 week after SO_2 inhalation exposures. All concentrations of SO_2 caused increases in caspase-3, -8, and -9 enzyme activity, but significance was reached only at 10.69 and 21.37 ppm. Higher levels of apoptotic cells were observed 1 week after inhalation exposures, with significant results at the two highest concentrations (1.28% at 10.69 ppm and 3.64% at 21.37 ppm). A few monocytes, neutrophils, and eosinophils were observed, and congestion and inflammation occurred (Bai and Meng, 2010). Overall, this study indicates that caspases, especially caspase-9, may be responsive to SO_2 exposures and regulate a concentration-dependent change from a normal cell environment to a pro-apoptotic cell environment.

In studies evaluating other endpoints, OVA-challenged asthmatic rats exposed to 2 ppm SO_2 showed increased expression of ICAM-1 (modulation of inflammation) gene in the bronchi and concurrent upregulation of MUC5AC gene expression, which is expected to result in increased mucous production (Li et al., 2007). Under similar exposure parameters, sensitized asthmatic rats showed elevated expression of endothelial growth factor and its receptor, as well as

increased COX-2 levels in the lungs and trachea, when compared against positive controls (Li et al., 2008).

The relevance of these effects to humans under conditions of normal ambient exposure is unclear.

9.3 Reproductive and Developmental Effects

The epidemiology literature described in Section 7.7.2.3 has provided some evidence that SO_2 exposures during *in utero* development, may be linked to potential effects on preterm birth and congenital heart defects. The mechanism by which these endpoints could occur is unknown, however, it could be theorized that the oxidative effects of SO_2 may affect the placenta, as the end term placenta is susceptible to inflammatory signals that may regulate the timing of parturition (Cella et al., 2010; Li et al., 2011; Mittal et al., 2011; Voltolini et al., 2012). It could also be theorized that oxidative effects could affect the progression of neural crest cell migration and differentiation through interference with gene expression (i.e.. Homeobox or Pax3 genes) (Meng and Liu, 2007; Ergonul et al., 2007; Xie et al., 2007; Kirby and Waldo, 1995; Tümpel et al., 2002; Hobbs et al., 2005; Pani et al., 2002; Horal et al., 2004; Li et al., 2005; Roest et al., 2007; Chappell Jr. et al., 2009). These type of effects have been linked to several different major air pollutants and to some sources, and further research is needed to determine the exact nature of the effects, the implications for ongoing health, and most importantly the causative chain linking a particular pollutant(s) to the endpoints in question.

9.4 Susceptible and Vulnerable Populations

The use of the terms “susceptible population” and “vulnerable population” is varied across studies. In most cases “susceptibility” refers to biological or intrinsic factors affecting the individual response to chemical exposure (e.g. life stage, sex, genetics, pre-existing disease/conditions) while “vulnerability” refers to non-biological or extrinsic factors that influence a human being’s response to chemical exposure (e.g. SES, proximity to an emission source) (US EPA., 2012).

Populations vulnerable to SO_2 exposure include those likely to have higher exposures (e.g. those who live or work near emission sources, live in cold, dry environments, and have high levels of outdoor physical activity) and those with lower SES. Seasonal and spatial influences affect individual vulnerability to SO_2 exposures; as reported earlier, seasonal variation has been observed for ambient concentrations of SO_2, whereby the mean ambient concentrations were higher in winter than in other seasons (Campbell et al., 2005; Wheeler et al., 2008; Brown et al., 2009), likely due to decreased rates of atmospheric aqueous-phase oxidation.

Several subpopulations of humans have been identified as being susceptible to the effects of SO_2 following exposure to ambient concentrations. Identification of these populations is based upon the epidemiology literature, and where possible, the mechanisms by which these populations are rendered more sensitive to the effects of SO_2 have been identified.

9.4.1 Asthmatics

The literature has indicated that asthmatics are a subpopulation susceptible to adverse effects following SO_2 exposures. In Canada, asthma affects about 3 million people, representing 8.9%

of the population; of these, 60% do not have control of their disease (Statistics Canada, 2011; ASC, 2012).

As discussed in Sections 7.3.1.1, 7.3.2.1.2 and Section 9.1.3, respiratory effects experienced by asthmatics following SO_2 exposure appear to be more severe than among non-asthmatics, and they also appear to be mediated by a different mechanism than in non-asthmatics (Horstman et al., 1986; Linn et al., 1990; Gong Jr. et al., 1995; Barnes, 1996; Groneberg et al., 2004). Bronchoconstriction in asthmatics is the result of both parasympathetic pathways and inflammatory mediators. Specifically, it has been proposed that inflammation contributes to enhanced SO_2 sensitivity in asthmatics because it alters autonomic responses, enhances mediator release, and/or sensitizes vagus nerve afferents. These potential multiple pathways for asthma exacerbations mean that asthmatics experiencing adverse effects following SO_2 exposures may not be able to control their symptoms using normal medications.

There is also some epidemiologic evidence that asthmatic children are more sensitive to exacerbation of their asthma symptoms following SO_2 exposure (Boezen et al., 1999, 2005; v, 2000; Jalaludin et al., 2008). Though the observations from epidemiology of asthma incidence and ED visits are variable, it appears that a trend toward increased hospital admissions of children for asthma symptoms related to SO_2 exposures is associated with time spent outdoors (Samoli et al., 2011).

9.4.2 Humans in Utero

Recent epidemiology papers (Section 7.7) have indicated that there could be a correlation between SO_2 and various congenital anomalies to the heart and the incidence of cleft lip. Particularly, the literature indicates that the sensitive developmental period is the second month of gestation (more specifically, weeks 3–8). Several studies have indicated increased risk of aortic coartication and tetralogy of Fallot. Additional evidence of risks to the human embryo under situations of continuous exposure, for each increase in SO_2 concentration of 1 ppb has been found. Specifically, the risk of atrial septal defects increased when examining high vs. low exposure situations; the risk of ventricular septal defects increased with continuous exposures; the risk of coartication of the aorta increased with both continuous exposure and high vs. low exposure; the risk of tetralogy of Fallot increased under situations of continuous exposure (Dolk et al., 2010; Vrijheid et al., 2011). Though the literature is not well established at this time, there appears to be consistency in the risk of developing these congenital defects, and in some cases a concentration–response relationship has been postulated.

The incidence of cleft lip, with or without presentation of cleft palate (i.e. including cleft palate data), showed a weak positive association with SO_2 exposure, including a statistically significant elevated risk at the highest quartile of exposure (Marshall et al., 2010) .

All these effects could be attributed to disruption of neural crest migration (specifically, the cranial neural crest and the cardiac neural crest) during embryonic development (Gilbert, 2003). Speculative mechanistic explanations for these effects are provided in Section 9.3.

9.4.3 People with Reduced/Impaired Sense of Smell

People working in industries known to release high levels of SO_2, such as smelters, fossil-fuelled power plants, upstream oil and gas facilities, petroleum refineries, pulp and paper mills, and various transportation industries, experience higher levels of exposure. In addition to higher

levels of exposure, workers in these facilities sometimes experience impairment of olfactory function. These people might not react behaviourally to the smell of SO_2 in the same manner as those without an olfactory deficit (Doty et al., 1984) and thus be exposed to more SO_2. As discussed below with the elderly, people with an impaired or reduced sense of smell may still respond biologically to SO_2 despite being unable to detect the odour.

9.4.4 The Elderly

The ability to detect odour has been shown to decrease with age; therefore, seniors might not react to the smell of SO_2 in the same behavioural manner as those without an olfactory deficit (Doty et al., 1984) and thus be exposed to more SO_2. Older people may still respond biologically to SO_2 despite being unable to detect the odour.

Additionally, the elderly have decreased SOX activity (Constantin et al., 1996). In this study the investigators noted that the intensity of S-centered radical adducts increased and that the radical observed was primarily $^{\bullet}SO_3^{2-}$. This means the elderly may be more susceptible to oxidative damage following exposure to SO_2 than the general population due to decreased SOX activity.

Several epidemiology studies have provided results to indicate that the elderly may be more susceptible to death following exposure to air pollution than other age groups (see Section 7.5).

9.4.5 Children

Children and infants may be more susceptible to the effects of SO_2 because the lung continues to develop postnatally and into adolescence. The developing lung has been shown to be highly susceptible to damage. Additionally, children may have increased exposures because they generally spend more time outdoors, are highly active and have high minute ventilation.

There is some evidence from epidemiology studies that the risks of ED vists or hospitalizations for respiratory causes or asthma may be higher in children. There is no evidence from controlled human exposure studies that respiratory effects in adolescents are more severe than those observed in adults (US EPA, 2008).

10.0 Sulphur Dioxide as a Cause of Adverse Human Health Effects

An integrated discussion of the material presented from earlier sections of this document is presented below. The objectives of the discussion are to identify trends or causal relationships between ambient exposures to SO_2 and to determine whether adverse effects can be expected in the Canadian population. Upon atmospheric release, SO_2 gas is rapidly oxidized to SO_3 and H_2SO_4 and its anion, SO_4^{2-}. It may remain in the gaseous state, as SO_2 or one of its derivatives; it may nucleate to form particles; or it may form acid aerosols. For the purposes of this assessment, only gaseous SO_2 was considered.

To evaluate the weight of evidence, it is necessary to examine scientific evidence from all disciplines (toxicology, controlled human exposure evaluations, epidemiology, etc.) and to assess the collective evidence using established criteria for causal determination. These considerations include:

- the *strength* of the associations, including the magnitude and precision of the risk estimates and their statistical significance;
- the *robustness* of the associations to model specifications and adjustment for potential confounders such as weather, temporal trends, and co-occurring pollutants;
- the *consistency* of reported associations across studies and study designs conducted by different researchers in different locations and times;
- the *biological plausibility* of the associations in light of what is known about the effects of this chemical, referencing data from experimental studies or other sources demonstrating plausible biological mechanisms; and
- the *coherence* of the relationship between exposure to the chemical and related endpoints within and across animal toxicology, controlled human exposure, and various types of epidemiological studies.

These considerations, as well as others associated with the Bradford Hill criteria, are used to conclude whether the association of the chemical with a given health effect or a related set of health effects is causal, likely to be causal, suggestive of a causal relationship, or inadequate to conclude that the relationship is causal. The definition for each of these causal determinations is identical to the US EPA determinations, which are described in Table 10.1 below:

Table 10.1: US EPA weight of evidence for causal determination

Relationship	Description
Causal relationship	Evidence is sufficient to conclude that there is a causal relationship between relevant pollutant exposures and the health outcome. That is, a positive association has been observed between the pollutant and the outcome in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. Evidence includes, for example, controlled human exposure studies; or observational studies that cannot be explained by plausible alternatives or are supported by other lines of evidence (e.g. animal studies or mechanism of action information). Evidence includes replicated and consistent high-quality studies by multiple investigators.
Likely to be a causal relationship	Evidence is sufficient to conclude that a causal relationship is likely to exist between relevant pollutant exposures and the health outcome but important uncertainties remain. That is, a positive association has been observed between the pollutant and the outcome in studies in which chance and bias can be ruled out with reasonable confidence but potential issues remain. For example: a) observationsal studies show positive associations but copollutant exposures are difficult to address and/or other lines of evidence (controlled human exposure, animal or mechanism of action information) are limited or inconsistent, or b) animal evidence from multiple studies, sex, or species is positive but limited or no human data are available. Evidence generally includes replicated and high-quality studies by multiple investigators.
Suggestive of a causal relationship	Evidence is suggestive of a causal relationship between relevant pollutant exposures and the health outcome, but is limited because chance, bias and confounding cannot be ruled out. For example, at least one high-quality study shows a positive association but the results of other studies are inconsistent.
Inadequate to infer a causal relationship	Evidence is inadequate to determine that a causal relationship exists between relevant pollutant exposures and the health outcome. The available studies are of insufficient quantitiy, quality, consistency or statistical power to permit a conclusion regarding the presence or absence of an association between relevant pollutant exposure and the outcome.
Suggestive of no causal relationship	Evidence is suggestive of no causal relationship between relevant pollutant exposures and the health outcome. Several adequate studies, covering the full range of levels of exposure that human beings are known to encounter and considering sensitive subpopulations, are mutually consistent in not showing a positive association between exposure and the outcome at any level of exposure. The possibility of a very small elevation in risk at the levels of exposure studied can never be excluded.

Reference: (US EPA, 2008, p. 1-11)

If a causal relationship, a likely causal relationship, or a suggestive causal relationship is determined for an adverse health endpoint, the endpoint will be evaluated in the risk assessment portion of this document (Section 11.0).

10.1 Exposure and Dose in Canadians

Inhaled SO_2 is very water soluble. It is rapidly solubilized in the upper respiratory tract and can then be absorbed across nasal mucosa and the mucosal cells of the trachea. Once absorbed across mucosal cells, SO_2 is hydrolyzed to SO_3^{2-} and $^{\bullet}SO_3^{2-}$, with equilibrium products of HSO_3^- and H^+, which are taken up by the blood and distributed throughout the body. Sulphite oxidase oxidizes SO_3^{2-} to SO_4^{2-}, which is the major excretory form of sulphur in urine. The estimated reported half-life for SO_3^{2-} in humans is 15 min. The primary route of elimination has been identified as urinary excretion, mostly as SO_4^{2-}.

10.1.1 Environmental Exposure

Data from NAPS stations for the year 2011 (see Tables 5.1, 5.2, 5.3) indicated a pattern of generally low ambient air SO_2 concentrations with intermittent short peaks, as reflected by the much higher levels observed with the shorter averaging times. Urban areas had consistently higher levels of SO_2 than rural areas. Residential urban areas were considered the most relevant for the majority of the population and generally had the highest levels, although industrial areas were, as expected, slightly higher in some cases.

Additional supporting information generated by ambient Airpointer monitors improves upon NAPS data because the monitors are more sensitive for SO_2 analysis, providing a minute-by-minute analysis that captures short-term emission increases and the variability of SO_2 better than the integrated monitors, which average concentration over a given time frame (e.g. 1-h averaging time). These data also indicate that SO_2 levels are typically measured very close to the limit of detection, but that there are short-lived spikes in concentration. The frequency and intensity of the concentration spikes are related to the source of the SO_2 emissions and vary by location. The emission pattern shown in these data supports the assumption that acute exposures over chronic time frames are the best exposure parameter to model in Canadians.

Environmental data indicate that Canadians are being exposed to SO_2 at concentrations that may result in adverse health effects. This evidence also supports the assumption that acute exposures (or acute spikes in chronic exposure time frames) are the best exposure parameter to consider in Canadians.

For chronic exposures, the maximum annual average SO_2 concentration from the NAPS 2011 sites was 8.6 ppb for urban areas. For acute exposures, the maximum residential urban 24-h average concentration from the NAPS 2011 sites was 56 ppb and the maximum residential urban 1-h average was 314 ppb. The Airpointer data reported a maximum 10-min average of 322 ppb SO_2 from a site with a nearby industry. Note that the 10-min average is from a limited sample (three cities), and may not represent the full range of potential 10-min averages in Canada.

