REVIEW OF THE HEALTH RISKS ASSOCIATED WITH
Nitrogen Dioxide and Sulfur Dioxide
in Indoor Air

Report to Health Canada

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1 INTRODUCTION

The purpose of this report is to provide a review of the scientific literature on the health effects of nitrogen dioxide (NO\textsubscript{2}) and sulfur dioxide (SO\textsubscript{2}) which will be used as a background document by Health Canada in its process of revising the Exposure Guidelines for Residential Indoor Air Quality.

Specifically, the report reviews

- the chemical and physical properties of the two gases;
- the toxicological characteristics identified in animal studies, at exposure concentrations near the range of ambient human exposures;
- the expected levels of non-industrial indoor exposure of Canadians, with comparisons to other regions with and without comparable climates;
- the sources of indoor exposure, including the contribution of outdoor pollution to indoor levels;
- results of epidemiological studies of non-industrial indoor exposures (e.g., in homes, offices, and schools);
- where few or no studies of non-industrial indoor exposures are available, results of epidemiological studies of exposed workforces or of populations exposed to ambient pollution that was distinguishable from other air pollutants; and
- results of controlled human exposures in clinical settings.

Based on the evidence provided in the literature, we suggest lowest observable adverse effect levels (LOAEL) for both the acute and chronic effects of the two gases. Where possible, populations at higher risk of adverse health effects are identified.

Throughout the review, sources of uncertainty in the research findings and weaknesses in the study designs are discussed. Areas where there is a dearth of information are identified as avenues for future research.
2 Methods

2.1 Literature Search

Health Canada initially identified a list of 85 references related to this review. These were supplemented by an extensive search of bibliographic databases of the medical and scientific literature, listed below. All available years of all the databases were searched, between December 15th and December 31st 2001.

- BIOSIS Previews is a life sciences database that combines the journal reference content from Biological Abstracts with the content from Biological Abstracts/RRM, which covers reports, reviews and meetings. Covers 1970 forward.

- The Cochrane Controlled Trials Register (CCTR) is a bibliography of controlled trials individually identified by contributors to the Cochrane Collaboration.

- The Cochrane Database of Systematic Reviews (COCH) includes regularly updated systematic reviews of the effects of healthcare, as prepared by the Cochrane Collaboration.

- The Cambridge Scientific Abstracts (CSA) cover 15 science and engineering databases, including the Aluminium Industry Abstracts, the Aquatic Sciences and Fisheries Abstracts, the Ceramic Abstracts/World Ceramics Abstracts, the Conference Papers Index, the Copper Data Center Database, the Corrosion Abstracts, the Engineered Materials Abstracts, the Environmental Sciences and Pollution Management Database, the Materials Business File, the Mechanical Engineering Abstracts, METADEX, the Oceanic Abstracts, TOXLINE, WELDASEARCH, and the Zoological Record. Covers 1966 forward.

- The Database of Abstracts of Reviews of Effectiveness (DARE) contains critical assessments of systematic reviews from a variety of medical journals. The DARE records cover topics such as diagnosis, prevention, rehabilitation, screening and treatment.

- EMBASE indexes over 3,500 international journals focused on biomedical, pharmaceutical and other life sciences. Covers 1988 forward.

- Medline indexes over 3,600 international journals focused on clinical medicine, experimental medicine and health care. Some book chapters are also included. Covers 1965 forward, and includes some references between 1957 and 1965.

- PubMed is the US National Library of Medicine’s search service that provides access to over 11 million citations in Medline, PreMedline, and other related databases. Same years as Medline covered.

- The National Technical Information Service (NTIS) is the US government database of scientific, technical, and engineering information. Covers 1990 forward.

- Toxnet covers toxicology data from the Hazardous Substances Data Bank (HSDB), the Integrated Risk Management System (IRIS), the Chemical and Carcinogenesis Research Information System (CCRIS), and GENE-TOX. It also covers toxicology literature from TOXLINE, the Environmental Mutagen Information Center (EMIC), and the Developmental and Reproductive Toxicology and Environmental Teratology Information Center (DART/ETIC).
Each database was searched using the following four groups of keywords in the five combinations shown below. Boolean operators (in capitals) separate terms.

**Group 1**
"kerosine" OR "kerosene" OR "gas cooking" OR "gas heating" OR "gas stove" OR "gas stoves" OR "combustion products" OR "wood cooking" OR "wood burning" OR "wood stove" OR "wood stoves" OR "zamboni" OR "vehicle exhaust"

**Group 2**
"sulfur oxides" OR " sulphur oxides" OR " oxides of sulfur" OR "oxides of sulphur" OR "SO2" OR "sulfur dioxide" OR "sulphur dioxide" OR "NO2" OR "nitrogen oxides" OR "nitrogen dioxide" OR "oxides of nitrogen"

**Group 3**
"hospital" OR "ice rink" OR "indoor" OR "residential" OR "domestic" OR "indoor environment" OR "indoor pollution" OR "personal exposure" OR "classroom"

**Group 4**
"health effects" OR "asthma" OR "pulmonary function" OR "lung" OR "bronchial constriction" OR "respiratory" OR "diarrhea" OR "neurological" OR "cohort" OR "cancer" OR "toxicology" OR "controlled exposure studies" OR "cross-sectional" OR "epidemiology" OR "case-control"

The results of all searches were imported into Endnote (ISI ResearchSoft, Berkeley, CA) and duplicate references were removed. References for papers published before 1990 were moved to a separate file, and the 6000+ that remained were reviewed for relevance. Literature published prior to 1990 was not considered in the review, except where there was insufficient literature from that date forward and except for “classic” studies vital to the evidence. These exceptions are detailed below.

### 2.2 Inclusion and Exclusion Criteria

Articles specifically related to the following topics were sought for further review:

1. The measurement of indoor concentrations of nitrogen and/or sulfur dioxide. Pre-1990 papers were sought for SO₂ due to limited more recent material.

2. The measurement of personal exposure to nitrogen and/or sulfur dioxide.

3. Studies exploring the relationship between indoor and outdoor concentrations of nitrogen and/or sulfur dioxide. Pre-1990 papers were sought for SO₂ due to limited more recent material.
4. Epidemiological and clinical studies characterizing the relationships between indoor nitrogen and/or sulfur dioxide and human health.

5. Epidemiological studies focused on characterizing the relationship between outdoor sulfur dioxide ambient point sources and human health. Pre-1990 papers were sought due to limited post-1990 material.

6. Epidemiological studies focused on characterizing the relationship between occupational exposures to sulfur dioxide and human health. Pre-1990 papers were sought due to limited post-1990 material.

7. Any review articles covering one or more of the above topics.

Epidemiological and clinical studies which did not include quantitative exposure measurements were usually not considered relevant to the review, since they could not be used to suggest exposure guidelines. Case reports and case series without comparisons to control populations were not considered in the review. In some cases, “classic” studies (described below) that did not meet these criteria were also included in the literature summary.

To identify relevant articles, the references were sorted in Endnote by title and abstract (where available). The 3000+ references that contained at least one of the following keywords (or partial keywords) were moved to a new file for further review.

nitrogen dioxide  NO2  SOx  NO(sub)x  cook  heat
sulphur dioxide  SO2  NO(sub)2  SO(sub)x  gas  combustion
sulfur dioxide  NOx  SO(sub)2  burn

Any of these references that contained one or more of the following keywords (or partial keywords) were considered potentially relevant, and were moved to a new file to be systematically considered on an individual basis.

air  asthma  exposure  hospital  occupation  pulmonary
allergy  domestic  health  indoor  office  respiratory
arena  effect  home  lung  pollut  school

Of the resulting 1300+ references, those concerning experimental studies on animals or in-vitro cell cultures were removed to separate files, and those that were obviously irrelevant were deleted. All remaining articles (approximately 400) were collected from University of British Columbia (UBC) libraries, the Canada Institute for Science and Technical Information (CISTI), or elsewhere through UBC’s interlibrary loan service.
2.3 Categories of Studies

Once collected, the abstracts of all articles were reviewed and the papers were sorted into the seven categories described in Table 2.1, overleaf. In addition, the reference lists for several review articles were searched for consistently-cited papers published prior to 1990. These “classics” (approximately 25) were collected and sorted with the others. Any additional relevant articles cited in the papers already collected were identified and retrieved.