10.2 Health Effects from SO_2 Exposure in Canadians

10.2.1 Effects of Activity Level on Irritation from SO_2 Exposure

Irritant effects of SO_2 to the upper airway and the eye have been reported in healthy volunteers at exposure levels of 1 ppm and higher in combination with exercise. Increased activity level was also associated with adverse respiratory endpoints in asthmatics. Physiological data support the assertion that exercise exacerbates the irritant effects of SO_2 due to increased ventilation parameters, increased perfusion and greater exposure to the gas than occurs with individuals at rest. The exposure concentration at which irritation occurs appears to be greater than the Canadian maximum percentile ambient exposure concentration (8.6 ppb); therefore, irritation may not be a critical endpoint for threshold development. There is no evidence of irritation at ambient exposure concentrations in Canada.

10.2.2 Odour as a Health Endpoint

The published odour threshold for SO_2 was reported in Section 7.1 to be 0.5 ppm. The data do not support using the SO_2 odour threshold as a regulatory health endpoint because the threshold is greater than the most sensitive health effect endpoints.

10.2.3 Respiratory Morbidity—Short-term Exposure

There are several clinical biomarkers used to evaluate SO_2-mediated effects to the respiratory system: $FEV_{1,}$ PEFR, and sRaw. Forced expiratory volume, as FEV_1, is a measure of the volume of air that can be forcibly exhaled in one second, after full inspiration. It is the most reported criterion for AHR in humans. When a large reduction of FEV_1 occurs upon exposure to a chemical, it can be concluded that the chemical impairs normal bronchial ventilation through bronchoconstriction. Similarly, PEFR is a measure of an individual's maximum speed of expiration, measuring air flow through the bronchi using a flow meter; reductions in PEFR usually indicate constriction of the bronchi. Finally, sRaw is a passive plethsymographic method for determining airway resistance, by measuring the pressure change to airflow during tidal breathing (Bisgaard and Nielsen, 2005). It essentially reflects the overall dimensions of the airway.

There is considerable interindividual variability in baseline measures for these biomarkers, which must be carefully considered because this variability could lead to large percentage changes in biomarker measures, independent of SO_2 exposures.

Additionally, there is substantial interindividual variability in the responsiveness of these biomarkers to SO_2. For example, changes to FEV_1 and sRaw are highly variable within individuals, particularly at low SO_2 concentrations (van Thriel et al., 2010; Johns and Linn, 2011). In fact, even within the susceptible subpopulation of asthmatics, some asthmatics experienced adverse respiratory effects accompanied by respiratory symptoms at concentrations <0.4 ppm SO_2, while others exhibited no apparent response at concentrations approaching or exceeding 1.0 ppm (Johns and Linn, 2011). From the Canadian perspective, one observation by the US EPA (2008) is of importance. The agency reported that the majority of controlled human exposure studies have been conducted at 20–25°C and 70–85% relative humidity, and that there is some evidence of the respiratory effects of SO_2 being exacerbated when exposure occurs in cold or dry ambient conditions (Linn et al., 1983; Bethel et al., 1984). Cold and dry ambient conditions are typical of Canadian winters, and thus seasonal sensitivity should be accounted for in this analysis. Additionally, some of the literature evaluated assessed

the effect of temperature on the results of SO_2 exposure. It is important to note, whenever possible, the definition of a “cold” or “warm” day or month, as this varies considerably across the world. For example, a cold day in Taiwan is routinely described as less than 23 or 24°C. In Canada, that would be described as a warm day, given that a cool day is potentially defined at less than 15°C, and temperatures in winter can fall well below -20°C. By keeping these differences in mind, it is possible to accurately apply thermal or temporal data to an assessment of Canadian susceptibility.

10.2.3.1 Airway Inflammation, Oxidative Damage, and Cellular Apoptosis

The US EPA (2008) reported that at the time of its publication, there was insufficient evidence to conclude that exposure to SO_2 at ambient concentrations was associated with airway inflammation. Toxicological studies in guinea pigs, however, indicated that repeated exposures to SO_2, at concentrations as low as 0.1 ppm, may exacerbate inflammatory responses in allergic (sensitized) animals (Riedel et al., 1988; Park et al., 2001).

The literature published since the US EPA 2008 document indicated that under experimental conditions with high SO_2 exposure levels, direct oxidative effects resulting in elevated lipid peroxidation of lung tissue (Meng et al., 2003; Ergonul et al., 2007; Xie et al., 2007) cause inflammatory damage to rodent lung tissues (Meng et al., 2003). As a whole, these results, as well as other laboratory analyses (Meng and Liu, 2007; Ergonul et al., 2007; Xie et al., 2007) indicate that SO_2 exposure can cause oxidative damage to the lungs of mice, with prolonged exposure; however, since these effects were observed at higher exposure concentrations it is unclear whether these adverse oxidative effects would occur under conditions of normal ambient exposure.

Cell-mediated inflammation, particularly by activated neutrophils, may play a part in the inflammation described as occurring in lung tissue following SO_2 exposures under experimental conditions in both healthy and diseased laboratory animals. *In vitro* analyses of neutrophil responses have shown that exposure of neutrophils to Na_2SO_3 induced superoxide production via oxidative burst mechanisms in a concentration-dependent manner (Beck-Speier et al., 1994; Labbé et al., 1998). These effects were direct effects on the neutrophil, and not the result of modified neutrophil life span via inhibition of apoptosis (Labbé et al., 1998). *In vivo* analyses of BALF following SO_2 exposures to rodents supported the observation of cell-mediated inflammatory responses, with increased neutrophil counts (McLeod et al., 2007; Cai et al., 2008; Bai and Meng, 2010), and increased BALF ET-1 and TGF-β1 levels as compared to pre-exposure concentrations (these results were stronger under conditions of SO_2 exposure prior to challenge with OVA). A toxicological evaluation of airway inflammation in OVA-sensitized mice exposed to 50 ppb SO_2 was able to demonstrate airway epithelial injury resulting from neutrophilic inflammation after exposures lasting just 1 h/d over a period of 3 d (Cai et al., 2008). The authors also reported that SO_2 enhanced chronic allergic airway inflammation and promoted the development of subepithelial fibrosis, perhaps due to upregulation of ET-1 and TGF-β1, which are both known to have profibrotic activity (Cai et al., 2008). Similarly to the other inflammatory outcomes, the literature shows that upregulation of pro-inflammatory genes (TNF-α, IL-1β, iNOS, ICAM-1) occurs in both healthy (Xie et al., 2009; Yun et al., 2011) and diseased (Li et al., 2008; Xie et al., 2009) animals exposed to high levels of SO_2. These effects, observed in an exposure range higher than typical ambient levels, have largely been demonstrated to be concentration-dependent.

In a group of 16 humans, it was observed that exposures to up to 2 ppm SO_2 resulted in no associations between SO_2 and markers of airway inflammation, including FeNO (Raulf-Heimsoth et al., 2010). The only recent analysis (Liu et al., 2009b) evaluating the effect of SO_2 exposure on markers of oxidative stress and airway inflammation in children reported conflicting results for oxidative stress (increased TBARS, but no association with 8-isoprostane) and no association between SO_2 and FeNO and IL-6, using a 3-d averaging time (median SO_2 concentration: 5.6 ppb). Alternately, Moon et al. (2009) showed that in industrialized and highly populated cities, the incidence of upper respiratory symptoms (e.g. runny nose, sneezing) and the occurrence of ocular irritation and itching skin increased in primary school children at low concentrations, ranging from 2.17 to 5.80 ppb SO_2.

Analysis of apoptotic responses showed significantly increased mRNA and protein expression levels of c-myc, Ki-ras, and p53, as well as reduced expression levels of p16 and Rb at high concentration (20 ppm) exposures (Qin and Meng, 2010). The authors elected to evaluate c-myc and Ki-ras because they are known to have proto-oncogene activity; they studied p53, p16 and Rb because of their role as tumour suppressor genes. Exposures to up to 11 ppm SO_2 produced a concentration-dependent increase in the ratio of bax/bcl-2, indicating a shift to pro-apoptotic conditions as oxidative capacity was exceeded. This observation was supported by another study reporting that higher levels of exposure also induce apoptosis (Bai and Meng, 2005). At lower concentrations (2 ppm), an anti-apoptotic environment was reported with increased anti-apoptotic (bcl-2) and decreased pro-apoptotic (p53 and bax) mRNA and protein expression (Xie et al., 2009); this observation was non-significant when compared against negative controls, indicating that at low concentration normal cellular (anti-apoptotic) environments are maintained. Similarly, the lung tissue of rats challenged with OVA, as a disease model of asthma, had significantly elevated anti-apoptotic mRNA and protein expression and decreases in pro-apoptotic mRNA expression as compared to negative controls (Xie et al., 2009). Of note, the positive controls (rats exposed to OVA only) were also significantly elevated as compared to the negative controls (Xie et al., 2009), so it is impossible to rule out that the response was due to allergic sensitization from OVA exposure and not to the SO_2 exposure. Taken together, these results are equivocal, and there appears to be no evidence of SO_2 promoting apoptosis or influencing oncogene expression when these particular genes were evaluated.

However, evidence of a concentration-dependent switch from an anti-apoptotic cell environment to a pro-apoptotic cell environment is provided by a study evaluating upregulation of expression and activity of caspase proteases (Bai and Meng, 2010). Caspases are cysteine-dependent aspartate-directed proteases involved with cellular apoptosis, necrosis and inflammation. In particular, caspase-9 appeared to play a role in a concentration-dependent switch from normal cellular environments to pro-apoptotic environments. Higher levels of apoptotic cells were observed 1 week after inhalation exposures, with significant results at the two highest concentrations (Bai and Meng, 2010).

In studies evaluating other endpoints, OVA-challenged asthmatic rats exposed to 2 ppm SO_2 had increased expression of the ICAM-1 (modulation of inflammation) gene in the bronchi and concurrent upregulation of MUC5AC gene expression, which is expected to result in increased mucous production (Li et al., 2007). Under similar exposure parameters, sensitized asthmatic rats showed elevated expression of endothelial growth factor and its receptor, as well as

increased COX-2 levels in the lungs and trachea, when compared against positive controls (Li et al., 2008).

It is important to note that, with the exception of the controlled human exposure study, the exposures evaluated in the human epidemiology studies were at ambient concentrations orders of magnitude lower than the animal toxicology studies reported above. Consequently, the weight of evidence does not support a causal relationship between *ambient* SO_2 concentrations and severe inflammation or apoptosis in the airway of healthy or diseased humans, because exposure levels for which these responses occur are orders of magnitude above the ambient exposure concentration being considered in this assessment. Biological plausibility is not well demonstrated. The evidence is ***inadequate to infer a causal relationship*** between ambient SO_2 exposure and neutrophilic inflammation or oxidative burst in humans.

10.2.3.2 Lung Function Measurements and Hospitalization in Adults

The US EPA (2008) concluded that there is a causal relationship between respiratory morbidity in adults and short-term exposure to SO_2. The strongest evidence for this causal relationship came from controlled human exposure studies reporting respiratory symptoms and decreased lung function following peak exposures to SO_2 of 5–10 min duration. These effects have been observed consistently across studies involving asthmatics exercising at mild to moderate intensity (Sheppard et al., 1981; Bethel et al., 1985; Linn et al., 1987, 1988, 1990). Statistically significant decreases in lung function in asthmatics with increased ventilation rates, accompanied by respiratory symptoms (e.g. wheeze and chest tightness) were clearly demonstrated following exposure to 0.4–0.6 ppm SO_2. Some studies have also reported moderate to large decrements in respiratory endpoints of asthmatic subjects (5–30%) at exposures of 0.2–0.3 ppm SO_2, and though these results did not reach statistical significance, they do indicate a broader and lower range of effect.

The US EPA (2008) also found that in the asthmatic subpopulation, mainly represented by otherwise healthy asthmatics, both the magnitude of decrements in lung function and the percentage of individuals affected were consistently related to increased SO_2 exposure at concentrations between 0.2 and 1.0 ppm (Linn et al., 1983, 1984, 1987, 1988, 1990; Bethel et al., 1985; Gong Jr. et al., 1995; Trenga et al., 1999). Interestingly, the severity of individual asthma was not a predictor of individual sensitivity to SO_2. As such, information about sensitivity to the general asthmatic population cannot necessarily be extrapolated to the most sensitive asthmatics in the population.

Since the 2008 document, several epidemiological studies evaluating the effect of acute exposure to SO_2 in adults have been published, with animal studies evaluating similar endpoints. The results from these analyses show effects at lower exposure concentrations. In a study on healthy adult subjects, Steinvil et al. (2009) reported a statistically significant negative correlation between SO_2 at 2.8 ppb and FEV_1 or FVC (lag 3 d to lag 6 d). They found that SO_2 was the most potent air pollutant affecting short-term lung function parameters when compared against $PM_{10,}$ CO, NO_2 and O_3. Similar, but not statistically significant, results were presented by Son et al. (2010), who reported a significant negative association between SO_2 and FVC but not with FEV_1 at 8.6 ppb average exposure concentration. Additionally, controlled human exposure studies have consistently observed decrements in lung function (FEV_1, sRaw) at SO_2 exposure levels ranging from 0.2 to 1.0 ppm (van Thriel et al., 2010; Johns and Linn, 2011). Unfortunately, it is difficult to get a clear concentration–response curve for these data because

of high levels of variability within and among individuals (when exposed, and during baseline measurements), particularly at the lower SO_2 exposure concentrations.

In controlled human exposure studies, asthmatics exposed to SO_2 at concentrations greater than 0.4 ppm (for 5–10 min, at increased ventilation) showed lung function decrements and symptoms of asthma compared to lower exposure concentrations under the same conditions (Johns and Linn, 2011). The same data showed that at the lower concentrations (down to 0.2 ppm in chamber studies and 0.1 ppm with mouthpiece exposures), the onset of lung function decrements or asthma symptoms was isolated, indicating interindividual differences among asthmatics. The authors postulated that these differences were due to genetic polymorphisms that render some asthmatics more sensitive to SO_2 than others. An additional hypothesis, based upon the discussion in Section 9.1.3, is that the asthmatics sensitive to SO_2 exposure may have different vagal nociceptor phenotypes when compared against the general population or non-sensitive asthmatics. Further reanalysis of several controlled human exposure papers, using multi-level GLM, provided evidence of increased bronchoconstriction among asthmatics following exposures to 0.3 ppm SO_2 (Johns and Linn, 2011). Epidemiological evidence for effects of SO_2 on PEFR supports a positive relationship between SO_2 (daily mean = 1.73 ppb) and PEFR at lags 4 and 6 d, and changes to daily average PEFR at lag 4 d for asthmatics aged 13–78 (Wiwatanadate and Liwsrisakun, 2011). A weak correlation was found between SO_2 and co-pollutants $PM_{2.5}$, PM_{10}, CO, NO_2, and O_3. Using a single-pollutant model, the same authors reported that SO_2 at lag 5 d showed a weak, but statistically significant, positive association with nighttime asthma symptoms. Similarly, Canova et al. (2010) reported that increases in SO_2 exposure, as 4 ppb increments with a mean 24-h average of 1.36 ppb, were associated with a trend toward decrements in evening PEFR. The results became significant when a two-pollutant model was used for CO and SO_2. A separate cohort study was able to show that the risk of asthma increased by 4% after exposure to 39.8 ppb SO_2 (24-h average, lag 1 d) (Feo Brito et al., 2007). No relationship to asthma incidence was reported for individuals exposed to 2.4 ppb (24-h average) under the same study.

In 2008, the US EPA (2008) reported that studies of asthma ED visits and hospitalizations showed a small, positive association with ambient SO_2 concentrations. More recently, a Canadian study found no associations between ED visits for asthma and increases in SO_2 concentration of 5.1 ppb at lags 0, 1 or 2 d (Stieb et al., 2009). Similar results were reported in a Japanese study under mean SO_2 concentrations (24-h average) of 5.3 ppb (Abe et al., 2009). Interestingly, two studies evaluating the effect of SES, air pollution and asthmatic medical visits showed that asthmatics with lower SES were more likely to visit the doctor upon exposure to increases in SO_2 concentration (7 ppb in a Canadian study, 3.3 ppb in a Korean study (lag 3 d)) (Kim et al., 2007; Burra et al., 2009). Given that adverse effects are reported in the controlled human exposure study and epidemiology datasets after longer lag periods, it is possible that effects due to SES would be more pronounced after lag 4 d and improvements in study design would result in a clearer interpretation of the data.

Findings for effects of SO_2 exposure on COPD hospitalizations were equivocal. Two epidemiology studies reported findings in support of an association between SO_2 and ED visits or hospitalizations for COPD. In the first, a 2.20% increase in ED visits for chronic bronchitis, emphysema and other COPDs was reported per 4 ppb increase in SO_2 exposure (Migliaretti et al., 2007). The second study reported that exposure increases of 0.38 ppb (1 $\mu g/m^3$) resulted in significant increases in ED visits for chronic bronchitis after 1-d and 7-d lags (Leitte et al., 2009).

Three other studies reported no effects (Stieb et al., 2009; Milutinović et al., 2009; Peacock et al., 2011).

The US EPA (2008), after examination of several studies, found small, positive associations between ambient SO_2 concentrations and hospitalization and ED visits for all respiratory diseases, particularly among older adults (≥65 years). More recently, an Italian study reported a positive relationship between ED visits and SO_2 at concentrations of 1.3 ppb in warm seasons (not in other seasons) with a slight OR increase of 1.068 per 3.82 ppb SO_2 increment (Tramuto et al., 2011). Similarly, in India (Jayaraman, 2008), hospital admissions for respiratory diseases rose with a 1.082 increase in RR per 3.82 ppb increment in SO_2; however, the statistical significance of this effect was lost after controlling for co-pollutants CO, NO_2, O_3, SPM and RSPM. Influenza appears to not play a large role in hospitalization for respiratory disease (influenza was only shown to influence hospitalization for COPD) in a study evaluating hospital admissions per 3.82 ppb increase in average concentration of SO_2 (6.8 ppb) at lag 0–1 d (Wong et al., 2010a). Conversely, a study from China (Leitte et al., 2011) reported only non-significant associations between SO_2 concentration (lag 0 d and lag 5 d) and total respiratory ED visits for each IQR increase of 38.2 ppb. No associations were reported between SO_2 exposures and hospitalizations for severe brocholiolitis caused by RSV (Segala et al., 2008), respiratory disease (Chen et al., 2010) and pneumonia (Cheng et al., 2007; Chiu et al., 2009) in the more recent literature.

Issues related to interpretation of the epidemiology literature exist. First, it remains difficult to determine the role of confounding co-pollutants such as $PM_{2.5}$ and PM_{10} on the effects being reported; second, it remains difficult to unequivocally relate the 24-h average SO_2 concentrations typically assessed in epidemiologic studies with the peak exposures in the controlled human exposure studies (US EPA, 2008). To address these issues it is important to consider the controlled human exposure study data in conjunction with the epidemiology literature. Controlled human exposure studies support epidemiological observations, showing that SO_2 concentrations of 0.3–0.4 ppm result in lung function decrements and symptoms of asthma after relatively short time frames (e.g. lags 3 to 6 d). The epidemiology literature supports the role of SO_2 in exacerbating existing disease conditions, with environmental increases over background concentrations affecting PEFR and influencing ED visits; therefore the health benefits of even modest reductions in ambient SO_2 concentration can be inferred, and have been suggested in recent literature (Hedley et al., 2002).

As a whole, the data contained within the US EPA's 2008 document and the literature since 2008 provide evidence of ***a causal relationship*** between exposure to SO_2 and respiratory morbidity in adults, especially in relation to impairment of lung function. The observation that asthmatics may be a susceptible subpopulation, reacting to lower concentrations of SO_2, remains valid.

10.2.3.3 Lung Function Measurements and Hospitalization in Children

In 2008, the US EPA (2008) wrote that the epidemiological evidence, overall, was insufficient to conclude that short-term exposure to ambient SO_2 has an independent effect on lung function in the subpopulation of children. Numerous epidemiologic studies had observed associations between short-term (≥1 h, generally 24-h average) exposure to SO_2 and respiratory health effects in children. The associations between ambient SO_2 concentrations and several respiratory outcomes were generally consistent, with the large majority of studies showing

positive associations. At the time, however, causality could not be determined for an independent effect of SO_2 on lung function in children (as a susceptible subpopulation) (US EPA, 2008), primarily due to analytical limitations related to co-pollutants.

Many recent epidemiologic studies have examined the association between ambient SO_2 concentration and lung function parameters in asthmatic children. One recent paper provided evidence of significant diurnal exposure time frames and FEV_1 measurements (Dales et al., 2009). Specifically, an association with decreased FEV_1 and daytime SO_2 concentrations (mean 24-h average = 6 ppb) was observed in young Canadians aged 9–14; however, no correlations between evening or morning FEV_1 measurements were established. There were reported increases in the ORs of chest tightness for days with higher concentrations of SO_2 (≥8.8 ppb). The investigators found that SO_2 was weakly correlated to all co-pollutants evaluated ($PM_{2.5}$, O_3, and NO_2) (Dales et al., 2009). An alternate analysis of the same data reported that IQR range increases in 3-d average SO_2 concentrations (5.4 ppb) were associated with decreases in $FEF_{25–75\%}$ of FVC measurements (Liu et al., 2009b). A similar study examining asthmatic children from the ICAS found that SO_2 exposure (90th percentile, 5-d average = ~12 ppb) (lag 0–4 d) was associated with significantly lower FEV_1 and PEFR compared with concentrations at the 10th percentile, but it did not have an effect on asthma symptoms or school absence (O'Connor et al., 2008). A meta-analysis from China evaluated FEV_1, FVC and MMEF against ambient pollutants (Liu and Zhang, 2009). Measured concentrations of SO_2 ranged from 13 to 350 ppb. Significant decreases in FVC and FEV_1 were reported as SO_2 concentrations increased, particularly in the low concentration ranges. No significant correlation between SO_2 concentration and MMEF was observed. Similarly, a panel study of children aged 4–11 found that SO_2 exposures (lag 4 d) decreased evening PEFR but increased daily average PEFR, though there was no association with morning PEFR (Wiwatanadate and Trakultivakorn, 2010). The association remained even after adjusting for the co-pollutant O_3 (SO_2 was weakly associated with all co-pollutants ($PM_{2.5}$, PM_{10}, CO, O_3, NO_2). The lag time reported in these studies shows that acute exposures to SO_2 are of most concern for changes to lung function measurements, specifically FEV_1 and FVC, and that the adverse effects appear to be concentration-dependent at low concentration ranges.

Inconsistent results have been reported in studies examining the effects of SO_2 to children's ED visits. In asthmatics, an association has been made between IQR SO_2 concentration increments of 5 ppb and annual percentage increases in asthma admissions (Samoli et al., 2011). The reported mean SO_2 concentration was 6.4 ppb, and the effects were most severe in the spring; these effects was not significant after controlling for PM_{10}, indicating that PM_{10} is an important confounding factor. Similar non-significance was noted in an Italian study (mean SO_2 concentration 3.6 ppb) (Bedeschi et al., 2007). In contrast, an Australian study (Jalaludin et al., 2008) observed increased ED visits for asthmatic children aged 1–14 only at lag 0–1 d, and a Taiwanese study (Yeh et al., 2011) showed that seasonal changes to asthma hospitalizations following SO_2 exposures were greater in preschool- and primary-school-age children, but that seasonal variations had no effect on admission rates for adolescents. The US EPA (2008), after examination of several studies, found small, positive associations between ambient SO_2 concentrations and hospitalizations and ED visits for all respiratory diseases, particularly among children. More recently, Mansourian et al. (2011) reported that SO_2 was associated with a statistically significant increase in the number of respiratory hospital admissions at concentrations of 0.059 ppb; however, significantly high correlations with PM_{10} and CO were reported and multi-pollutant models were not assessed, so it is difficult to determine whether the

results were due to SO_2 alone. An Australian study (Lam, 2007) reported no significant observations for respiratory endpoints and ED visits upon exposure to 0.35 ppm in children younger than 6 years of age; however, an Iranian study (Mansourian et al., 2011) showed that respiratory hospital admissions increased upon exposure to a mean 24-h average SO_2 concentration of 0.059 ppb. In the case of the Iranian study PM_{10} and CO showed higher correlations, though multi-pollutant models were not assessed.

Issues related to interpretation of the epidemiology literature, as outlined in Section 10.2.3.2, persist. First, it remains difficult to determine the role of confounding co-pollutants such as $PM_{2.5}$ and PM_{10} on the effects being reported; second, it remains difficult to unequivocally relate the 24-h average SO_2 concentrations typically assessed in epidemiologic studies to the peak exposures in the controlled human exposure studies (US EPA, 2008). No controlled human exposure data are available to facilitate interpretation of the epidemiological data. Contrary to the literature with adult subjects, the epidemiology literature does not currently support the role of SO_2 in exacerbating existing disease conditions or influencing ED visits for children independent of other known air pollutants, though it is likely that the SO_2 pollution fraction is a contributor. The epidemiology literature does identify lung function changes, the most sensitive endpoint being FEV_1, after exposures to SO_2 at concentrations as low as 6 ppb. Seasonal influences and activity patterns do, however, appear to have an important role in the manifestation of adverse effects to children following environmental exposures to ambient SO_2 concentrations.

The epidemiology data is ***suggestive of a causal relationship*** between exposure to SO_2 and respiratory morbidity in children. Consistently positive associations continue to be reported between incremental increases in SO_2 concentration as low as 5.4 ppb and morbidity (as decreased FEV_1 and FVC). The observed associations are, for the most part, robust enough to be maintained after adjustment for co-pollutants; however, they are impacted by study characteristics such as spatial distribution patterns, as well as seasonal/diurnal trends and activity patterns.

The literature suggests that SO_2 may increase asthma-related ED visits or hospitalizations, but issues with confounding factors and co-pollutants such as PM_{10} have not been well characterized. It appears that time spent outdoors, related to springtime activity patterns, influences seasonal trends in ED visits and hospitalizations for asthma.

10.2.4 Respiratory Morbidity—Chronic Exposure

A major consideration in evaluating SO_2-related health effects in long-term epidemiologic studies is the high correlation among the pollutant levels observed, particularly between long-term averages for SO_2 and PM. The lack of evidence available to the evaluation of (potential) confounding by co-pollutants restricted the ability of the US EPA (2008) to make a causal determination based on these studies; it concluded that the available evidence from the epidemiologic and animal toxicological studies was inadequate to infer that respiratory effects occur from long-term exposure to SO_2 at ambient concentrations.

More recently, the ISAAC, working with annual mean SO_2 concentrations of 4.8 ppb in 2002, found significant associations between SO_2 and prevalence of recent, severe asthma; nocturnal dry cough, rhinitis, and rhinoconjunctivitis (Arnedo-Pena et al., 2009). A separate epidemiology survey found that exposure to 4 ppb increases in SO_2 (annual medians ranged from 1.5 to 3.6 ppb) resulted in reduction of mean FEV_1 (Forbes et al., 2009a). These findings were not

supported by numerous other studies. A Canadian evaluation of asthmatic children in the ISAAC cohort (Sahsuvaroglu et al., 2009) reported no significant associations between chronic exposures to SO_2 and asthma symptoms. Similarly, a Taiwanese study (Hwang and Lee, 2010) in children aged 12–14 found no association between SO_2 concentrations (3-year mean 4.3 ppb) and brochitic symptoms in both asthmatic and non-asthmatic children. Furthermore, the NHIS study showed that SO_2 concentrations of 3.9 ppb (annual mean) were not associated with respiratory allergy or hay fever in children (Parker et al., 2009).

A Canadian study examining elderly patients (>65 years) reported that SO_2 was not associated with hospitalizations for pneumonia (Neupane et al., 2010). And a British study, examining individuals with PiZZ genotype (α-1-antitrypsin deficiency) found that SO_2 increases of 0.4 ppb (mean SO_2 per year decline = 1.6 ppb) were not associated with mean changes in FEV_1 or in gas transfer coefficient (Wood et al., 2010). A Japanese study (Shima, 2007) reported higher serum CRP and wheeze upon exposure to SO_2 ranging from 4.3 to 6.3 ppb (annual mean), but no association with asthma symptoms; however, these results appear to have been confounded by a NO_2 signal.

The human and animal data on respiratory morbidity from chronic exposures to SO_2 since the US EPA report remain unconvincing of any association. The recent, very limited, epidemiologic data show no consistent associations between long-term exposure to SO_2 and lung function, respiratory symptoms for asthma, or allergy. Two studies reported an association between SO_2 exposure and asthma symptoms or FEV_1, respectively. Another one showed an association between SO_2 exposure and CRP, but reported high correlations between SO_2 and co-pollutants. All the other studies reviewed reported no clear associations between chronic SO_2 exposures and respiratory morbidity.

The limited number of epidemiological studies, the equivocal nature of results related to chronic exposures, and the lack of animal toxicity studies for long-term SO_2 exposures render the weight of evidence ***inadequate to infer a causal relationship*** between respiratory morbidity and long-term exposure to SO_2 at ambient concentrations.

10.2.5 Cardiovascular Effects—Short-term Exposure

The US EPA (2008) determined that despite some positive findings, evidence from controlled human exposure and epidemiologic studies of HRV in healthy individuals, as well as those with asthma or CVD, was inconsistent. Plausible modes of action (e.g. vagally mediated irritant responses and oxidative injury) that might explain short-term SO_2 effects on the cardiovascular system were summarized in the EPA document. Consideration of these modes of action in light of findings from additional animal toxicological, controlled human exposure and epidemiologic studies led to the conclusion that the evidence as a whole is inadequate to infer a causal relationship. The inconsistency of the evidence, the lack of coherence across and within disciplines, as well as the limitations inherent to the observational epidemiology (e.g. inadequate control of co-pollutant exposures) contributed to their earlier decision.