Table 2.1 Categories of Papers Reviewed

<table>
<thead>
<tr>
<th>Category</th>
<th>Approximate Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review</td>
<td>45</td>
<td>Includes all review articles.</td>
</tr>
<tr>
<td>Exposure Only</td>
<td>80</td>
<td>Includes all articles for which personal and/or indoor concentrations were measured without reporting health effects.</td>
</tr>
<tr>
<td>Indoor/Outdoor</td>
<td>10</td>
<td>Includes studies aimed at characterizing the relationship between indoor and outdoor pollutant levels.</td>
</tr>
<tr>
<td>Epi/Exposure</td>
<td>50</td>
<td>Includes all epidemiological studies for which personal and/or indoor concentrations were measured.</td>
</tr>
<tr>
<td>Epi/No Exposure</td>
<td>40</td>
<td>Includes epidemiological studies focussed on the presence of pollutant sources rather than measurements of actual concentration.</td>
</tr>
<tr>
<td>Clinical</td>
<td>100</td>
<td>Includes all clinical and experimental studies on human subjects.</td>
</tr>
<tr>
<td>Ambient</td>
<td>75</td>
<td>Includes studies focussed on the links between human health and ambient air pollution.</td>
</tr>
<tr>
<td>Discard</td>
<td>60</td>
<td>Includes articles that were identified as irrelevant after reading their abstracts.</td>
</tr>
</tbody>
</table>
3 NITROGEN DIOXIDE (NO₂)

3.1 Properties and Sources

Information in this section has been drawn from the following sources:


Nitrogen dioxide is a corrosive and oxidizing reddish-orange-brown gas with a characteristic pungent odour. It belongs to the highly reactive NOₓ (nitrogen oxides) family. The major nitrogen oxides present in indoor air are NO (nitric oxide) and NO₂ (nitrogen dioxide), although other species, such as HNO₃ (nitric acid) and HONO (nitrous acid) are also present in measurable quantities. Table 3.1 summarizes some of the physical and chemical properties of NO₂.

<table>
<thead>
<tr>
<th>PROPERTY</th>
<th>CAS #</th>
<th>Synonyms</th>
<th>Molecular Formula</th>
<th>Structural Formula</th>
<th>Molecular Weight</th>
<th>Air Concentration Units Conversion</th>
<th>Colour</th>
<th>Odour</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS #</td>
<td>10102-44-0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 mg/m³ = 0.53 ppm at 101.3 kPa</td>
<td>Yellowish to dark brown in liquid form; reddish-brown in gaseous form</td>
<td></td>
</tr>
<tr>
<td>Synonyms</td>
<td>dinitrogen tetroxide, nitrogen peroxide, nitrogen oxide, nitrito, nitro</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molecular Formula</td>
<td>NO₂</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structural Formula</td>
<td>O=N–O</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>46.01 g/mol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Air Concentration Units</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Conversion</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Colour</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odour</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melting Point</td>
<td>-11.2°C at 101.3 kPa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boiling Point</td>
<td>21.2°C at 101.3 kPa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Critical Temperature</td>
<td>158.2°C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vapour Pressure</td>
<td>101.33 kPa at 21.1°C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vapour Density</td>
<td>1.58 (air = 1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specific Gravity</td>
<td>1.45 at 20°C (water = 1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solubility in Water</td>
<td>Reacts to form nitric acid (HNO₃) and nitrous acid (HONO)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solubility in Other Liquids</td>
<td>Soluble in alkalies, chloroform, carbon disulfide, concentrated nitric acids and concentrated sulfuric acids</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stability</td>
<td>Normally stable. Thermally decomposes to nitric oxide (NO) and oxygen at temperatures greater than 160°C.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flammability</td>
<td>Does not burn.</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
The reactivity of \( \text{NO}_2 \) plays a significant role in photochemical smog production, as described in the reactions listed below. \( \text{NO}_2 \) produces red-brown discoloration and reduces visibility in the polluted lower troposphere.

\[
\text{NO}_2 + h\nu \rightarrow \text{O} + \text{NO} \quad (1)
\]
\[
\text{O} + \text{O}_2 \rightarrow \text{O}_3 \quad (2)
\]

*Atmospheric Production of \( \text{NO}_2 \)*

\( \text{NO}_2 \) is produced from NO in the atmosphere by the following reactions:

\[
2\text{NO} + \text{O}_2 \rightarrow 2\text{NO}_2 \text{ (slow in ambient air, only important when NO > 1 ppm) (3)}
\]
\[
\text{NO} + \text{O}_3 \rightarrow \text{NO}_2 + \text{O}_2^* \quad (4)
\]
\[
\text{HO}_2^* + \text{NO} \rightarrow \text{NO}_2 + \text{OH}^* \quad (5)
\]
\[
\text{RO}_2^* + \text{NO} \rightarrow \text{RO}^* + \text{NO}_2 \quad (6)
\]

Natural sources of \( \text{NO}_x \) include the burning of biomass (forest fires), organic decay, and lightning. Reactions 4, 5 and 6 are fast, but formation of \( \text{NO}_2 \) in ambient air is predominantly from reactions 4 and 5.

### 3.1.1 Anthropogenic Sources of \( \text{NO}_2 \)

The global nitrogen cycle involves a total flux of approximately \( 350 \times 10^6 \) tons per year, \( 60 \times 10^6 \) tons of which are estimated to be from atmospheric release of \( \text{NO}_x \) from anthropogenic sources. The combustion of fossil fuels and biomass are the most important sources of atmospheric nitrogen, and it is estimated that 5-10% by volume of total \( \text{NO}_x \) emissions from these sources is in the form of \( \text{NO}_2 \).

### 3.1.2 Indoor Sources of \( \text{NO}_2 \)

\( \text{NO}_2 \) exposure indoors can be from outdoor or indoor sources. Indoor \( \text{NO}_2 \) sources include gas-fired appliances (stoves, ovens, etc.), unvented gas space heaters, unvented kerosene heaters, wood stoves, and environmental tobacco smoke. As in ambient air, the primary nitrogen oxide emitted by indoor sources is \( \text{NO} \), which is converted in open flames and in air to \( \text{NO}_2 \).

Indoor sources can contribute significantly to personal exposures. The average level in homes without identified indoor \( \text{NO}_2 \) sources is generally about half of the outdoor level. In homes with gas stoves, kerosene heaters, or unvented gas space heaters, indoor levels can often exceed outdoor levels.
3.1.3 Indoor Nitrogen Oxides Chemistry

Several studies have evaluated the fate of indoor NO\textsubscript{2} in relation to indoor surface reactions and the subsequent formation of reaction products such as HONO [Brauer et al., 1991]. Lee and colleagues [2002] reported that indoor HONO was highly correlated with indoor NO\textsubscript{2} concentrations and corresponded to approximately 17\% of the measured NO\textsubscript{2} concentrations. The relevance of the conversion of NO\textsubscript{2} to HONO to health impacts is that different indoor environments and sources may result in different HONO levels at a given NO\textsubscript{2} concentration. Given that there have been some demonstrations of human health impacts resulting from HONO exposure [Rasmussen et al., 1995], it has been hypothesized that differences in the HONO:NO\textsubscript{2} ratio may account for some of the observed differences in the results of studies of the health effects of NO\textsubscript{2}.

3.2 Toxicologic Characteristics

Section 3.5 reviews the large number of clinical experiments which have exposed human volunteers to nitrogen dioxide. Because the human exposure trials are considered most relevant to human health outcomes, the animal toxicology literature is only briefly summarized here, using the following reviews as a basis.


Following the example set by other reviews of nitrogen oxides [Schlensinger, 2000; US EPA, 1997], this section will place emphasis on the results of experimental animal studies conducted with NO\textsubscript{2} concentrations of 5 ppm (9400 ug/m\textsuperscript{3}) or less, as these are considered to be most relevant to human populations.