The limited recent epidemiology literature has not advanced the science greatly, except that the trend in the literature is now toward SO_2 having a mild effect on measures of cardiovascular morbidity. Specifically, investigators observed a 5.26% decrease in pulse wave velocity with a 1.91 ppb increase in SO_2 exposure (Lenters et al., 2010)) and a weak correlation with changes to blood pressure at exposures of 5.1 ppb (Choi et al., 2007) and with changes to pulse at an

IQR increase of 3 ppb in SO_2 exposure (Goldberg et al., 2008). Other results, such as the effects of SO_2 on stroke and blood vessel diseases, were less clear. One Canadian study showed increased RR of stroke in adults aged 20–64 (10.3%) for an IQR increase of 2.3 ppb SO_2 (Szyszkowicz, 2008); however, an Asian study (Wong et al., 2010a) did not find a significant association with stroke for each 3.82 ppb increase in SO_2 concentration. Wong et al. (2010a) did report a 1.25% excess risk of heart disease in those ≥65 years for each 3.82 ppb increase in SO_2. Dales et al. (2010) found a significant association between the RRs of venous thrombosis and pulmonary embolism for each 5.85 ppb increase in SO_2 concentration; however, the RRs were decreased to near parity in multi-pollutant analyses. The authors reported that those ≥64 years had higher RRs for adverse effects than those younger than 64.

Two studies showed increased risk of cardiovascular ED visits/hospitalization following exposure to SO_2. Ito et al. (2011) reported an approximately 1.2% excess risk for hospitalization for CVD at lag 0 d with each IQR increase of 6 ppb SO_2; and Guo et al., (2009) observed a weakly increased OR of 1.013 for ED visits related to CVD in a multi-pollutant analyses with NO_2. A multi-city study of ED visits for cardiac conditions (angina, MI, heart failure, dysrhythmia/conduction disturbance) found a positive association between SO_2 and incidence of angina and MI, and a negative association with cardiac arrhythmia (Stieb et al., 2009). One study identified an increased risk of hospital admission due to CVD associated with SO_2; however, results became non-significant in multi-pollutant analysis (Chen et al., 2010). Other studies did not find associations between SO_2 and CHF (Yang, 2008), ED visits for cardiac arrhythmias (Santos et al., 2008), transmural infarctions (Rich et al., 2010), hospital admissions for MI (Hsieh et al., 2010), hospital admissions for cardiac arrest (Silverman et al., 2010), hospital admissions for IHD or cerebrovascular disease (Bell et al., 2008a) or out-of-hospital cardiac arrest (Dennekamp et al., 2010). Where mortality from CVD was reported, the mortality estimates were related to short lag periods (lag 0, 1 d) and appeared to be concentration-dependent.

No significant associations, especially after adjustment for co-pollutants, were found between SO_2 and biomarkers of inflammation and coagulation, such as IL-6, CRP, soluble ICAM-1, lipoprotein-associated phospholipase A_2, plasma total homocysteine, fibrinogen, and von Willebrand Factor (Peters et al., 2007; Rückerl et al., 2007; Baccarelli et al., 2007; Hildebrandt et al., 2009; Steinvil et al., 2009; Thompson et al., 2010; Brüske et al., 2011). No causal associations have been made between SO_2 exposures and inflammatory markers of CVD.

Issues remain in terms of interpretation of the epidemiology literature. It continues to be difficult to determine the role of confounding co-pollutants such as $PM_{2.5}$ and PM_{10} on the effects being reported; in addition, unequivocally relating the 24-h average SO_2 concentrations typically assessed in epidemiologic studies with the peak exposures in the controlled human exposure studies (US EPA, 2008) remains difficult to achieve. No controlled human exposure study data are available to facilitate interpretation of the epidemiological data. Based upon the equivocal nature of results for other cardiovascular endpoints, the epidemiology data is ***inadequate to infer a causal relationship*** between short term exposure to SO_2 and cardiovascular effects. Consistently positive associations continue to be reported between incremental increases in SO_2 concentration as low as 1.91 ppb and decreased HRV in adults; however, there is not enough information to infer causality.

10.2.6 Cardiovascular Effects—Chronic Exposure

The US EPA (2008) did not draw any conclusions on the effect of long-term exposure to SO_2 and cardiovascular health, due to limited data.

The two studies published from 2008 to 2011, which evaluated chronic exposures to SO_2 and cardiovascular events, did not provide any insights into the subject, due to the equivocal nature of the results. No conclusions can be made at this time due to lack of coherence within the information available combined with an overall insufficiency of data.

10.2.7 Mortality—Short-term Exposure

The US EPA (2008) concluded that epidemiologic evidence about the effect of short-term exposure to SO_2 on non-accidental all-cause mortality and cardiopulmonary mortality is suggestive of a causal relationship at ambient concentrations. Consistently positive associations were reported between SO_2 and mortality in the epidemiologic literature; however, the observed associations were not robust enough to be maintained after adjustment for co-pollutants.

Several epidemiology papers have been published from 2007 to 2011 evaluating the association between SO_2 and mortality. All the papers presented are time-series epidemiology studies, with the exception of two meta-analyses. This section will focus on the endpoints of all-cause mortality, respiratory mortality and cardiovascular mortality, specifically; if other significant mortality endpoints were identified in the papers, they will be identified for information purposes. Two European studies reported no significant effects of SO_2 concentration on mortality estimates (Neuberger et al., 2007; Stanković et al., 2007); however, many other studies showed effects.

One American study (Ito et al., 2011) presented data showing no excess risk of cardiovascular mortality following IQR increases of 6 ppb SO_2 for any season. Conversely, one Asian study evaluating seasonal differences in all-cause mortality and cardiovascular mortality found that mortality estimates were increased in winter when the 75th percentile exposure was compared against the 25th percentile exposure (Liang et al., 2009). The reported mean 24-h average concentration of SO_2 was 1.84 ppb in winter, and no significant increases in risk were reported for other seasons. Additionally, these researchers observed that respiratory and cardiovascular mortality estimates in an elderly subset (aged ≥65) trended toward increased risk in both multi-pollutant and single-pollutant models in the winter. The conflicting nature of these results may reflect differences in housing standards in Asian vs. North American countries. For the purposes of this report, the North American standards will be given more weight because they better reflect exposure parameters to Canadians. With respect to the North American results, the risk estimates were not affected by measured SO_2 concentrations stratified by season.

One Australian study showed major increases in all-cause mortality of up to 22.3% for each 1 ppb increment in SO_2 at lag 0 d, with a 12.1% increase in all-cause mortality when the mean daily concentration of SO_2 exceeded 3.15 ppb (Hu et al., 2008). Similarly, a Latin-American study (Cakmak et al., 2011) evaluating all-cause mortality found an increased risk of 1.089 per IQR increment of SO_2; IQR concentrations were presented for each city, and ranged from 5.76 to 10.4 ppb. Results stratified by age showed increased risk as the population ages, with the difference in risk estimate between those aged <64 and those ≥85 being statistically significant. Perhaps the most interesting study was by Kowalska et al. (2008), who performed an analysis of differences in risk estimates for an area of Poland that had experienced decreases in SO_2

concentration over time. Increases in all-cause mortality and cardiorespiratory mortality were found for each 1 ppb SO_2 increment, but RR estimates reported for this study illustrated that the estimates were lower for the more recent time frame—likely due to decreased ambient SO_2 concentrations. This indicates that reductions to ambient concentrations (as 24-h averages) over the years (from 21.76 ppb to 13.44 ppb) resulted in measured health benefits to mortality outcomes, even when considered against spikes in air concentration.

Several Asian studies based upon the PAPA cohort evaluated endpoints for all-cause, respiratory and cardiovascular mortality. The results were interesting; they demonstrated that SO_2 mortality effect estimates may be highly spatially specific and that associations may be distorted when the analysis is performed over large spatially distinct areas. For the PAPA analyses, the reported 24-h average SO_2 concentrations ranged from 5.04 to 16.79 ppb, and the co-pollutants PM_{10}, NO_2 and O_3 were assessed. The two meta-analyses (Wong et al., 2010b; Kan et al., 2010) showed that the combined random effects risk estimates found no significant associations for mortality endpoints using results from five cities; analyses specific to each city yielded different results. For example, city-specific analyses for Shanghai, China, and Taipei, Taiwan, found that a 3.82 ppb increase in SO_2 was not significantly associated with all-cause, cardiovascular and respiratory mortality outcomes (Kan et al., 2008, 2010). A separate city-specific analysis for Wuhan, China, found significant increases in mortality from all-cause, cardiovascular, and respiratory endpoints following 3.82 ppb SO_2 increments (lag 0–1 d) (Qian et al., 2010). In multi-pollutant models, estimated effects were stronger for SO_2 alone than when co-pollutants were evaluated, which indicated that some confounding was occurring. Further PAPA evaluation (Vichit-Vadakan et al., 2010) reported a significant percentage increase in excess risk for respiratory mortality in children <1 year (50.2%) per an IQR (2.10 ppb) increase in SO_2 concentration. It was unclear whether these results were representative across the PAPA cohort.

A study using the PAPA data, but not officially part of the PAPA report, evaluated the risk of all-cause, cardiovascular or respiratory mortality on populations in Hong Kong, Shanghai, and Wuhan, China; and Bangkok, Thailand (Wong et al., 2008b). The researchers reported a significant excess risk that ranged from 0.87% to 1.61% for all-cause mortality, from 1.28% to 2.11% for respiratory mortality, and from 0.91% to 1.47% for cardiovascular mortality with each 3.82-ppb increase in average SO_2 concentration (at lag 0–1 d). The reported 24-h averages ranged from 5.04 to 14.96 ppb and the co-pollutants PM_{10}, NO_2 and O_3 were evaluated.

Other Asian analyses support the PAPA results (Wong et al., 2008a; Ou et al., 2008; Liang et al., 2009), reporting significant increases in relative risk of mortality for some endpoints using single-pollutant regression models. Two studies evaluated the risk of increased mortality with a 3.82 ppb rise in SO_2 concentration in those with lower SES (Wong et al., 2008a; Ou et al., 2008). They both reported significant associations between SO_2 and all-cause and cardiovascular mortality in that subpopulation.

Taken together, the Asian data indicate that effect estimates may be spatially specific and that associations may be distorted when the analysis is performed over large spatially distinct areas. The analysis of each city separately, rather than providing pooled estimates, results in statistically significant increases in mortality outcomes. When the data were pooled, as in the PAPA meta-analyses, the combined random effects risk estimates found no significant associations for mortality endpoints. Contrasted against city-specific analyses of the same data,

this implies that data from spatially restricted analyses may carry greater weight than those encapsulating multiple, spatially distinct, areas. This spatial effect differs from what has been observed for other air pollutants, but could be attributed to the source-specific nature of SO_2 release, coupled with the rapid environmental reactions that change SO_2 from a gas to a particle. Alternatively, the lack of association observed in the multi-city analyses may reflect limitations in the analysis (e.g. differences in monitor locations and availability and quality of information about potential effect modifiers).

The more recent evidence for links between SO_2 and lung cancer mortality is equivocal. It appears that the incidence of lung cancer mortality may be elevated following chronic exposures to SO_2 at higher environmental concentrations (e.g. >19 ppb); however, this observation has only been made in Asian countries (Katanoda et al., 2011; Cao et al., 2011), and no association has been made between SO_2 and initiation of lung cancer. The European cohort studies (Beelen et al., 2008a, 2008b) showed no increase in lung cancer mortality for each 7.63 ppb increment in SO_2 concentration. In studies where the risk of lung cancer mortality was reported to increase, the risk levels reported were a 4.2% increase (Chinese) or a hazard ratio of 1.26 (Japanese) per 3.82 ppb increase in SO_2 (Katanoda et al., 2011; Cao et al., 2011). The most pressing concern with the Chinese study (Cao et al., 2011) was that it did not adjust for the most common confounding pollutant, $PM_{2.5}$. Because of this omission in the analysis, it is difficult to determine the relevance of the results. In the Japanese study, PM was addressed as a co-pollutant; however, the $PM_{2.5}$ concentration was estimated rather than directly measured. The estimate was derived by applying a SPM-to-$PM_{2.5}$ ratio of 0.7 to the SPM data (Katanoda et al., 2011). Additional concern surrounding the relevance of the $PM_{2.5}$ adjustment relates to differences in SPM analysis between sites, and the limited data on the composition of the SPM over time. Thus it is unclear whether the SPM-to-$PM_{2.5}$ ratio presents an accurate representation of the $PM_{2.5}$ concentration, and interpretation of these results is difficult, especially given the very high hazard ratio (which is unsupported by other analyses using stronger epidemiological techniques).

Results from multi-city studies suggest that the mortality effect estimates for cardiovascular and respiratory causes were generally larger than that for all-cause mortality, although in some cases the effects were not statistically significant. The US EPA (2008) stated that the lack of statistical significance could be due to reduced statistical power in examining cause-specific associations. In these studies, the effect estimates for respiratory mortality were suggestive of a stronger association of SO_2 with respiratory mortality than with cardiovascular mortality. This finding is consistent with the observed greater effects of SO_2 on respiratory morbidity than on cardiovascular morbidity. Multi-city study results also suggested that SO_2-mortality excess risk estimates may be confounded to some extent by co-pollutants, making it difficult to definitively ascribe effects to SO_2 alone.

The mortality effect estimates were not as stable across multi-pollutant models, and this instability in effect estimates from multi-city studies suggests confounding between SO_2 and PM and/or NO_2. The interpretation of multi-pollutant model results requires caution, therefore, because of confounding of results by co-pollutants and the influence of variations in measurement error. Very limited information was available to determine possible interaction effects between SO_2 and PM or other co-pollutants.

As a whole, the epidemiology data continue to provide evidence of the effect of short-term exposure to SO_2 on all-cause mortality and cardiopulmonary mortality. Positive associations

continue to be reported between incremental increases in SO_2 concentration as low as 1 ppb and mortality. Additionally, the health benefits of even modest reductions in ambient SO_2 concentration have been illustrated (Kowalska et al., 2008). The observed associations are, for the most part, robust enough to be maintained after adjustment for co-pollutants; however, they are impacted by study characteristics such as spatial distribution patterns and seasonal trends. As such, the epidemiology data is strongly ***suggestive of a causal relationship*** between short term SO_2 exposure and all-cause and cardiopulmonary mortality at ambient concentrations.

10.2.8 Mortality—Chronic Exposure

The US EPA (2008) concluded that the available epidemiologic evidence on the effect of long-term exposure to SO_2 on mortality is inadequate to infer a causal relationship at this time. As with earlier assessments, an association can be made between long-term exposure to SO_2 and mortality, but there were concerns about whether the observed association was due to SO_2 alone.

Five cohort studies evaluating the effect of SO_2 exposure over chronic time frames were identified. Results of a spatial analysis for the ACS cohort indicated weak, but statistically significant, associations (with adjusted hazard ratios) between 5 ppb incremental changes in SO_2 concentration and all-cause mortality (1.02), cardiopulmonary mortality (1.02), and IHD (1.04) (Krewski et al., 2009). Unfortunately, the mean air concentration of SO_2 used for this analysis was 9.71 ppb, based upon 1980 levels, so it was difficult to determine whether these effects remain representative of the Canadian population.

Associations between SO_2 exposure and cardiorespiratory mortality were evaluated for residents of Brisbane, Australia. For a reported ambient SO_2 concentration of 5.4 ppb, the RR of cardiorespiratory mortality associated with a 1 ppb increment in annual average concentration of SO_2 was 1.047 in both the single-pollutant and multi-pollutant models (Wang et al., 2009). Analysis based upon the China National Hypertension Follow-up Survey showed strong increases in percentage risk of cardiovascular (3.2%), respiratory (3.2%), or all-cause mortality (1.8%) associated with a 3.82 ppb increment in SO_2 in the adjusted model (Cao et al., 2011). The associations of SO_2 with these mortality indices did not change appreciably after adding the co-pollutants TSP or NO_X into the models.

A retrospective cohort study of people aged 35–103 found no associations between SO_2 and cerebrovascular or cardiovascular mortality (Zhang et al., 2011). The study was based in Shenyang, China, a heavily industrialized city, with a reported mean annual level of SO_2 of 24.05 ppb (range: 9.92–40.46 ppb). The authors did, however, indicate that any SO_2 effects may have been masked by high pollutant concentrations of NO_2 and PM_{10}. However, a similar result was presented by Katanoda et al. (2011), who reported a non-statistically significant increased incidence of mortality for COPD and SO_2 exposure.

The equivocal results described above for measures of mortality associated with long-term exposure to SO_2, taken in consideration with the pre-existing literature, are ***inadequate to infer a causal relationship*** at this time. However, a trend is emerging in support of adverse health effects, measured as mortality outcomes, following SO_2 increases as low as 1 ppb over ambient concentrations. As with earlier assessments, an association can be made between long-term exposure to SO_2 and mortality, but concerns remain about whether the observed associations are plausible at ambient concentrations reported for Canada, and whether they are due to SO_2 alone, or to SO_2 as a chronic pollutant, rather than to transient spikes in SO_2 exposure.

10.2.9 Carcinogenicity and Genotoxicity

The US EPA (2008) found that SO_2 and its metabolite SO_3^{2-} were not mutagenic; nor were they found to cause DNA damage *in vitro*. Examination of toxicological literature and epidemiologic data indicated that SO_2 at high concentrations may cause DNA damage, but that carcinogenesis, co-carcinogenesis (Benzo-[a]-pyrene, suspended PM, diesel exhaust particles, diethylnitrosamine) or tumour promotion are not evident. Epidemiologic evidence from studies examining associations between long-term exposure to ambient SO_2 and risk of lung cancer incidence and mortality was inconclusive.

Animal studies have provided limited insight into the possible effects of SO_2 on genotoxicity and carcinogenicity. At levels of exposure orders of magnitude higher than reported in the epidemiology literature, SO_2 is not observed to have genotoxic effects (Ziemann et al., 2010). Sulphur dioxide at similarly high concentrations may, however, affect normal cell cycle regulation. One study has shown possible upregulation of proto-oncogenes and downregulation of tumour suppressor genes, though the most relevant tumor suppression gene, p53, was upregulated (Qin and Meng, 2010). Upregulation of p53, a major cell regulatory protein, is likely to be in response to the increased cellular proliferation and initiation of negative regulatory mechanisms that come into play during normal homeostasis. The overall finding of upregulation of proto-oncogenes and downregulation of tumour suppressor genes, reported in the carcinogenesis analysis (see Section 7) as well as the respiratory analysis (see Section 9), may provide biological plausibility for mortality from lung cancer due to the exposure-related carcinogenicity observed in the Asian epidemiology studies, when people were exposed to high levels of SO_2 and co-pollutants. Taken as a whole, the likelihood of changes to cancer-related genes is unclear at this time.

The human and animal data on the carcinogenicity or genotoxicity of SO_2 since the US EPA report do not support a causal relationship. Though some human epidemiological studies have reported increased lung cancer mortality following chronic SO_2 exposures, concerns about study design, the lack of supporting epidemiological or toxicological data—which does not indicate that SO_2 is involved with initiation of lung cancer—and ambient SO_2 concentrations higher than the Canadian maximum exposure concentration (8.6 ppb) based on NAPS data, make the weight of evidence ***inadequate to infer a causal relationship*** at this time. This determination is in line with the International Agency for Research on Cancer (IARC), which has listed SO_2 as a Group 3 chemical (IARC, 1997), meaning that it is not classifiable regarding carcinogenicity to humans due to limited or inadequate evidence.

10.2.10 Reproductive and Developmental Effects

The limited number of studies addressing preterm delivery, IUGR, birth defects, neonatal hospitalizations, and infant mortality resulted in the US EPA (2008) not drawing conclusions regarding the effect of SO_2 on these outcomes. Considerations when evaluating the reproductive and developmental datasets were outlined by the agency and remain applicable. Limitations to epidemiology studies looking at birth records have been reviewed (Buescher et al., 1993; Piper et al., 1993). The authors reported that birth certificate data vary with respect to reliability by specific variables. Reliable variables included birth weight, maternal age, race, and insurance status. Gestational age, parity and delivery type (vaginal vs. Caesarean) were considered reasonably reliable, but obstetrical complications and maternal lifestyle factors such as smoking and alcohol consumption were found not to be reliable. Controlling for potential confounders was also identified as a study design issue. Most of these studies adequately

controlled for maternal education, parity, age, and sex of child, but many did not adjust for SES, occupational exposures, indoor pollution levels, maternal smoking, alcohol use, prenatal care, or concurrent temperature exposures, although fetal growth is associated with all of these factors. Accordingly, comparisons across studies must be made with caution. While most studies analyzed average SO_2 exposure for the whole pregnancy, many also considered exposure during specific trimesters, or other time periods (e.g. first and last months of gestation). The time-specific exposure periods were undertaken to ascertain whether there are biological mechanisms or critical exposure time points that are most relevant for air pollution exposures and adverse birth outcomes.

Trends in epidemiology were, however, identified by the US EPA (2008), including positive associations between SO_2 exposure and LBW (Wang et al., 1997; Bobak, 2000; Ha et al., 2001; Maisonet et al., 2001; Lee et al., 2003; Liu et al., 2003; Yang et al., 2003; Gouveia et al., 2003; Mohorovic, 2004; Lin et al., 2004; Dugandzic et al., 2006; Bell et al., 2007). Specifically, an RR of 1.14 was reported for each 5 ppb increase in SO_2 concentration (Dugandzic et al., 2006), a result similar to that found in a Canadian study by Liu et al. (2003), who reported that maternal exposure during the first month of pregnancy was associated with 1.11-fold increased risk of LBW at exposure concentrations of 4.9 ppb (mean 24-h average). Similarly, interesting associations were presented related to RR of preterm birth for each 5 ppb increase in SO_2 concentration (1.04). Liu et al. (2003) reported an OR for preterm birth of 1.09 (95% CI 1.01–1.19) with a 5 ppb increase in SO_2. Additionally, a study of cardiac birth defects and oral clefts (Gilboa et al., 2005) found that the OR for isolated ventricular septal defects was 2.16 after maternal exposure to concentrations ≥2.7 ppb SO_2 during weeks 3–8 of pregnancy.

The more recent literature evaluating reproductive and developmental effects of SO_2 has provided insights into the effects of SO_2 on human embryos that may result in preterm delivery, LBW, congenital malformations, postnatal infant mortality, and increased incidence of asthma following *in utero* exposures. A review by Shah and Balkhair (2011) provides an excellent description of the issues surrounding integration of air exposure data from reproductive, teratogenic and developmental epidemiology reported for a given gestational exposure. As with all air pollution models, there are problems associated with modelling single- vs. multi-pollutants, with co-pollutants, with interpretation of monitoring data, and with consistency across birth records (including how birth outcomes are registered). However, with reproductive exposures, the specific type and timing of exposure takes on greater importance, because the adverse effect will vary greatly by gestational age. Thus, one of the more significant challenges associated with gestational exposures is how data are averaged. Most studies average exposure for a given period of time; however, for gestational exposures, the effects to the fetus of chronic moderate exposures may be vastly different than the effects of chronic low-level exposure with acute peaks; both of which, when averaged, may be designated as “moderate” exposures. This is a significant challenge and makes integration and synthesis of analysis for these studies much more difficult than for conventional air pollution epidemiology studies.

10.2.10.1 Pre-term Birth

Some recent studies have found a positive association between pre-term birth and exposure to SO_2 at concentrations greater than 3 ppb (Jalaludin et al., 2007; Jiang et al., 2007), while no association or negative associations have been observed in other studies (Brauer et al., 2008b; Darrow et al., 2009). The results provided conflicting lines of evidence, but possible reasons for these discrepancies between positive and negative associations are related to the time of

exposure being evaluated and the effect of co-pollutants that might not be accounted for in data using all births, including those not close to monitoring stations. The strongest evidence for an effect of SO_2 on preterm birth was for late-trimester exposures, with a Chinese study finding an 11.89% increase in preterm birth per 3.82 ppb increment in 8-week average levels of SO_2 (for exposures lasting at least 8 weeks before birth) (Jiang et al., 2007). These effects were only reported for the last 8 weeks prior to birth, (not for earlier time points, or in studies that did not stratify exposure by trimester), which indicates that chronic exposures of 8 weeks or more to SO_2 may have an impact on preterm birth outcomes. Though only a few studies have been identified examining these outcomes, the literature as a whole indicates that increases in SO_2 exposures may influence the risk of preterm birth outcomes. In mammals, including humans, the end-term placenta is susceptible to placental inflammatory signals that may regulate the timing of parturition (Cella et al., 2010; Mittal et al., 2011; Li et al., 2011; Voltolini et al., 2012). Sulphur dioxide has been found to induce inflammatory pathways in humans, usually following oxidative insult. Since the placental response described here should only occur when the antioxidant capacity of the placenta is overwhelmed during late-term gestation, it is highly likely that this effect would be in response to high-level acute exposures occurring over a chronic time frame, and that acute exposures are the best exposure parameter to consider in Canadians. Taken as a whole, and given the uncertainty surrounding the mechanism by which preterm birth would be related to SO_2 exposure, the weight of evidence is weakly ***suggestive of a causal relationship*** between SO_2 and preterm birth during the final trimester of gestation.

10.2.10.2 Congenital Heart Defects

Congenital heart defects occur in approximately 1 in 100–150 Canadian babies (Health Canada, 2002) and are among the most common structural anomalies diagnosed in Canada. They are the leading cause of deaths attributable to congenital anomalies in Canada; the national infant mortality rate directly due to congenial heart defects for the combined three years 1996–1998 was 4.7 per 10,000 live births (Health Canada, 2002). The majority of isolated congenital heart defects are multifactorially inherited, as identified by the Public Health Agency of Canada in its document *Congenital Anomalies in Canada: A perinatal health report, 2002* (Health Canada, 2002). It is, however, important to consider that there are known environmental risk factors and that SO_2 may be one of the pollutants involved in initiation of these defects. Several studies support the observation that SO_2 exposures during the first trimester of gestation are related to congenital heart defects, specifically aortic coartication and tetralogy of Fallot. These effects have been associated with ambient SO_2 concentrations averaged over weeks 3–8 of gestation in the range of 1.3 to 5.7 ppb, and the effects may be concentration-dependent, as some studies found increased risk with increasing SO_2 concentrations (Vrijheid et al., 2011).

In several of the epidemiology studies evaluating congenital heart defects, the OR for congenital anomalies was derived for SO_2 by using quartiles of SO_2 exposure. In the case of Rankin et al. (2009) it was reported relative to the lowest quartile during the first 3 months of pregnancy. The Dadvand et al. (2011a) study used a similar approach, whereby two sets of logistic regression models were built for continuous and categorical (extracted as quartiles) variables for exposure level for weeks 3–8 of pregnancy. The first quartile was treated as the reference group and subsequent quartiles were compared against it to estimate the OR and to investigate concentration–response relationships in consecutive quartiles of exposure. This less conventional “descriptive statistics” approach provides very little information for quantitative interpretation; specifically, it is impossible to determine the average exposure (medians and quartiles were reported, but this does not give a good indication of the mean exposure—only

indications of the values at the 25th, 50th and 75th percentiles). Given the variability in exposure approach, it was decided that only mean exposures can allow for meaningful comparison between datasets in this particular literature. Thus it is impractical to interpret these papers with respect to other papers in the body of literature; accordingly, the results of these papers have been included in the weight of evidence discussion but excluded from the risk characterization analysis at this time. Despite some concerns related to methodology, the incidence of these congenital heart defects following SO_2 exposures is consistently reported in the literature; the weight of evidence, considered in conjunction with the biological plausibility (discussed in Section 9), and exposure scenarios consistent with the Canadian experience, is weakly ***suggestive of a causal relationship*** between SO_2 exposures and congenital heart defects.

10.2.10.3 Cleft Lip and Cleft Palate

One study found a positive association between development of cleft lip, with or without presentation of cleft palate, and SO_2 exposure greater than 7 ppb, including a statistically significant elevated risk at the highest quartile of exposure (Marshall et al., 2010). No other studies were identified that looked at similar outcomes. The results of this study are equivocal, at best, because the incidence of cleft palate was shown to experience a non-statistically significant decrease. Cleft lip and cleft palate occur by the same mechanism during embryonic development; therefore, increased incidence of one with decreased incidence of the other is difficult to interpret in terms of causality without the benefit of additional analyses looking at, for example, nutritional deficiency as a cofactor. Despite some concerns related to the consistency of effect between incidence of cleft lip and cleft palate with increased SO_2 exposure concentrations, and the lack of papers assessing similar endpoints, it is important to consider this endpoint in light of other congenital malformations. As discussed in Section 9, even though cleft lip and cleft palate arise from the same mechanism, this mechanism is temporal in nature. If the *in utero* exposure to toxic insult varies by even a few hours it is likely that the effect will be significantly different—ranging from a severe effect to no effect at all. When evaluated with other congenital malformations that share similar mechanisms, such as congenital heart defects, the evidence is theoretically supportive of a causal relationship. However, given the speculative nature regarding the mechanism of teratogenic action on the manifestation of cleft palate and cleft lip at this time, the evidence is ***inadequate to infer a causal relationship*** regarding the effect of SO_2 on incidence of cleft lip or cleft palate.

10.2.10.4 Other Endpoints

Inconsistent evidence for decreases in birth weight (Brauer et al., 2008b; Bell et al., 2008; Naschimento and Moreira, 2009; Darrow et al., 2011), and postnatal infant mortality (Hajat et al., 2007; Woodruff et al., 2008; Son et al., 2008) and limited evidence for reductions in abdominal circumference and biparietal diameter of the fetus (Hansen et al., 2008), and for effects of *in utero* SO_2 exposure and asthma in children (Clark et al., 2010), did not allow for the determination of causality because the respective databases were ***inadequate to infer a causal relationship.***

10.3 Discussion of Biological Plausibility

Biological plausibility considers whether the effect noted in the literature has a possible or known biological mechanism to explain why researchers have observed these results, and whether that mechanism is likely to be active for the maximum Canadian ambient exposure concentrations described in this document. Biological plausibility was considered as part of the overall discussion of risk to health whenever possible. Formal conclusions about biological plausibility are presented in the sections below.