3.2.1 Biochemistry

NO\textsubscript{2}-induced lipid peroxidation has been detected at exposure levels between 0.04-5 ppm (75-9,400 ug/m\textsuperscript{3}) in live animals and in \textit{in vitro} systems. Lipid peroxidation results in the alteration of phospholipids, leading to changes in the physical state of membrane tissue, disruption of enzyme activity, and subsequent impairment of membrane function. It is believed to be an important biochemical mechanism in NO\textsubscript{2} toxicity, contributing to many of the other effects associated with exposure.

Nitrogen dioxide exposures between 1-10 ppm (1880-18800 ug/m\textsuperscript{3}) have also been shown to disrupt the function of non-membranous enzymes in the lung, potentially leading to damage of important structural proteins. Because NO\textsubscript{2} is an oxidant, much of
the research concerned with mitigation of these toxic effects has been centred on antioxidants such as glutathione, vitamin E and vitamin C, the protective effects of which have been demonstrated in both \textit{in vivo} and \textit{in vitro} systems.

3.2.2 Pulmonary Effects

Research indicates that ciliated bronchial epithelial cells are sensitive to the effects of \( \text{NO}_2 \) exposure at levels ranging from 0.5-5 ppm (940-9,400 \( \text{ug/m}^3 \)). Damage sustained to the cilia results in reduced mucociliary clearance. It has also been demonstrated that similar levels of nitrogen dioxide (0.3-4 ppm) affect the structure and function of the alveolar macrophages that are responsible for absorbing waste material and pathogenic microorganisms. The severity of these effects is dependant on the magnitude and duration of the exposure studied.

Chronic exposure (52 weeks or more) to \( \text{NO}_2 \) concentrations between 0.5-6 ppm (940-11,280 \( \text{ug/m}^3 \)) has resulted in the reduction of end-expiratory volume, vital capacity, and forced expiratory flow rate, and in increased airway responsiveness to histamine. It is interesting to note that more significant changes were generally observed in studies that superimposed peak concentrations on the baseline exposure. It is also important to note that in many cases the results of different studies with similar designs simply do not agree, and that many lung function studies conducted at the aforementioned concentrations reported no significant findings. This is analogous to the disparities observed in human clinical studies, discussed in section 3.5.

3.2.3 Immune Response

The effect of inhaled nitrogen dioxide on immune response is an important manifestation of \( \text{NO}_2 \) toxicity. Acute, sub-chronic and chronic exposures to concentrations ranging from 0.2-5 ppm (370-9400 \( \text{ug/m}^3 \)) have resulted in compromised immune response at different functional levels.

To begin, the previously discussed damage to ciliated cells and alveolar macrophages reduces the effectiveness of early response mechanisms, and allows infectious agents to move more easily between the environment and potential hosts. If these agents cannot be removed from the respiratory tract, the next stage of immune response is provided by lymphocytes which circulate in body fluids (B-cells) or cluster in lymph organs (T-cells) and identify antigens and replicate the appropriate antibodies. Short- and long-term exposure to nitrogen dioxide has been shown to reduce lymphocyte counts, and to suppress the speed at which they are capable of synthesizing antibodies.

The significance of these results has been seen in comparative mortality trials, in which control and \( \text{NO}_2 \)-exposed animals are subsequently exposed to bacteria or viruses, and the number of deaths in each group are compared. Studies using different species and different exposure levels have consistently demonstrated \( \text{NO}_2 \)-induced suppression of immune response, but results have varied markedly between specific infectious agents. Unfortunately, little of this research has been done with agents that specifically target the
respiratory tract, and the effect of NO₂ on host response to respiratory diseases is largely unknown.

3.2.4 Other Effects

There has been some concern about the possible carcinogenic effects of nitrogen dioxide, mostly due to the fact that exposure can result in nitrate in the blood, which, after further reactions in the body, may produce nitrogen-based carcinogens. There is little hard evidence to support any link between nitrogen dioxide exposure and cancer, and the few studies that have shown any significant tumour development (after chronic exposure to 10 ppm) have been severely criticized by the scientific community for methodologic faults. Nitrogen dioxide has not been classified by the International Agency for Research on Cancer (IARC).

Research concerning the genotoxicity of NO₂ is limited, and the interpretation of the results remains unclear. Most studies are conducted in vitro at concentrations much greater than 5 ppm with varied and unpredictable findings. Hamster cells exposed to 1-8 ppm (1880-15,000 ug/m³) have yielded equally inconclusive results about the nature of the relationship between NO₂ exposure and changes to DNA at lower concentrations.

Finally, there is some limited evidence supporting the potential for NO₂ to affect extrapulmonary endpoints, such as birth weight, blood chemistry, and liver function. The data do not provide consistent evidence in either direction. This work is a reminder, however, that biochemical changes induced by NO₂ have the potential to affect the whole body, and not just the respiratory system.

3.3 Personal and Indoor Exposure to NO₂

A total of 83 separate studies were reviewed to compile the following information regarding indoor NO₂ sources and concentrations and major determinants of exposure. The studies that were reviewed were conducted mainly in North America or Western Europe. Three were conducted in Canada. Table 3.2 (overleaf) indicates the number of studies from different locations.

The articles, including their quantitative information about exposure levels, are summarized in Table 3.3, which can be found at the back of this report.
Table 3.2 Numbers of Studies of Personal and Indoor NO\textsubscript{2} Exposure, by Continent and Country

<table>
<thead>
<tr>
<th>LOCATION</th>
<th>NUMBER OF STUDIES</th>
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<tbody>
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<tr>
<td>Croatia</td>
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<td>Sweden</td>
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<tr>
<td>Greece</td>
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<tr>
<td>Italy</td>
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<tr>
<td>Bulgaria</td>
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<tr>
<td>Switzerland</td>
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<td>Norway</td>
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<tr>
<td>Denmark</td>
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</tr>
<tr>
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<td>Singapore</td>
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<td>Australia</td>
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<td>Middle East (Bahrain)</td>
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<tr>
<td>Africa (South Africa)</td>
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<td>International Studies</td>
<td>2</td>
</tr>
<tr>
<td>Unspecified</td>
<td>2</td>
</tr>
</tbody>
</table>

3.3.1 Indoor Sources of NO\textsubscript{2}

Gas-Fired Appliances

Numerous studies have shown that residences with gas stoves or gas heaters have higher NO\textsubscript{2} levels than those with electric appliances [Speizer et al., 1980; Berwick et al., 1989; Melia et al., 1990; Quakenboss et al., 1991; Adgate et al., 1992; Lambert et al., 1992; Saga et al., 1992; Infante-Rivard, 1993; Spengler et al., 1994; Lee et al., 1995; Sega et al., 1995; Arashidani et al., 1996; Linaker et al., 1996; Ross 1996; Cotterill et al., 1997; Farrow et al., 1997; Lolova et al., 1997; Pilotto et al., 1997; Alm et al., 1998; Bernard et
al., 1998; Garrett et al., 1998; Levy 1998; Monn et al., 1998; Cyrys et al., 2000; Lee et al., 2000; Smith et al., 2000; Dennekamp et al., 2001; Kousa et al., 2001; Ponsonby et al., 2001; Rjinders et al., 2001; Rotko et al., 2001; Lee et al., 2002]. These studies were conducted in locations with different climates and population densities and in a variety of countries, indicating that the impact of gas stoves and heaters on indoor NO$_2$ concentrations is universal and consistent, although there is variability in the quantitative impact of these appliances. A study by Neas et al. [1991] indicated that gas sources were associated with an increase in long-term average NO$_2$ concentrations of approximately 28 ug/m$^3$ (15 ppb) which, depending upon outdoor concentrations, could correspond to a doubling of outdoor levels. A more recent study [Levy, 1998] suggests that gas appliances are associated with more modest increases, approximately 70% greater than outdoor concentrations.

An international study conducted in 19 cities in 15 different countries indicated that gas ranges, as well as kerosene heaters and environmental tobacco smoke were significant predictors of increased personal exposures to NO$_2$ [Levy, 1998]. Some of these studies included only a few homes with gas stoves [Rotko et al., 2001; Infante-Rivard, 1993], but even in these cases, an increase in levels was observed.

**Pilot Lights**

Three studies specifically evaluated the impact of gas stove pilot lights on indoor NO$_2$ levels [Lambert et al., 1992; Spengler et al., 1994; Lee et al., 1995]. In all cases, gas stoves with pilot lights were associated with higher NO$_2$ levels in the home compared to gas stoves without pilot lights. Spengler et al. [1994] found a 5.3 ug/m$^3$ (10 ppb) increase in personal exposures for gas stoves with pilot lights compared to a 2.1 ug/m$^3$ (4 ppb) increase for gas stoves without pilot lights. Lambert et al. [1992] reported similar results.

**Ventilation**

Three studies assessed the impact of gas stove and/or heater ventilation on NO$_2$ levels indoors [Ponsonby et al., 2001; Smith et al., 2000; Dennekamp et al., 2001]. Ponsonby et al. [2001] and Smith et al. [2000] both reported that unvented gas stoves and heaters were associated with higher NO$_2$ levels inside the home than vented gas stoves or electric stoves. Posonby et al. [2001] reported a geometric mean concentration of 7.9 ppb (14.8 ug/m$^3$) for homes with electrical heating and cooking appliances, a 3.3 ppb (6.2 ug/m$^3$) increase in the geometric mean for homes with ventilated gas heaters and a 6.6 ppb (12.4 ug/m$^3$) increase in the geometric mean for homes with unvented gas heaters. A controlled experiment on electrical versus gas stoves conducted by Dennekamp et al., [2001] indicated that no NO$_2$ is released when cooking on an electric stove. NO$_2$ concentrations of up to 1880 ug/m$^3$ (996 ppb) were reported for cooking on an unvented gas range with all four rings lit. The peak concentration was dependent upon the specific cooking activity being conducted. No NO$_2$ was measured when the gas stove was turned off.
**Hot Water Heaters (Geyser)**

In the Netherlands, unvented gas-fired hot water heaters (“geysers”) were a historical source of elevated indoor concentrations. Five studies indicated that homes with these heaters had higher levels of NO$_2$ than those without [Fischer et al., 1989; Brunekreef et al., 1990; Dijkstra et al., 1990; Houthuysen et al., 1990; Noy et al., 1990]. As with gas stoves, venting of the heaters was shown to have an effect on NO$_2$ levels. These studies reported that homes with unvented geysers had indoor concentrations that were 20–40 ug/m$^3$ (10–21 ppb) higher than the concentrations in homes with vented geysers. Homes with vented geysers had NO$_2$ concentrations that were 20-44 ug/m$^3$ (7.5-38 ppb) higher than homes without geysers.

**Kerosene Heaters**

Six studies found kerosene heaters to be associated with higher NO$_2$ levels [Berwick et al., 1989, Maeda, Nitta and Nakai 1992, Kawamoto et al., 1993, Arashidani et al., 1996, Farrow et al., 1997, Kulkarni et al., 1998, Levy 1998]. Although the quantitative impact of kerosene heaters varies from study to study, increases as high as 130 ug/m$^3$ (70 ppb) compared to homes with no gas appliances have been reported, producing a 10-fold increase in personal exposures [Adgate et al., 1992, Kawamoto et al., 1993]. Arashidani et al. [1996] conducted an experimental study that evaluated emissions from different heaters with different types of ventilation under controlled conditions; they found that ventilation could reduce NO$_2$ levels indoors.

**Environmental Tobacco Smoke**

In contrast to the sources described above, there is weaker evidence associating environmental tobacco smoke with increased indoor NO$_2$ levels. Three studies showed no association between NO$_2$ levels and smoking [Madany and Danish 1991; Hackney et al., 1992; Kawamoto et al., 1993]. Positive associations between smoking and indoor concentrations were reported in six studies [Linaker et al., 1996; Farrow et al., 1997; Alm et al., 1998; Levy 1998; Monn et al., 1998; Cyrys et al., 2000]. Cyrys et al. [2000] reported an 18% increase in NO$_2$ levels indoors due to the presence of a smoker, while Monn et al. [1998] reported that the personal exposure of individuals who smoked was between 2-6 ug/m$^3$ (1 – 3 ppb) higher than for non-smokers.

### 3.3.2 Outdoor Sources of NO$_2$

In addition to indoor sources of NO$_2$, infiltration of NO$_2$ from outdoor air also contributes to indoor concentrations. The absolute increase in indoor NO$_2$ concentrations due to contaminated outdoor air and the proportion of indoor NO$_2$ that can be attributed to outdoor versus indoor sources will clearly vary from location to location, depending upon outdoor NO$_2$ concentrations and infiltration rates.
Traffic

Eight studies reported an association between indoor NO2 levels and levels of or proximity to traffic [Ekberg 1995; Mukala et al., 1996; Farrow et al., 1997; Nayebzadeh et al., 1999; Norback et al., 2000; Gauvin et al., 2001; Rijinders et al., 2001; Rotko et al., 2001]. Three studies showed an association between indoor levels of NO2 and outdoor concentrations [Liao et al., 1991; Garrett et al., 1998; Chao and Law 2000]. Cyrys et al [2000] and Sega [1995] found that outdoor levels were associated with indoor levels during the summer when windows were opened.

Four studies showed that indoor levels of NO2 are higher in urban compared to rural areas, possibly due to differences in traffic [Chan et al., 1990; Mukala et al., 1996; Raaschou et al., 1997; Cyrys et al., 2000], though one study by Fischer et al [1989] did not measure any urban:rural difference.

Season

Relatively few studies explicitly evaluated the impact of season on indoor NO2 concentrations. As part of the Harvard Six Cities Study, Neas et al. [1991] demonstrated that indoor levels were higher in winter than in summer in all cities, in homes with a major indoor NO2 source. On average indoor concentrations were 7.8 ppb (14.7 ug/m³) higher in winter than in summer in these homes. This seasonal effect was not observed for homes without an indoor source [Neas et al., 1991]. Adgate et al.[1992] reported similar findings for a smaller number of homes in North Carolina. An extended study in Albuquerque reported that indoor NO2 concentrations can vary significantly from year to year [Schwab et al., 1993]. Winter concentrations were 6-12 ppb (11 – 23 ug/m³) higher than summer concentrations for homes with a gas stove with a pilot light, and 6-8 ppb (11-15 ug/m³) higher for homes with a gas stove without a pilot light. Sega et al. [1995] reported on measurements conducted in Zagreb, Croatia and concluded that outdoor concentrations contributed more to indoor concentrations in summer than in winter.

In homes without gas stoves, indoor concentrations were higher in summer than in winter while the opposite was true for homes with NO2 sources. Neas et al. [1991] reported a similar relationship in summer for the cities with the highest outdoor NO2 concentrations. Similar summer relationships were also reported for residential measurements in Hamburg and Erfurt, Germany [Cyrys et al., 2000]. Camuffo et al. [1999] reported that indoor concentrations in a museum in Venice did not differ by season even though outdoor NO2 concentrations were significantly higher in the winter. The authors suggested that in summer, air exchange, and consequently the penetration of NO2, was greater.

Together these studies indicate that indoor concentrations are determined by a complex interaction between the outdoor concentration, the ventilation rate and the presence of indoor sources. For environments with indoor sources, winter concentrations tend to be higher due decreased air exchange and, in some cases, increased use of the source appliance. In indoor environments without sources, summer concentrations tend to be
higher than winter concentrations due to increased air exchange in summer, although this relationship in also dependent upon the level and seasonal differences in outdoor NO₂ concentrations.