10.3.1 General Population

Based upon a discussion of potential mechanisms of toxic action provided in Section 9, and supported by the personal exposure modelling in Section 8, the following biological plausibility of effects observed in both toxicological and epidemiological literature in the general population has been determined for the following endpoints:

- Changes to respiratory morbidity in healthy adults, asthmatic adults, and healthy children
    - Increased risk of asthma symptoms
    - Increased risk of bronchoconstriction
    - Increased risk of lung function changes (as decrements in FVC and FEV_1)
- Increased risk of mortality from short-term exposure, particularly in the elderly
- Increased risk of preterm birth to babies exposed *in utero*
- Increased risk of congenital heart malformation to babies exposed *in utero*

Biological plausibility for other endpoints, such as cleft lip or cleft palate and decreased HRV, is theoretically possible; however, the epidemiology and mechanistic kinetics by which these effects are mediated are not clear at this point. Therefore, the evidence for biological plausibility at this time is suggestive only.

10.3.2 Susceptible Subpopulations

Biological plausibility for increased susceptibility to adverse effects from SO_2 exposures has been established for the following subpopulations under Canadian ambient exposure concentrations:

- asthmatics
- the developing embryo/fetus
- children
- the elderly, and
- those with olfactory impairments.

11.0 Risk Characterization

This section will only characterize risk for adverse health endpoints identified in Section 10 for which the weight of evidence shows a causal relationship, a likely causal relationship, or a suggestive causal relationship. A summary of the findings of Section 10 is presented in Table 11.1 below.

Table 11.1: Summary of the human health effects assessment conclusions

Endpoint	Exposure duration	Effects	US EPA (2008) conclusion	Health Canada conclusion
Respiratory morbidity	Short term	Respiratory symptoms, lung function, airways inflammation, airway hyperresponsiveness, ED visits/hospitalizations	Causal relationship (No separate conclusion on subpopulation of children)	Causal relationship (adults)
				Suggestive of a causal relationship (children)
	Long term	Respiratory symptoms and lung function	Inadequate to infer a causal relationship	Inadequate to infer a causal relationship
Cardiovascular morbidity	Short term	ED visits/hospitalizations	Inadequate to infer a causal relationship	Inadequate to infer a causal relationship
	Long term	Blood markers, arterial stiffness	No conclusion	No conclusion
Mortality	Short term	Non-accidental and cardiopulmonary	Suggestive of a causal relationship	Suggestive of a causal relationship
	Long term	Non-accidental and cardiopulmonary	Inadequate to infer a causal relationship	Inadequate to infer a causal relationship
Carcinogenicity		DNA damage, carcinogenesis, co-carcinogenesis or tumour promotion, incidence of lung cancer	Inadequate to infer a causal relationship	Inadequate to infer a causal relationship
Developmental		Congenital heart defects	No conclusion	Weakly Suggestive of a causal relationship

Endpoint	Exposure duration	Effects	US EPA (2008) conclusion	Health Canada conclusion
Reproductive/ Developmental		Preterm delivery	No conclusion	Weakly Suggestive of a causal relationship
		IUGR, cleft lip and cleft palate, neonatal hospitalization and infant mortality	No conclusion	Inadequate to infer a causal relationship
Prenatal and neonatal outcomes		LBW	Inadequate to infer a causal relationship	Inadequate to infer a causal relationship

11.1 Characterizing Exposure

Since 1970, total SO_2 levels have decreased by 96% in Canada, largely as a result of pollution reduction programs that limited SO_2 emissions and the use of alternative (low-sulphur) fuels.

Environmental data indicate that Canadians are being exposed to SO_2 at concentrations that may result in health effects. The evidence also supports the assumption that acute exposures (or acute spikes in chronic exposure time frames) are the best exposure parameter to consider in Canadians. Since data is available for multiple time points, the following approach was undertaken to model the most relevant personal exposure scenarios.

11.1.1 Chronic Exposure

For chronic exposures, the maximum annual average was selected from the NAPS data presented in Table 5.3, to represent the worst-case scenario for both urban and rural exposures. The exposure value used was a maximum annual average for urban areas of 8.6 ppb SO_2.

11.1.2 Acute Exposure

For acute or short-term exposures, the maximum 24-h, 1-h and 10-min averages given in Tables 5.1, 5.2 and 5.4 were employed. The values used were the maximum daily average for residential urban areas from the NAPS (2011) data of 56 ppb SO_2, the maximum 1-h average for residential urban areas from NAPS (2011) of 314 ppb SO_2, and the maximum 10-min average for an industrial site from the Airpointer (2009–2011) data of 322 ppb SO_2.

11.1.3 Indoor Exposure

The vast majority of samples taken for SO_2 in Health Canada indoor air studies in Montreal, QC, Halifax, NS, and Edmonton, AB, were below the detection level; therefore the detection limit of 1.2 ppb was used to calculate a worst-case exposure estimate, which was employed in the personal exposure modelling.

11.1.4 Personal Exposure Models

Results generated from the CAPEM2 and CMP applied dose models (Section 8) show that there are differences in personal dose (reported as serum sulphite body burdens by age group) from similar exposure to SO_2. This can best be explained by differences in the ratio of body weight to inhalation volume, and to some degree, activity patterns. For the purpose of comparison against reported body burdens of serum sulphite in humans, the adult maximum value for each averaging time was used for analyses. Based upon the known serum sulphite concentration body burden (15.86 μg/kg-bw), and the assumption that 99% of the exposed SO_2 is metabolized to serum sulphite, the predicted increase in body burden of SO_2, as serum sulphite, is 30%, 150%, and 154% for exposures measured as maximum 24-h average, 1-h average, and 10-min average, respectively. In the case of chronic exposures, the predicted increase of adult body burden serum sulphite was 2% and 1.7% for exposures measured as annual averages for urban or rural NAPS stations, respectively.

The results obtained using these models cannot be directly applied to any epidemiological or toxicological evaluation of the effects of SO_2; however, they are relevant to interpretation of the observed epidemiological effects. Serum sulphite levels can, at this time, only be considered with respect to systemic effects of SO_2 exposure. Based upon the results of the acute and chronic exposure models, it would appear that only acute exposures as modelled by the CMP model result in predicted body burden increases that are likely to affect human health. Of the effects outlined in Section 7, the systemic acute effects to consider include some cardiac and some *in utero* effects; both of which appear to be attributable to spikes in exposure rather than to chronic exposures. Of note: most lung effects are due to direct action of SO_2 on the pulmonary nervous system and would not be well correlated to systemic effects of increased serum sulphite body burdens, so these effects cannot be justified for consideration using systemic exposure models.

Thus there is moderate confidence that some acute effects reported in the literature could be attributed to systemic effects of SO_2 exposure, despite, in most cases, a weak signal compared against the same result for other pollutants. Accordingly, we can explore the biological plausibility of various mechanisms or modes of action with greater confidence that these effects are realistic, based upon predicted increases to SO_2 body burdens.

11.2 Characterizing Risk to Human Health

Characterization of the risk to humans following SO_2 exposure will only be performed for those items for which the weight of evidence was suggestive of a causal relationship or supportive of a positive association. When evaluating this section, it is important to keep in mind that there are factors that may influence individual susceptibility and vulnerability (see Section 9.4) as well as environmental factors that may affect the severity of effects in Canadians.

11.2.1 Respiratory Morbidity

11.2.1.1 Lung Function Measurements and Hospitalization in Adults

The data contained within the US EPA (2008) document as well as in the literature since 2007 show a causal relationship between exposure to SO_2 and respiratory morbidity in adults, measured as changes to lung function. The observation that asthmatics may be a susceptible subpopulation, reacting to lower concentrations of SO_2, remains valid.

The US EPA evaluated three controlled human exposure experiments on asthmatics. In the first, it was reported that, in 22% of the exposed asthmatics, the concentration of SO_2 needed to produce a doubling of sRaw compared to clean air exposure was <0.5 ppm. Two subjects experienced moderate decrements in lung function following exposure to SO_2 at concentrations ≤0.3 ppm for 10 min. More recently, it was reported that respiratory symptoms (shortness of breath, wheeze, and chest tightness) increased in a concentration-dependent manner. It was also noted that increasing SO_2 concentration had a greater effect on sRaw and FEV_1 changes than increasing exercise level; specifically, exposure to 0.5 ppm SO_2 during light exercise evoked a more severe symptomatic response than heavy exercise in clean air. Similarly, significant correlations were reported between decreased FEV_1 and increased respiratory symptoms following 10-min SO_2 exposures (0.5 ppm) via mouthpiece. Interestingly, the severity of individual asthma was not a predictor of individual sensitivity to SO_2.

In the literature unique to this analysis, one of the more relevant animal toxicology studies reported airway epithelial injury resulting from neutrophilic inflammation in OVA-challenged mice after exposures to 50 ppb SO_2 for just 1 h/d over a period of 3 d. The epidemiology papers lend support to the assumption that there are effects on lung function after short-term exposures to concentrations as low as a mean 24-h average of 1.73 ppb, but effects were not observed on hospitalizations for asthma with increases in SO_2 concentration of 5.1 ppb at lags 0, 1 or 2 d. The Canadian maximum concentration for the 24-h averaging time is 56 ppb, and it represents the worst-case scenario for short-term exposures in this assessment. Since the worst-case Canadian exposure level (56 ppb) is higher than the critical effect dose from the epidemiology (1.73 ppb), this suggests a risk to the Canadian population (particularly those living close to emission sources) for adverse effects from SO_2. These exposures may be influenced by co-pollutants or confounding factors, both of which are common to exposure scenarios for the general Canadian population under ambient exposure conditions.

The effects of co-pollutants and confounding factors cannot be fully ruled out in epidemiology studies; therefore, the LOAEC is 0.4 ppm, a value taken for lung function decrements from controlled human exposure studies of asthmatics exposed to SO_2 for 5–10 min at increased ventilation (see Chapter 7). This LOAEC value, rather than the epidemiological or toxicological data, should be used to develop an RfC, because it is derived from controlled, human, experimental data. Although not statistically significant, individuals have been reported to react at lower levels in controlled human exposure studies (i.e. 0.2 ppm), this value was compared to the Canadian maximum for the 10-min averaging time (0.322 ppm). Since the worst-case Canadian exposure level (322 ppb) is higher than the effect dose for some participants in the controlled human exposure studies (200 ppb), this suggests a risk to the Canadian population, especially asthmatics, for adverse effects from SO_2.

Uncertainty: There is high certainty that these effects are observed in humans because they are based upon human controlled exposure studies. There is high certainty that Canadians are exposed to SO_2 in the air at concentrations that could cause these effects. Biological plausibility for respiratory morbidity in adults has been demonstrated in both the epidemiology literature and controlled human exposure settings. Additionally, the mechanisms by which SO_2 elicits or may elicit an asthmatic response have been well described. No seriously confounding factors are expected for this endpoint, as most studies are reasonably well controlled and designed to account for confounding factors.

11.2.1.2 Lung Function Measurements and Hospitalization in Children

The data contained within the US EPA document as well as in the literature since 2007 are suggestive of a causal relationship between exposure to SO_2 and respiratory morbidity in children. The literature also suggests that SO_2 may negatively influence asthma-related ED visits or hospitalizations, but issues with confounding factors and co-pollutants such as PM_{10} have not been well characterized. It appears that time spent outdoors, related to springtime activity patterns, influences seasonal trends in ED visits and hospitalizations for asthma.

The epidemiology literature identifies lung function changes (the most sensitive endpoint being FEV_1) in asthmatics after exposures to SO_2 at concentrations as low as a 24-h mean of 6 ppb with an IQR of from 2.3 ppb to 8.8 ppb. The Canadian maximum concentration for the 24-h averaging time is 56 ppb, and represents the worst-case short-term exposure scenario for this assessment. Since the worst-case Canadian exposure level is higher than the critical effect dose, this suggests that there is a risk to the Canadian population (particularly those living close to emission sources) for adverse effects from SO_2. Time spent outdoors (related to springtime activity patterns) influences seasonal trends in ED visits and hospitalizations due to asthma. These exposures may also be influenced by co-pollutants or confounding factors, both of which are common to exposure scenarios for the general Canadian population under ambient exposure conditions. The effects of co-pollutants and confounding factors cannot be fully ruled out in epidemiology studies, but no controlled human exposure study data were available to support these observations. Contrary to the literature with adult subjects, the epidemiology literature does not currently support the role of SO_2 in exacerbating existing disease conditions in children or influencing their ED visits independent of other known air pollutants, though it is likely that the SO_2 pollution fraction is a contributor. An RfC for adults will consider population uncertainty related to age differences, and this should result in an RfC protective of children as well as all other members of the population.

Uncertainty: There is high certainty that these effects are relevant to humans because they are based upon human epidemiology papers. There is high certainty that Canadians are exposed to SO_2 in the air at concentrations that could cause these effects. There is medium-level confidence in the exposure concentration required to elicit asthmatic responses. Biological plausibility for these endpoints has been demonstrated, and it is supported by both the epidemiology literature and controlled human exposure studies. Additionally, the mechanisms by which SO_2 elicits or may elicit adverse respiratory responses have been well described.

11.2.2 Mortality

11.2.2.1 Mortality from Acute Exposure

The US EPA concluded that epidemiologic evidence on the effect of short-term exposure to SO_2 on non-accidental all-cause mortality and cardiopulmonary mortality is suggestive of a causal relationship at ambient concentrations; the literature since 2007 supports this association but not to the point of causality. On this basis, the epidemiology data is suggestive of a causal relationship between SO_2 exposure and all-cause and cardiopulmonary mortality at ambient concentrations.

The epidemiology data continue to provide evidence of the effect of short-term exposure to SO_2 on all-cause mortality and cardiopulmonary mortality. Positive associations continue to be reported between SO_2 mean daily exposures as low as 1 ppb and mortality in the epidemiologic literature. Additionally, the health benefits of even modest reductions in ambient SO_2

concentration have been suggested. The Canadian maximum concentration for the 24-h averaging time is 56 ppb, and it represents the worst-case short-term exposure scenario for this assessment. Since the worst-case Canadian exposure level (56 ppb) is higher than the critical effect dose (1 ppb), this suggests that there is a risk to the Canadian population (particularly those living close to emission sources) for adverse effects from SO_2.

The observed associations are, for the most part, robust enough to be maintained after adjustment for co-pollutants; however, they are impacted by study characteristics such as spatial distribution patterns and by seasonal trends. Experimental exposures may be influenced by co-pollutants or confounding factors, both of which are common to exposure scenarios for the general Canadian population under ambient exposure conditions. The mortality data are based upon incremental increases in SO_2 concentration of 1 ppb. The RfC for adults should be protective of mortality endpoints; the risk of mortality from acute emission increases will need to be controlled using other measures.

Uncertainty: There is high certainty that these effects are relevant to humans because they are based upon human epidemiology papers. There is high certainty that Canadians are exposed to SO_2 in the air at concentrations that could cause these effects. No seriously confounding factors are expected for this endpoint, as most studies are well controlled and well designed to account for confounding factors; however, interpretation of results from single- versus multi-pollutant models is complicated by potential interaction among co-pollutants and differing degrees of measurement error for correlated pollutants. Only a few studies specifically examined possible interactions among the co-pollutants, and this is a source of medium-level uncertainty.