### 3.3.3 NO₂ Exposure in Ice Rinks

Major non-residential, indoor sources of exposure are ice rinks. [Paulozzi et al., 1993; Bergland et al., 1994; Brauer and Spengler 1994; Lee et al., 1994; Lee et al., 1994; Yoon et al., 1996; Brauer et al., 1997; Pennanen et al., 1997; Rosenlund et al., 1999]. High indoor NO₂ levels in these facilities have been associated with the use of propane fuelled ice resurfacers and lack of mechanical ventilation. Indoor concentrations in ice rinks are typically 10 times higher than outdoor concentrations and may be extremely high (> 2000 ppb). Bergland et al., [1994] reported that children who ice skate have higher personal NO₂ exposures than children who do not skate.

### 3.3.4 Summary

Gas stoves, kerosene heaters and gas-fired hot water heaters (geysers) all increase NO₂ levels in the home. This has also been the case for non-industrial occupational settings (schools and offices). The magnitude of the increase is dependent on ventilation (homes with less ventilation generally report higher concentrations). For homes with gas stoves or heaters, the presence of a pilot light and the frequency of use (in the winter, heaters tend to be used more than in the summer) also affect the magnitude of the indoor source. Outdoor sources, such as traffic can also contribute to indoor levels, especially in urbanized areas. This association is stronger in the summer when outdoor air is readily introduced indoors through windows. Smoking may also contribute to elevated indoor NO₂ levels. The indoor air volume may also be associated with indoor NO₂ levels [Sega et al., 1992; Kulkarni et al., 1998], as smaller homes are expected to have higher indoor concentrations for a given source emission rate. Many studies have shown that short-term peak exposures to NO₂ from exposure to unvented gas stoves have reached levels that exceed national standards. While gas fireplaces were not evaluated as specific sources in the literature that was reviewed, there is little reason to believe that they would in fact be major sources as they are vented. It is expected that the impact of unvented gas fireplaces would be similar to unvented gas heaters that are discussed in detail in this report.

In an Australian study, lower socio-economic class was found to result in higher NO₂ levels in the home, by about 2 ug/m³ (4ppb) [Ciuk et al., 2001]. No such relationship was found by Rotko et al. [2001] who measured lower NO₂ personal exposures among unemployed men in Finland; this result may have been confounded by a lower use of appliances among the unemployed. More study is required before drawing any conclusions on the effect of economic status on NO₂ exposure.

Ice rinks, especially those with propane fuelled ice resurfacers, have been consistently found to have high NO₂ concentrations. There have been incidents when the levels of NO₂ were high enough to cause acute adverse human health outcomes. Given the
popularity of ice-skating and associated activities in Canada, exposures in ice rinks may be an important source of population exposure to NO$_2$.

Many investigators have commented on the problems with using outdoor ambient monitoring data as a surrogate estimate of indoor concentrations or personal exposure to NO$_2$ [Bergland et al., 1994; Alm et al., 1998; Gauvin et al., 2001; Kousa et al., 2001]. Outdoor levels tend to be lower than and only moderately correlated with the levels measured indoors, suggesting that reliance on ambient monitoring to predict indoor exposure is not appropriate. In an international survey, the correlation between outdoor concentrations and personal exposures across all locations was 0.57, lower than the correlation between indoor concentrations and exposures ($r = 0.75$) [Levy 1998]. Similar results have been reported in other studies, with lower correlations between outdoor concentrations and personal exposures ($r = 0.5 – 0.6$) generally observed when indoor sources are present or operating [Alm et al., 1998].

### 3.4 Epidemiological Studies of Populations Exposed to NO$_2$

A total of forty-one epidemiological papers were reviewed, three of which report on a single study. Thirty-four of these papers were published in 1990 or later, and seven “classic” studies published prior to 1990 were included. The general characteristics of these papers are summarized in Table 3.4, and the specific details of each are summarized in Table 3.5 at the back of this report. With a few exceptions, we limited the review to those studies in which NO$_2$ measurements (either measurements of indoor concentrations or personal exposures) were made. Numerous studies comparing individuals living in homes with or without suspected NO$_2$ sources were not considered. In the studies that were evaluated, NO$_2$ exposures or indoor concentrations varied between “zero” ppb and 292 ppb (549 ug/m$^3$). In addition, two studies evaluated somewhat higher exposures associated with industrial and ice arena exposure: 11 ppb to 1254 ppb (21-2542 ug/m$^3$).

Although many of the studies considered more than one health outcome, the majority focused on general respiratory symptoms and diseases. These studies typically relied on subject self-reporting through questionnaires and/or diaries.
Table 3.4 Numbers of Epidemiological Studies of NO\textsubscript{2}, by Study Design and Characteristics

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>NUMBER OF STUDIES</th>
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<td>Children</td>
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<tr>
<td><strong>Measured Outcome</strong></td>
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<tr>
<td>Respiratory Symptoms, Illnesses and Diseases</td>
<td>33</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
</tr>
</tbody>
</table>

*total is greater than 41 (the number of studies) because several studies evaluated several different groups.

3.4.1 Studies of Respiratory Symptoms and Disease

*Adults*

Five studies reported on respiratory symptoms and diseases in adults exposed to indoor NO\textsubscript{2}; two of these found a positive association between NO\textsubscript{2} exposure and respiratory health. In a cross-sectional study conducted by Koo et al. [1990], 24-hour indoor NO\textsubscript{2} samples were collected for 319 women, and a dose-response relationship was reported for multiple respiratory symptoms with increasing NO\textsubscript{2} concentration. In another cross-sectional study, conducted by Maeda et al., [1992], 48-hour personal, indoor and outdoor exposures were measured for 1,991 women living in three zones (defined by their proximity to heavy traffic). Women in zone A (within 20 m of a major road) had a mean personal exposure of 83 ug/m\textsuperscript{3} (44 ppb), and had significantly higher prevalence of chronic phlegm, chronic wheezing and shortness of breath than women in zone B (20-150 m from a major road, mean personal exposure of 37 ppb) and zone C (residential neighbourhood, mean personal exposure of 29 ppb).
The other three studies [Hackney et al., 1992; Smith et al., 2000; and Kilpelainen et al., 2001] found no significant relationship between indoor and/or personal NO$_2$ exposure and increased incidence of respiratory symptoms. The 28 subjects studied by Hackney et al. [1992] were older (aged 45-70), physician-diagnosed COPD patients with a history of heavy smoking and low FEV$_1$, and the 76 adult subjects studied by Smith et al. [2000] were physician-diagnosed asthmatics. In Hackney et al. [1992], subjects self-monitored for personal exposure (passive badges), lung-function (spirometry) and clinical status (diaries) on a 24-hour basis for two weeks. Halfway through each week some subjects were exposed for 4-hours to 560 ug/m$^3$ (300 ppb) NO$_2$ in an environmental chamber, and some were exposed to ambient air, and the results for both groups were compared. Although no significant associations between NO$_2$ and lung function were found, the clinical aspect of this study may reduce its relevance to populations exposed to ambient conditions.

**Infants**

Six studies reported on the association between NO$_2$ exposure and respiratory symptoms and illnesses in children less than two years of age. Of these, only Samet et al. [1992] reported results that indicated some relationship between NO$_2$ and respiratory health effects. 411 infants were followed for 2 years after birth. The incidence of respiratory illness was found to be highest in winter (1.6/100 days, upper tract; 1.0/100 days, lower tract) when indoor NO$_2$ levels were highest in gas-heated homes (approximately 75% of the homes in the study). In 1993, Samet et al. published another study involving the same cohort. All subjects (823) who had participated in at least 30 days of follow-up were grouped into three exposure categories (0-20 ppb, 20-40 ppb and greater than 40 ppb) and no significant association between NO$_2$ and incidence of respiratory illness was found. In studies of similar cohorts, Ogston et al. [1985] and Farrow et al. [1997] found no significant association between NO$_2$ exposure and the respiratory health of infants.

In a nested case-control study conducted by Magnus et al. [1998], the NO$_2$ exposure of 153 infants who developed two or more episodes of persistent (longer than 4 weeks) bronchial obstruction was compared to that of controls matched on date of birth. Parallel monitoring was carried in the homes of cases (mean concentration = 15.7 ug/m$^3$ or 8.3 ppb) and controls (mean concentration = 15.4 ug/m$^3$ or 8.2 ppb).