11.2.3 In Utero *Developmental Effects*

11.2.3.1 Congenital Heart Malformation and Preterm Birth

As discussed in Section 7.7, the US EPA reported one study showing an OR of 2.16 for isolated ventricular septal defects after maternal exposure to ≥2.7 ppb SO_2 during weeks 3–8 of pregnancy. Additional information since 2008 has allowed a conclusion that exposure to SO_2 is weakly suggestive of a causal relationship with congenital heart malformations.

The recent literature indicates that congenital malformations may occur in a concentration-dependent manner, with some studies showing increased risk with SO_2 concentration increments of as little as 1 ppb. It is possible that vulnerable populations, for example those in proximity to emission sources and spikes in SO_2 emissions, are being exposed to SO_2 concentrations at levels that could pose a risk.

The US EPA (2008) reported that there was some evidence of preterm birth from a Canadian study, but there was not enough information to permit a further assessment. Additional information published since 2007 has been found that is weakly suggestive of a causal relationship between SO_2 and preterm birth during the final trimester of gestation.

Newer epidemiology supports an association between SO_2 exposure and preterm birth at daily average concentrations as low as 3.6 ppb. The strongest evidence for an effect of SO_2 on preterm birth was for late-trimester exposures, particularly over the last 8 weeks prior to birth. This indicates that chronic exposures of 8 weeks or more to SO_2 may have an impact on preterm birth outcomes. The exposure concentrations reported in the literature are less than the

Canadian maximum annual ambient exposure concentration (8.6 ppb) from the NAPS data, indicating a potential risk to the Canadian population.

Uncertainty for in utero endpoints: There is high certainty that these effects are relevant to humans because they are based upon human epidemiology papers. There is high certainty that Canadians are exposed to SO_2 in the air at concentrations that could cause these effects. However, for congenital heart malformation, there is low certainty about the actual effective concentration, due to a lack of data examining real-time exposure over the course of the pregnancy. There is moderate certainty that the time frame of importance is between weeks 3 and 8 of gestation, but there is low certainty regarding the exact time point at which the critical effects occur. There is also low certainty about the mechanisms by which these effects occur, though there is moderate confidence in the biological plausibility of the hypothesized mechanisms by which these effects may arise. For preterm birth, there is some uncertainty in the degree of influence of SO_2 because of conflicting lines of evidence in the literature, and the apparent effect of co-pollutants. There ismoderate confidence in the biological plausibility of this effect, based upon the possible mechanism of action by which these effects may arise.

11.2.4 Derivation of a Reference Concentration for human health

The assessment identified the strongest evidence of causality to be between short term SO_2 exposures and respiratory morbidity, based largely on the 5-10 minute controlled human exposure studies. There was less evidence of causality and/or insufficient controlled human exposure studies to directly derive reference concentrations for the 1 hour, 24 hour or annual time periods, although derivation of a value from the epidemiology could be considered. The effects of co-pollutants and confounding factors cannot be fully ruled-out in epidemiology studies; therefore, the Reference concentration (RfC) is based on the statistically significant lowest-observed adverse effect concentration (LOAEC) of 0.4 ppm resulting in lung function decrements from controlled human exposure studies of asthmatics exposed to SO_2 for 5-10 minutes, at increased ventilation (US EPA, 2008, Johns and Linn, 2011, WHO, 2005).

Although the above studies exposed a susceptible subpopulation (i.e. asthmatics), further sensitivity was observed with some participants reacting at lower concentrations (e.g. as low as 0.2 ppm in chamber studies and 0.1 ppm in mouthpiece exposures (Johns and Linn, 2011)). A lower threshold has not been identified for asthmatics (Horstman et al., 1986, US EPA, 2008, Johns and Linn, 2011, WHO, 2005). Additionally, the studies are usually conducted at room temperature, while some increase in response has been noted when sulfur dioxide is administered in cold dry air (WHO, 2005). The studies generally have small sample sizes (e.g. 15 to 20 people) and participants are usually young adults who are otherwise healthy, therefore it is expected that further susceptibility in the population due to genetic factors or other factors like age and disease status may result in a lower level of response.

The much lower levels at which effects are observed in the epidemiology data, which represents larger study populations and therefore more genetic, age and health status diversity also supports the potential for effects at concentrations below those used in controlled-exposure studies. The epidemiology database lends support to effects on respiratory morbidity occurring after short-term exposures to concentrations as low as a mean 24-h average of 1.73 ppb or a maximum 24-h average of 4 ppb. One Canadian study reported effects at a mean daily 1-h maximum of 62 ppb. It should be noted that epidemiological studies often show correlations between multiple pollutants, making identifying a causal association between one particular air

pollutant and the observed effect difficult. In the US EPA analysis, studies were identified which observed statistically significant positive associations between ambient SO_2 and respiratory related emergency department visits and hospitalizations, in multi-pollutant models with PM, in the range of 99th percentile 1 hour daily maximums of 75-150 ppb. Several additional studies identified positive associations down to a 99th percentile 1 hour daily maximum of 50 ppb (U.S. EPA, 2010).

There is further uncertainty related to the potential impact of intermittent spikes of higher concentrations of SO_2 on endpoints other than respiratory morbidity, including mortality, reproductive and developmental effects. To account for the uncertainties mentioned above and considering the supporting evidence from the epidemiology, an uncertainty factor of 6 was applied to result in a 10 minute RfC of 67 ppb, which is expected to be protective of human health, including sensitive subpopulations like asthmatics.

12.0 Conclusions

Based upon the available information there is an adverse health risk to the Canadian population from exposure to ambient concentrations of SO_2. The evidence supports a causal relationship between exposure to ambient levels of SO_2 and respiratory morbidity in adults, particularly in the asthmatic subpopulation. Similarly, the literature supports a positive association between exposure to SO_2 and respiratory morbidity in children.

The available information is suggestive of a causal relationship between SO_2 exposures and all-cause and cardiopulonary mortality at ambient exposure concentrations, particularly in persons over 40 years of age (most strongly associated with the elderly). Additional evidence is weakly suggestive of a causal relationship with several reproductive/developmental outcomes.

12.1 Public Health Impacts

Although the magnitude(s) of the risk of health effects, for which positive associations have been made in the epidemiology with respect to SO_2 exposures, are relatively small, they present important impacts on public health due to the number of people potentially affected.

The subpopulations that appear to have increased susceptibility to the health effects represent a considerable proportion of the population, with asthmatics and the elderly alone accounting for 8.9% and 14.8% of Canadians, respectively (Statistics Canada, 2011; ASC, 2012). Similarly, with respect to the amount of SO_2-related mortality, Judek et al. (2004) estimated that 8% of total non-accidental mortality in urban census divisions in Canada between 1998 and 2000 was due to air pollution (described by a multi-pollutant model of PM, O_3, NO_2, SO_2 and CO) and that most of this was due to long-term exposure to ambient fine PM, which has a strong signal correlation to SO_2.

Less clear-cut, with respect to percentage influence on Canadians, are the effects on babies exposed *in utero,* particularly with respect to the implication of an increased incidence in preterm birth, which has known economic impacts (Public Health Agency of Canada, 2008; Health Canada, 2008).

12.2 Recommendations

It is recommended that the current National Ambient Air Quality Objectives be revised or new Ambient Air Quality Objectives or Standards be introduced with consideration of the following:

1. The strongest evidence of causality was between short term SO_2 exposures and respiratory morbidity, based largely on the 5-10 minute controlled human exposure studies. A 10-min human health reference concentration of 67 ppb has been identified in the assessment.
2. The more recent literature also adds to the weight of evidence for a “suggestive of causal” relationship between non-accidental and cardiopulmonary mortality risks and short-term exposures to SO_2.
3. Additional endpoints (reproductive/developmental) have been identified based on the more recent literature. Although these endpoints have also been designated as having a weakly “suggestive of causal” relationship with SO_2 exposures, the database is limited.

4. Intermittent spikes in exposures are linked to respiratory morbidity and are suspected for most other endpoints, including reproductive/developmental. Current Canadian monitoring data support that the highest Canadian exposures are likely to be to intermittent spikes in concentrations. Mechanistic and personal exposure modeling also support intermittent spikes in exposure as being relevant to the health effects observed.
5. There is "inadequate evidence to infer a causal relationship" between long term exposures of SO_2 and health effects.

12.3 Research Needs

More research is required on the following subjects:

1) epidemiologic evaluation of SO_2 adverse health effects;
2) controlled human exposure evaluation of SO_2 at ambient air concentrations to support epidemiological observations, and facilitate identification of threshold concentrations;
3) information on how temperature affects the human response to SO_2 exposure;
4) effects of phenotypic differences to respiratory nerve endings on sensitivity to inhaled SO_2 (e.g. activation of acid-sensitive ion channels vs. C-fibres);
5) effects of phenotypic differences to respiratory nerve endings on asthmatic responses, particularly with respect to therapeutic options for treatment following pollutant exposure;
6) confirmation of the mechanism by which SO_2 (may) induce changes to heart rate variability (e.g. respiratory sinus activation);
7) effects of *in utero* SO_2 exposure to the end-term placenta, with respect to preterm birth;
8) effects of *in utero* SO_2 exposure to embryonic development (e.g. neural crest cell migration and differentiation), specifically:
    a. incidence of congenital heart malformation in Canada
    b. incidence of palate closure in Canada
    c. incidence of asthma in children after birth
9) effects of *in utero* SO_2 exposure on postnatal behaviour and learning in children;
10) relevance of neurogenic inflammation, following SO_2 exposures, to human respiratory morbidity;
11) effects of SES on ED visits for asthma after longer lag periods.

13.0 Glossary

AATD	α-1-antitrypsin deficiency
ACh	acetylcholine
ACS	American Cancer Society
AHR	airway hyperresponsiveness
atm	atmosphere
atm- m^3/mol	atmosphere per cubic metre per mole
ATPase	adenosine triphosphatase
ATSDR	Agency for Toxic Substances and Disease Registry
BALF	bronchioalveolar lavage fluid
bax	pro-apoptotic gene
bcl-2	anti-apoptotic gene
BNP	B-type natriuretic peptide
BS	black smoke
CAMP	Childhood Asthma Management Program (study)
CAPEM	Canadian Air Personal Exposure Model
CASRN	Chemical Abstract System Registration Number
CHF	congestive heart failure
CI	confidence interval
cm^2	centimetre squared
cm^3	cubic centimetre
CMP	Chemicals Management Plan
c-myc	proto-oncogene
CO	carbon monoxide
COPD	chronic obstructive pulmonary disease
COX-2	cyclooxygenase-2
CRP	C-reactive protein
CVD	cardiovascular disease
DNA	deoxyribonucleic acid
ED	emergency department
EGF	endothelial growth factor

EGFR	endothelial growth factor receptor
ER	excess risk
ET-1	endothelin-1
$FEF_{25–75\%}$	forced expiratory flow between 25% and 75% of forced vital capacity
FeNO	exhaled nitric oxide
FEV_1	forced expiratory volume in the first second (the volume of air that can be forcibly exhaled in one second after taking a deep breath)
FVC	forced vital capacity
g/L	grams per litre
g/mol	grams per mole
GAM	Generalized Additive Model
GLM	Generalized Linear Model
H^+	hydrogen ion
H_2O	water
H_2O_2	hydrogen peroxide
HO_2	hydroperoxyl
Hox	*Homeobox* gene
HOXA	*Homeobox-A* gene
HRV	heart rate variability
H_2SO_3	sulphurous acid
H_2SO_4	sulphuric acid
HSO_3	hydrogen sulphite
HSO_3^-	bisulphite
ICAM-1	intercellular adhesion molecule-1
ICAS	Inner-City Asthma Study
ICD	implantable/implanted cardioverter-defibrillator
IgE	immunoglobulin-E
IL-1β	interleukin-1beta
IL-6	interleukin-6
IL-8	interleukin-8
INCHEM	World Health Organization database
iNOS	induced nitric oxide synthase
IQR	interquartile range

ISAAC	International Study of Asthma and Allergies
8-isoPGF$_{2\alpha}$	8-isoprostaglandin F2α
IUGR	intrauterine growth restriction
IVF	*in vitro* fertilization
KCO	gas transfer coefficient
Kg	kilogram
Kg-bw	kilogram-bodyweight
Ki-ras	proto-oncogene
kPa	kilopascals
L/min	litres per minute
L/mm	litres per millimetre
LBW	low birth weight
M_1	muscarinic receptor-1
M_2	muscarinic receptor-2
M_3	muscarinic receptor-3
m^3/d	cubic metre per day
mg/m^3	milligrams per metre cubed
mL	millilitre
MMEF	maximal mid-expiratory flow
mRNA	messenger ribonucleic acid (RNA)
mmol/kg-bw	millimole per kilogram body weight
NAAQS	National Ambient Air Quality Standard
NALF	nasal lavage fluid
NAPS	National Air Pollution Surveillance
NATA	National Scale Air Toxics Assessments
NCICAS	National Cooperative Inner-City Asthma Study
NCX	forward-mode sodium-calcium exchange pumps
NH_3	ammonia
NHAPS	National Human Activity Pattern Survey
NHIS	National Health Interview Survey
nmol/ml	nanomoles per millilitre
NO	nitric oxide

NO_2	nitrogen dioxide
NO_2^-	nitrite ion
NO_x	nitrous oxides
NO_3	nitrogen trioxide
N_2O_5	dinitrogen pentoxide
O	elemental oxygen
O_2	oxygen
O_3	ozone
$^{\bullet}OH$	hydroxyl radical
OR	odds ratio
OVA	ovalbumin
p16	tumour suppressor gene
p53	tumour suppressor gene
PAPA	Public Health and Air Pollution in Asia (study)
PEACE	Pollution Effects on Asthmatic Children in Europe (study)
PEFR	peak expiratory flow rate
pH	power of hydrogen
PiZZ	genotype resulting in AATD
ppb	parts per billion
PM	particulate matter
$PM_{2.5}$	particulate matter of an aerodynamic size less than 2.5 micrometers
PM_{10}	particulate matter of an aerodynamic size less than 10 micrometers
ppm	parts per million
QT interval	the time for both ventricular depolarization and repolarization to occur
Rb	tumor suppressor gene
RfC	reference concentration
RR	relative risk
RSPM	respirable suspended particulate matter
$R\text{-}S\text{-}SO_3^-$	S-sulfonate
RSV	respiratory syncytial virus
SAR	slowly adapting receptors
SD	standard deviation
SES	socioeconomic status

SERCA	sarcoplasmic reticulum calcium ATPase
SO_2	sulphur dioxide
SO_3	sulphur trioxide
$^{\bullet}SO_3^{2-}$	sulphur trioxide radical
SO_3^{2-}	sulphite
SO_4^{2-}	sulphate
SO_x	sulphur oxides
SOX	sulphite oxidase enzyme
$S_2O_3^{2-}$	thiosulphate
SPM	suspended particulate matter
TBARS	thiobarbituric acid reactive substances
TGF-β1	transforming growth factor – beta1
TNF-α	tumor necrosis factor-alpha
TRPA1	transient receptor potential ankyrin 1
TRPV1	transient receptor potential cation channel subfamily V member 1
TRPV4	transient receptor potential cation channel subfamily V member 4
TSP	total suspended particles
$\mu g/m^3$	micrograms per metre cubed
μg/kg-bw/d	microgram per kilogram of body weight per day
μM	microMolar (micromoles per litre)
US EPA	United States Environmental Protection Agency
WHO	World Health Organization
y	year

14.0 References

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Appendix A: CAPEM Model

Health Canada developed the CAPEM model to determine Canadian exposure to chemicals under different fuel exposure scenarios. The model can be applied to other scenarios, including exposure to airborne contaminants such as SO_2. The model used in this evaluation was updated in 2010 by Golder Associates as CAPEM2.

A.1 Model Structure

The CAPEM2 is designed to quantify a range of probable chemical exposures that Canadian residents may receive from the inhalation of ambient and defined microenvironment (ME) air. The model uses specific ME chemical concentration data, in combination with age-specific time-activity distribution data, and applies appropriate inhalation rates and body weights to develop distributions of potential exposures through a series of calculation routines. The time-activity patterns are critically important in estimating potential exposures to airborne chemicals, as the concentration of a given chemical in air can be strongly dependent on location, making exposure highly linked to the time spent in various locations. In addition, the level of physical activity within a specific environment will dictate the inhalation rate and is therefore an important factor in the estimation of potential exposures.

The receptor groups, time-activity patterns, inhalation rates, body weight distributions, and exposure equations used in the CAPEM2 to estimate potential exposure are described in detail below.

The CAPEM2 uses a probabilistic approach for estimating the inhalation exposures. With each iteration of the model, the CAPEM2 defines the following: the MEs encountered on a given day, the time (min/d) spent within those MEs, the receptor's level of activity within each ME and the associated inhalation rates, and the receptor's body weight. Using these data, the CAPEM2 estimates the exposure resulting from the time spent in the MEs encountered each day. To determine the daily exposure from inhalation for each receptor group, the CAPEM2 adds the exposures from each ME encountered within that day.

The general equation describing the model is as follows:

$$\text{Daily exposure intake (mg/kg/d)} = \Sigma\, AC_i \times IHR_i \times ET_i \times CF \times 1/BW \qquad (1)$$

where

AC_i = chemical vapour air concentration in ME i ($\mu g/m^3$)

IHR = activity-level specific inhalation rate in ME i (L/min)

ET_i = time spent in ME i (min/d)

CF = conversion factor (mg/μg)

BW = body weight (kg)

The CAPEM2 was developed into a Monte Carlo environment using the @Risk 4.5 application.

A.1.1 Receptor Groups

The CAPEM2 was designed to estimate potential exposure to chemicals derived specifically from automobile fuel uses, though it can be used for other inhalation model exposure scenarios. Potential receptors include all age groups and genders. The male and female receptors evaluated with the CAPEM2 include the following age groups: 0–0.5, 0.5–4, 5–11, 12–19, 20–59, and ≥65 years. The input data are designed to be representative of both genders; thus the output can be applied to both males and females.

A.1.2 Time-activity Patterns

The CAPEM2 evaluates age-group-specific exposures to airborne chemicals in the following MEs: indoor at home, in the shower, indoor–non-home locations, outdoors, in a vehicle, in an outdoor parking garage, and at a gas station pump island. For this assessment, only the following categories were considered:

- Indoor at home
- Indoor–non-home
- Outdoors
- In-vehicle

The CAPEM2 uses probabilistic distributions of age-specific time-activity data for 6 age groups, which were derived from population survey data collected by Health Canada and reported in *It's About Time: The Canadian Human Activity Pattern Survey* (Leech et al., 2002). The time-activity database used included population-weighted data from four Canadian cities (Edmonton, Toronto, St. John's, and Vancouver) for both winter and summer.

The age groups evaluated by Health Canada in the population surveys matched those included in the CAPEM2. For each age group, the survey provided information regarding the amount of time that respondents spent in each ME at specific activity levels; the time range was 0–1440 min/d. The time spent in an ME during each iteration of the CAPEM2 was derived by sampling the survey with a cumulative probability distribution function using the @Risk 4.5 program.

Activity patterns may differ between genders; this could result in different exposures to environmental pollutants. As the sample size in the Canadian time-activity survey was not sufficient to accurately determine the gender-specific time-activity for some of the age groups, the CAPEM2 outputs are not gender specific.

A.1.3 Inhalation Rates

The activity levels dictate the age-specific inhalation rates used in the exposure model. By definition, activity level for time spent in the shower, in an outdoor parking garage, and outdoors at a gas station pump island is considered light. Similarly, driving an automobile is predefined as a very light activity. For the remaining MEs (indoor–at home, indoor–non-home locations, and outdoors), *The Canadian Human Activity Pattern Survey* provided information for a variety of activity levels. Table A.1 summarizes the activity levels for which survey data are provided and the ME that those activities are associated with.

Table A.1: Summary of activity levels by environment

Environment	Possible activity levels
Indoor–at home	Resting, very light, light, light to moderate, heavy
Indoor–non-home locations	Resting, very light, light, light to moderate, heavy
Outdoors	Resting, very light, light, light to moderate, heavy
Showering	Light
Outdoor–parking garage	Light
Outdoor–gas station pump	Light
In-vehicle	Very light

The CAPEM2 uses a distribution of inhalation rates that correspond to the activity levels shown in Table A.1. Table A.2 summarizes the distributions used to define the activity-level-dependent inhalation rates.

Table A.2: Summary of age and activity-specific inhalation rates

		Activity-specific inhalation rate (L/min)					
		Receptor group age (years)					
		0–0.5	0.5–4	5–11	12–19	20–59	≥60
		Distribution type					
Activity level	**Distribution statistics**	**Normal**	**Lognormal**	**Lognormal**	**Lognormal**	**Lognormal**	**Lognormal**
Rest	Mean	1.05	3.8	6.6	7.4	7.5	7.2
	SD*	0.42	1.3	1.3	1.3	1.4	1.3
Very light	Mean	2.05	6.0	10.2	10.8	10.9	10.0
	SD	0.82	1.5	1.3	1.3	1.4	1.3
Light	Mean	2.05	8.0	13.7	15.1	14.0	14.2
	SD	0.82	1.6	1.3	1.3	1.3	1.3
Light to moderate	Mean	3.44	14.9	16.1	20.6	26.0	26.8
	SD	1.38	1.4	1.3	1.2	1.2	1.2
Heavy	Mean		22.8	37.4	46.9	44.5	54.3
	SD		5.4	8.9	7.4	9.7	9.2

*Standard deviation

A 1.4 Body Weight Distributions

The age-specific body weight distributions used in the CAPEM2 were derived from Health Canada's *Exposure Factors for Assessing Total Daily Intake of Priority Substances by the General Population of Canada*. A summary of these age-specific body weight distributions is provided in Table A3.

Table A.3: Summary of body weight distributions

	Body weight (kg)			
Age (years)	**Distribution type**	**Distribution inputs**	**Input values**	**Standard deviation (SD)**
0–0.5	Lognormal	Mean, SD	7.7	1.4
0.5–4	Lognormal	Mean, SD	15.4	1.4
5–11	Lognormal	Mean, SD	30.6	1.5
12–19	Lognormal	Mean, SD	59.1	1.2
20–59	Lognormal	Mean, SD	69.5	1.2
≥60	Lognormal	Mean, SD	70.3	1.2

A.1.5 Chemical Concentrations

Exposure to chemicals is dependent on both the concentration of the chemical in the medium of interest and the intake rate of that medium. Although the CAPEM2 can evaluate exposures in both air and water, only the potential exposure via inhalation was investigated in this study. The CAPEM2 currently uses only point (deterministic) estimates for chemical concentrations; future versions may include the distributions of chemicals in the media.

A.2 The CAPEM2 Sequence

The CAPEM2 model runs through a user-defined number of iterations and, with each iteration, exposure times, inhalation rates, body weights, and water ingestion rates are randomly chosen from the distribution of possible inputs. The first step in executing the model is to define the number of iterations for the model run and to input the chemical concentration for each medium. The model then identifies the activities to be performed in a given iteration based on the fraction of survey respondents that participated in a specific activity. The duration and activity level for the activities performed are selected using the time-activity data from the Canadian Human Activity Pattern Survey (CHAPS). For each activity level, an inhalation rate is chosen using the data summarized in Table A2.

Because the available time-activity patterns are not dependent on each other, the model may select time-activity durations that total to more or less than a full day (1440 min). To compensate for this, the model employs a linear scaling function to reduce or increase the activity durations so the total duration for all activities is 1440 min/d. This specific scaling step is not shown in Figure A1, but does occur within each model iteration.

Once the activities, their activity levels, and the inhalation rates have been selected, the model chooses an age-appropriate body weight. The data selected by the model are used as input to the equation to compute a chemical-specific exposure for the air exposure pathway. The model then selects an age-appropriate daily water consumption rate, and using this data in conjunction with the body weight, computes a chemical-specific exposure for the ingestion exposure pathway. (Note that drinking water consumption was not considered as part of this project.) Finally, the inhalation and ingestion exposures are added, to yield an overall chemical-specific exposure for that iteration. The model calculates a new series of potential exposures for each of the iterations to yield a distribution of potential chemical exposures for each age group, and then creates Microsoft Excel output sheets summarizing the results of the exposure analysis.

A.3 Quantification of Time-Weighted Exposure

The TWE is an expression of the daily relative levels to which an individual would be exposed. It represents the 24-h average of the concentration for a compound in a specific ME multiplied by the time spent in this specific ME (equation (2)). The sum of the time spent in the various MEs must be equivalent to 1440 min (24 h).

The general equation is as follows:

$$TWE = (C\,ME_x \times TA\,ME_x) + (C\,MEy \times TA\,MEy) \ldots../1440\ \text{min} \qquad (2)$$

where

$C\,ME_x$ = Concentration in ME x ($\mu g/m^3$)

$TA\,ME_x$ = Time spent in ME x (min/d)

Appendix B: Tables

Table B.1: Ambient and outdoor [+] concentrations of SO_2

Reference	Study description	Season	Mean concentrations (ppb)*	Summary of results/notes
(Leaderer et al., 1999)	Virginia and Connecticut, USA. August 1994 to January 1998. Harvard glass honeycomb denuder/filters pack sampler used. Measurements were taken for a duration of 24 h. Indoor, outdoor and ambient air samples were collected from 281 non-smoking homes with/without kerosene heaters.	Winter (months included as winter not reported)	Outside homes: 4 ± 2.15	Indoor concentrations are shown for comparison. Outdoor measurements were greater than indoor measurements in the winter in homes without kerosene heaters. Outdoor measurements were greater than indoor measurements in the summer. Outdoor and ambient concentrations were similar in the summer.
		Summer (months included as summer not reported)	Outside homes: 1.3 ± 1.7 Ambient (Regional site): 1.2 ± 0.6	
(Chen et al., 2001)	Fort Meade, MD. June 1999 to July 2000. Modified commercial pulsed UV fluorescence instrument used. 24-h measurements were taken for 4 intensive periods. Seasonal variations in outdoor concentrations were investigated in a highly populated and industrialized area. Measurements were made at one location in a broad open field, 2 km from the nearest major highway.	Fall 1999 (Oct)	2.7 ± 2.2	The highest SO_2 levels were observed around noon. In addition, within the period of the study, the greatest SO_2 levels occurred in the winter.
		Winter 2000 (Jan)	4.3 ± 2.3	
		Spring 2000 (Apr)	2.7 ± 1.8	
		Summer 2000 (Jul)	3.4 ± 2.9	
(Environment Canada, 2001)	Canada (various cities). 2000. Data obtained from Environment Canada for a large number of cities across the country.	All seasons	Median range (24-h average): 0–10	Data obtained from National Air Pollution Surveillance Network.
(Campbell et al., 2005)	Sequoia National Park, CA. 1999. Honeycomb denuder/filter pack air pollution sampler. Measurements taken for two 24- h long periods every month. Measurements were made at five sites in the park.	Summer (May, Jun, Jul, Aug, Sept, Oct, Nov)	Mean range: 0.23 to 0.50 (0.6–1.3 µg/m^3)	Concentrations of SO_2 in the park were low and concentrations declined significantly with increasing elevation and distance from the pollution source area. SO_2 concentrations were significantly lower at the end of September.

Reference	Study description	Season	Mean concentrations (ppb)*	Summary of results/notes
(Campbell et al., 2005)	Toronto, ON. 1997–2000. Fixed monitoring stations. Hourly means based on season and AQI levels. Existing hourly pollution data were obtained from 4 NAPS monitoring sites operated by the MOE.	Winter (Dec, Jan, Feb)	5.5 ± 0.5	The difference between measured concentrations in winter and summer was significant ($p<0.0001$). SO_2 concentrations peaked just after mid d.
		Summer (Jun, Jul, Aug)	4.2 ± 0.7	
(Wheeler et al., 2008)	Windsor, ON. 2004. 3M Passive badges used. Measurements were collected in all four seasons for two-week integrated periods. 54 samplers were fixed across the city on light poles.	Winter (Feb)	6.9 ± 1.9	SO_2 levels were generally greater in winter than other seasons. Significant correlations ($p<0.0001$) between pollutants for all seasons were observed. Winter measurements seem to be most representative of the annual concentrations and the summer season the least representative. The monitoring sites were located in areas to identify spatial and seasonal variability of the air pollutants.
		Spring (May)	4.8 ± 0.8	
		Summer (Aug)	6.7 ± 1.3	
		Fall (Oct)	4.0 ± 0.8	
(Brown et al., 2009)	Boston, MA. 1999–2000. Passive badges and pulsed fluorescent monitor used. Ambient measurements were taken from a stationary ambient monitoring site located at the Harvard School of Public Health in Boston. 24-h ambient concentrations were measured. Sampling conducted for 7 consecutive days. 28 and 35 measurements for winter and summer, respectively, from 15 homes.	Winter 1999 – 2000 (Nov, Dec, Jan)	Ambient: 11.3 ± 5.9	Study looked at the relationship between personal and ambient SO_2 concentrations.
		Summer 2000 (Jun, Jul)	Ambient: 3.6 ± 1.1	
(Schwab et al., 2009)	New York, NY. 1995–2005. Thermo environmental Model 43BS pulsed fluorescence analyzer used. Data collected in min/h averages. Outdoor measurements were made at one rural site in New York State (Pinnacle State Park).	All seasons	Mean range: 0.8 to 6.8	Concentrations were estimated from Figure 3. The highest average SO_2 concentrations were measured in the winter months. A decrease in SO_2 concentration was observed between 2000 and early 2005.

* Concentrations provided in brackets represent the original units in which the concentrations were reported.

[+] For the purpose of this table, the term ‘ambient concentration’ refers to a measurement taken from a fixed central site monitor (e.g., monitoring networks) and ‘outdoor concentration’ refers to a measurement taken outdoors (e.g. outside at a residence) which may be done by a variety of measurement methods.