In their study of a cohort of children aged 6 to 10, Speizer et al. [1980] reported that children living in homes with gas stoves had a significant increase in respiratory illness before the age of 2 (OR = 1.1, 95% CI: 1.0-1.3). The retrospective exposure information came from a questionnaire distributed to the parents and guardians of the 8,866 subjects; NO$_2$ exposures were not measured.

**Children**

Twenty-two studies (one of which resulted in three papers) reported on the relationship between NO$_2$ exposure and respiratory symptoms and diseases in children older than two years of age. The study populations for eight of these included identified asthmatics, and
five of them focussed on the development of asthma as the health outcome of interest. Infante-Rivard [1993] and Garrett et al. [1998] drew the similar conclusion that children from homes with elevated levels of NO\textsubscript{2} are at an increased risk of developing asthma. Infante-Rivard [1993] reported NO\textsubscript{2} concentration differences of greater than 28 \textmu g/m\textsuperscript{3} (15 ppb) between the Montreal homes of 3- and 4-year-old asthmatic children and their age-matched non-asthmatic controls (OR = 10.5, 95% CI: 3.5-40). Garrett et al. [1998] report an increased risk of asthma in 7- to 14-year-olds living in homes with gas stoves (OR = 2.2, 95% CI: 1.1-4.5). In contrast, Smedje et al. [1997], Ciuk et al. [2001] and Ponsonby et al. [2001] found no significant relationship between NO\textsubscript{2} exposure and asthma prevalence. Four of these studies included fewer than 350 subjects (Smedje et al. [1997] had 627 subjects), and three were conducted in Australia, which may limit their applicability to Canadian circumstances.

In a cross-sectional study comparing the environments of asthmatic children (n = 30) and non-asthmatic children (n = 202), Quackenboss et al. [1991] found that children living in homes with high levels of NO\textsubscript{2} were at increased risk of suffering from allergic symptoms. The estimated odds ratio per 10 \textmu g/m\textsuperscript{3} (5 ppb) increase in exposure was 1.6 (95% CI: 1.0-2.5) for asthmatics, and 1.2 (95% CI: 1.0-1.4) for non-asthmatics. No association was found between NO\textsubscript{2} concentration and other respiratory symptoms. In a case-control study comparing children with chronic respiratory illnesses (n = 128) to age- and location-matched controls (n = 103), Hoek et al. [1984] found no significant association between residential NO\textsubscript{2} concentrations (ranging from 110 to 789 \textmu g/m\textsuperscript{3} in the kitchen; 58 to 420 ppb) and respiratory symptoms. In a study involving only asthmatic subjects, Smith et al. [2000] report that personal NO\textsubscript{2} exposure (ranging from 22 to 126 \textmu g/m\textsuperscript{3}; 12 to 67 ppb) was not significantly associated with exacerbations of asthmatic symptoms. Once again, these three studies were relatively small in size, which limits the detection of general patterns, something that must be considered when interpreting the reported results.

Of the remaining fourteen studies, nine found some significant association between NO\textsubscript{2} exposure and respiratory symptoms [Melia et al., 1979; Berwick et al., 1989; Neas et al., 1991; Maeda et al., 1992; Mukala et al., 1996, 1999 and 2000; Pilotto et al., 1997; Roselund and Bluhm, 1999; Sanyal and Maduna, 2000; and Shima and Adachi, 2000], while the other five did not [Speizer et al., 1980; Melia et al., 1982; Dijkstra et al., 1990; Koo et al., 1990; and Gomzi et al., 1999]. In 1973, a cohort of 4,827 children aged 6 to 11 was established with the goal of determining whether or not the presence of a gas stove in the home had any impact on their respiratory health. Melia et al. [1979] followed the cohort for four years, and it was found that the crude and adjusted (age, sex, social class, smokers and latitude) prevalence of one or more respiratory symptom or disease was higher in children from homes with gas stoves than in those from homes with electric stoves. It was also reported that the crude prevalence of cough in boys and chest colds in girls was higher for those from homes with gas stoves. These trends applied only to children living in urban areas; no association between gas stoves and respiratory health was found for children living in rural areas.
Four other studies considered the effect of the presence of an NO\textsubscript{2} source inside or near to the home. Berwick \textit{et al.} [1989], Maeda \textit{et al.} [1992] and Sanyal and Maduna [2000] report associations between respiratory symptoms and NO\textsubscript{2} sources. Berwick \textit{et al.} [1989] studied 121 children younger than 13 (mean age 6.7) and reported that children younger than 7 who lived in homes with kerosene heaters had a higher incidence of respiratory symptoms and illness than those with electric heating. Indoor exposures of 30 ug/m\textsuperscript{3} (16 ppb) or greater were associated with and odds ratio of 2.3 (95\% CI: 1.7-4.8). Maeda \textit{et al.} [1992] studied 305 children living at different distances from a busy road, and found that those living up to 20 meters from the road (which corresponded with the highest personal NO\textsubscript{2} exposure, measured for adult subjects) had a significant increase in the prevalence of chronic phlegm. Sanyal and Maduna studied 1,820 children under the age of 14 and found that the prevalence of respiratory illness was higher for those living in residences where wood, coal and kerosene were used for cooking. Although Speizer \textit{et al.} [1980] reported a significant association between gas stoves and respiratory illness before the age of two, no association was found between current exposure and prevalence of respiratory symptoms in the cohort.

Other research has placed more emphasis on the direct relationship between measured NO\textsubscript{2} exposures and respiratory health outcomes. Melia \textit{et al.} [1982] further investigated the trends discussed above with a cross-sectional population of 5 and 6 year olds living in homes with gas stoves. Weeklong NO\textsubscript{2} measurements were made in bedrooms and living rooms, and children were separated into three exposure categories: less than 38 ug/m\textsuperscript{3} (20 ppb), between 38 and 76 ug/m\textsuperscript{3} (20 and 40 ppb), and greater than 76 ug/m\textsuperscript{3} (40 ppb). For both sexes, the unadjusted prevalences of one or more respiratory conditions were positively associated with living room concentrations, but this relationship disappeared after adjusting for age, sex, social class, smokers in the household and humidity. The authors point out that NO\textsubscript{2}-related health effects might be difficult to detect in such a small population sample.

Koo \textit{et al.} [1990] conducted a similar cross-sectional study with 362 children (mean age 10) and collected samples every 24 hours instead of every 7 days, but no significant association was found between the measured NO\textsubscript{2} levels and respiratory symptoms. Also in 1990 Dijkstra \textit{et al.} published the results of a relatively large longitudinal study, in which 1,051 children aged 6 to 12 were followed for two years. Nitrogen dioxide concentrations between 11 and 33 ug/m\textsuperscript{3} (5.9 – 17.7 ppb) were recorded in homes with no indoor source, and between 11 and 67 ug/m\textsuperscript{3} (5.9 – 35.5 ppb) in homes with a source, but no association between these concentrations and the respiratory health of the children was found. Gomzi \textit{et al.} [1999] monitored NO\textsubscript{2} in conjunction with ammonia and particulate matter at two Croatian schools. No direct relationship between reported respiratory symptoms and mean concentrations of 8-12 ug/m\textsuperscript{3} (4-6 ppb) NO\textsubscript{2} were found.

In 1991, Neas \textit{et al.} published a study reporting that a 28 ug/m\textsuperscript{3} (15 ppb) increase in annual household NO\textsubscript{2} concentrations was associated with increased incidence of lower respiratory symptoms (OR = 1.4, 95\% CI = 1.1-1.7). 1,567 children between 7 and 11 years of age participated, and this trend was more pronounced in girls than in boys. Pilotto \textit{et al.} [1997] studied 388 subjects between 6 and 11 years of age living in homes...
with unvented gas appliances. It was reported that NO\(_2\) concentrations greater than 150 ug/m\(^3\) (80 ppb) were positively associated with sore throats, colds and absences from school of 3 days or longer. Statistically significant dose-response relationships were found for rates of cough with phlegm, sore throat, and absences from school. Similarly, Shima and Adachi [2000] found a significant increase in the incidence of bronchitis, wheeze and asthma associated with indoor NO\(_2\) concentrations among 824 children aged 9 and 10. In three papers resulting from a prospective cohort study involving 172 6-year-old children, Mukala et al. [1996; 1999; 2000] reported an increased risk of cough with increasing NO\(_2\) exposure (RR = 1.5, 95% CI = 1.0-2.3), especially evident in the highest exposure group (greater than 27.2 ug/m\(^3\), or 14.5 ppb) in winter (RR = 3.6; 95% CI = 1.4-9.3).

Finally, Roselund and Blumm [1999] compared a population of 99 adolescent hockey players exposed to high NO\(_2\) concentrations at an ice arena to 56 unexposed controls. Risk ratios for many respiratory symptoms were high. In order to determine what level of NO\(_2\) concentration was associated with these health effects, the investigators attempted to re-create the conditions in the arena at the time of exposure. Concentrations up to 2,400 ug/m\(^3\) (1,250 ppb) were recorded, but it is not certain that concentrations were in the same range at the time of exposure.

While inconsistencies remain, the studies reviewed do provide some evidence that children, but not necessarily infants, are a population subgroup that may be susceptible to respiratory symptoms associated with NO\(_2\) exposure. The relatively large study conducted by Neas et al. [1991] indicated an increased risk of respiratory symptoms for 7-11 year old children associated with relatively small differences in long-term exposures to NO\(_2\). These findings are consistent with those of Melia et al. [1979], who compared children living in homes with gas versus electrical appliances.

3.4.2 Studies of Lung Function

Adults

Five studies reported on pulmonary function in adults and NO\(_2\) exposure; two of these were conducted with subjects from sensitive sub-populations. In a study involving 16 asthmatics, Ng et al. [2001] investigated lung function response to NO\(_2\) exposure during use of gas-fired stoves. Short-term cooking resulted in concentrations between 0.03 and 490 ug/m\(^3\) (0.016 and 260 ppb) with a mean of 121 ug/m\(^3\) (64 ppb). These levels were associated with a mean decrease of 3.4% (95% CI = 0.8-5.9%) in peak expiratory flow rate (PEFR). The authors also noted that longer cooking times resulted in smaller changes in PEFR, but were associated with increased use of bronchodilators. Hackney et al. [1992] reported no significant association between NO\(_2\) and lung function in 26 COPD subjects.

Two of the studies in healthy populations reported a significant decrease in lung function associated with NO\(_2\) exposure. Schindler et al. [1998] reported that a 10 ug/m\(^3\) (5 ppb) increase in long-term average NO\(_2\) exposure resulted in a decrease of 2.9% (95% CI =
2.1-3.8%) in forced vital capacity (FVC), though no significant change in forced expiratory volume (FEV$_1$) was found. Considerable variability was observed in the measured personal exposures due to outdoor sources in some areas included in the study, and therefore exposure-related differences in lung function may be due, in part, to the presence of other air pollutants. Fisher et al. [1989] also showed a significant decrease in lung function associated with NO$_2$ exposure although this finding was limited to those study subjects living in a rural area. Maeda et al. [1992] reported no association between NO$_2$ exposure and lung function. Together these studies do not provide strong support for an association between indoor NO$_2$ exposure and reduced pulmonary function.

**Children**

Eight studies reported on associations between NO$_2$ exposure and children’s lung function. Three included asthmatic subjects, and all of these found a significant association between NO$_2$ and reduced lung function. Quackenboss et al. [1991] (studying 30 asthmatic children aged 6 to 15 years) report a 40 L/min decrement in PEFR for every 20 ug/m$^3$ (19 ppb) increase in NO$_2$. Additional decrements of morning PEFR were seen in children whose bedrooms had high NO$_2$ concentrations. Linaker et al. [2000] studied 114 asthmatic children (aged 7 to 12 years) and reported a dose-response relationship between the number of episodes of reduced PEFR and increasing NO$_2$ exposure. Ponsonby et al. [2001] found that FEV$_1$/FVC was reduced for children with higher NO$_2$ exposures, for children living in homes with gas heaters, and for children who were not mite-sensitized. No differences between asthmatic and non-asthmatic subjects were reported.

Of the remaining studies of healthy subjects, only Speizer et al. [1980] report a significant, but small, association between NO$_2$ and lung function. Children living in homes with gas stoves were found to have slightly decreased FVC and FEV$_1$ compared to children living in homes with electric stoves. Brunekreef et al. [1990], Dijkstra et al. [1990], Demissie et al. [1998] and Mukala et al. [1999] all found no association between NO$_2$ exposure and pulmonary function in children.

### 3.4.3 Studies of Other Health Outcomes

**Adults**

Bernard et al. [1997] studied 107 smoking adults (who smoked fewer than 10 cigarettes per day) and compared personal NO$_2$ exposures to levels of plasma anti-oxidants. An inverse relationship was found between NO$_2$ concentrations and levels of uric acid and glutathione (GSH), in men only. No correlation was found between NO$_2$ and malondialdehyde (MDA) or B-carotene. Giroux et al. [1998] studied male nitrogen fertilizer workers and found that those most exposed to hydrogenated and oxygenated nitrogen compounds had the highest levels of serum nitrates. Norback et al. [2000] report that nasal patency decreased with NO$_2$ exposure, while levels of lysozyme and eosinophil cationic protein (ECP) increased.
Infants and Children

Beyond the standard respiratory symptoms commonly studied, some investigators included other symptoms such as abdominal pain, diarrhoea, fever, dizziness, and headache. Of the four studies that reported on these symptoms [Quackenboss et al., 1991; Mukala et al., 1996 and 1999; Farrow et al., 1997; and Sanyal and Maduna, 2000], only Farrow et al. [1997] report significant findings. An increase in incidence of diarrhoea was associated with a doubling of indoor NO\textsubscript{2} exposure (OR = 1.4, 95% CI = 1.1-1.7) in a cohort of 921 infants aged 3 to 12 months. In another study focussed on urinary excretion, Adgate et al. [1992] reported no relationship between NO\textsubscript{2} and hydroxyproline to creatine ratios.

3.5 Studies of Controlled Human Exposures to NO\textsubscript{2}

3.5.1 Overview of Studies

A total of 34 controlled human exposure studies were reviewed, 32 of which were published between 1990 and 2001. Summaries of all these studies can be found in Table 3.6, located at the end of this report. The two pre-1990 studies [Orehek et al., 1976; Goings et al., 1989] were “classic” studies, frequently referred to in the literature. In addition, two meta analyses [Folinsbee et al., 1992; Rasmussen et al., 1992] and one review article [Samet et al., 1990] which focused on pre-1990 studies were examined.

Within the 34 studies, subjects ranged from 8 to 85 years of age. Most studies focussed on adults aged 18 to 50 years of age; only a few focussed on children or the elderly. Some or all of the subjects in about half of the studies had asthma of varying degrees of severity, and three studies included subjects diagnosed with chronic obstructive pulmonary disease (COPD). Other subjects were generally healthy non-smokers.

In these studies, subjects were exposed to NO\textsubscript{2} via mouthpieces or in environmental chambers of differing size and design. Nitrogen dioxide concentrations ranged from 94 to 5,640 \textmu g/m\textsuperscript{3} (50 to 3,000 ppb), though most exposures were between 188 and 3,760 \textmu g/m\textsuperscript{3} (100 and 2,000 ppb). In many of the studies, the subjects were exposed to NO\textsubscript{2} as well as ambient, filtered, or clean air to provide baseline or control information. Subjects often performed light to moderate exercise, a strategy used to increase the amount of pollutant inhaled per unit time and to evaluate interactions between NO\textsubscript{2} exposure and exercise (which can induce asthmatic episodes).

Several physiological effects of inhaled NO\textsubscript{2} were investigated. The primary focus of most studies was to monitor changes in lung function, through spirometric measurements such as forced expiratory volume in 1 second (FEV\textsubscript{1}), forced vital capacity (FVC), and airway responsiveness through body plethysmography measuring specific airway resistance (SRaw). In many of the studies, subjects were exposed to NO\textsubscript{2} and then “challenged” with an agent known to cause bronchoconstriction, such as carbachol, methacholine, histamine, or cold air. Some studies evaluated the effects of NO\textsubscript{2} on the
characteristics of lung biochemical indicators collected with bronchoalveolar lavage (BAL), changes in cardiac output, alveolar permeability and whole blood and/or serum characteristics.

3.5.2 Studies of Lung Function and Airway Responsiveness

Healthy Subjects

Two of the ten studies that involved healthy subjects reported that NO₂ exposure had some direct impact on lung function. Significant decreases in the mean FVC and FEV₁ (0.17 and 0.11 L, respectively) were reported by Blomberg et al. [1999] after the first of four consecutive daily 4-hour exposures to 3,760 ug/m³ (2,000 ppb) of nitrogen dioxide. Similarly, “day of observation” was the only statistically significant factor affecting lung function in consecutive daily exposures conducted by Goings et al. [1989]. Subjects were exposed to 3,760 or 5,640 ug/m³ (2,000 or 3,000 ppb) NO₂ for two hours, and a small (2%) decrease in FVC and FEV₁ was seen between day 0 and day 1, but not between any of the other days.

Of the remaining eight studies, two reported that exposure to NO₂ (and NO₂ in combination with other pollutants) had some impact on lung function performance in bronchial provocation challenges. Frampton et al. [1991] found a greater carbachol-induced decrease in FVC and FEV₁ in subjects exposed to 2,820 ug/m³ (1,500 ppb) NO₂ than in those exposed to 1,128 or 94 ug/m³ (600 or 50 ppb), but found no significant association between NO₂ exposure alone and lung function. Hazucha et al. [1994] used a methacholine challenge to assess the effects of NO₂ on subsequent O₃-induced lung function response. Female subjects were exposed to air or 1,128 ug/m³ (600 ppb) NO₂ followed by 590 ug/m³ (300 ppb) O₃; the methacholine dose required to reduce the FEV₁ by 10% was 1.7 mg/mL after the NO₂/O₃ combination. In comparison, the control (clean air) methacholine dose was 14.3 mg/mL and the dose for O₃ alone was 5.6 mg/mL. These results suggest that a combined exposure NO₂ and O₃ is associated with bronchial hyperresponsiveness. Exposure to 1,128 ug/m³ NO₂ alone had no significant impact on lung function or bronchial responsiveness.

Rasmussen et al. [1990, 1992], Hackney et al. [1992], Morrow et al. [1992], Vagaggini et al. [1996] and Chambers and Ayers [2001] all reported no significant association between NO₂ exposure and lung function in healthy adult volunteers.

Asthmatic Subjects

Seven of the seventeen studies involving asthmatic volunteers focussed on the direct impact of NO₂ on lung function. Roger et al. [1990] found that a 75-minute exposure to 564 ug/m³ (300 ppb) NO₂ with intermittent exercise resulted in significantly increased specific airway resistance (SRaw) (4.0 cmH₂Osec for cases; 3.2 for controls) and decreased FEV₁ (13% for cases; 7% for controls) in male subjects. Tunnicliffe et al. [1994] report that subjects exposed to 752 ug/m³ (400 ppb) for 1 hour via mouthpiece showed mean 4% decrease in FEV₁, while those exposed to 188 ug/m³ (100 ppb) showed
no significant change. Jorres et al. [1995] report that asthmatic subjects had a small drop in mean FEV\(_1\) after a 3-hour exposure of 188 ug/m\(^3\) (100 ppb). Volunteers exposed to 564 ug/m\(^3\) (300 ppb) NO\(_2\) for three hours [Avol et al., 1992] showed a significant drop in lung function between hours 0 and 1, but not between hours 1 and 3. Studies conducted by Rasmussen et al. [1990], Jorres and Magnussen [1991] and Vagaggini et al. [1996] found no direct impact of NO\(_2\) on measures of lung function in asthmatic volunteers.

The remaining ten studies assessed the effects of NO\(_2\) on subjects’ airway responsiveness to known allergens and bronchoconstrictors. Orehek et al. [1976] found that 1-hour exposures to 188 and 376 ug/m\(^3\) (100 and 200 ppb) enhanced the effects of carbachol in 13 of 20 volunteers. The mean dose necessary to induce a two-fold increase in airway resistance was reduced from 0.66 mg to 0.36 mg. Jorres and Magnussen [1990] reported that 30 minutes exposure to 470 ug/m\(^3\) (250 ppb) reduced the PV\(_{100}\)SR\(_{aw}\) (mean provocative ventilation necessary to increase SR\(_{aw}\) by 100%) by 19%.

Both Salome et al. [1996] and Strand et al. [1996] reported increased responsiveness to histamine during and after exposure to 1,128 and 488 ug/m\(^3\) (600 and 260 ppb) NO\(_2\), respectively. Similarly Strand et al. [1997, 1998] and Jenkins et al. [1999] found that exposure to NO\(_2\) in combination with allergen inhalation led to decreased lung function. Strand et al. [1997] report a 6.6% decrease in peak expiratory flow and a 4.4% decrease in late phase FEV\(_1\) [1998] for mild asthmatics exposed to 490 ug/m\(^3\) (260 ppb) NO\(_2\) for 30 minutes. Jenkins et al. [1999] found that mild, non-smoking asthmatics were not significantly impacted by exposure to 376 ug/m\(^3\) (200 ppb) NO\(_2\) for 6 hours, but that 752 ug/m\(^3\) (400 ppb) resulted in a significant decrease in the PD\(_{20}\)FEV\(_1\) (dose of allergen necessary to decrease the baseline FEV\(_1\) by 20%) after 3 hours. Interestingly, Devalia et al. reported that a 6-hour exposure to 752 ug/m\(^3\) (400 ppb) NO\(_2\) in combination with 522 ug/m\(^3\) (200 ppb) SO\(_2\) produced in a significant decrease in the PD\(_{20}\)FEV\(_1\), a result not seen when NO\(_2\) alone was administered.

Huang et al. report that mite-sensitive asthmatic children exposed for 5 minutes to air from the Taipei Tunnel (183 to 313 ug/m\(^3\) SO\(_2\); 846 to 940 ug/m\(^3\) NO\(_2\)) followed by methacholine and/or inhaled allergen showed no change in pulmonary function.

**Subjects with COPD**

Three studies investigated subjects with COPD to assess the possibility that these patients exhibit enhanced sensitivity to the effects of NO\(_2\) exposure. Vagaggini et al. [1996] studied 7 healthy, 8 asthmatic and 7 COPD (mean age 58 years) volunteers. All were exposed to 564 ug/m\(^3\) (300 ppb) NO\(_2\) for 1 hour with intermittent periods of moderate exercise. COPD patients showed a slight but significant decrease (3%) in FEV\(_1\) 2 hours after exposure. Morrow et al. [1992] studied 20 elderly normal and 20 COPD (mean age 60 years) volunteers exposed to 564 ug/m\(^3\) (300 ppb) NO\(_2\) for four hours, and found that the COPD subjects demonstrated progressive decrements in FVC and FEV\(_1\) (to 8.2 and 4.8%, respectively) over the four-hour period. Hackney et al. [1992] studied 26 volunteers with physician-diagnosed COPD (aged 45-70), a history of heavy smoking, and low FEV\(_1\). Subjects were exposed to ambient air or 564 ug/m\(^3\) (300 ppb) for four
hours with periods of intermittent exercise, and no significant association between lung function and NO₂ exposure was observed.

3.5.3 Studies of Lavage Fluids

Studies of biochemical markers, in addition to providing information regarding the toxicological mechanism of action, may indicate sub-clinical effects of exposure. Nine of the eighteen studies published since 1994 looked for changes in the chemistry and cytology of lavage fluid, before and after exposure to NO₂. Of these, seven involved only healthy volunteers, one included only asthmatic volunteers, and one included both. None of these studies were conducted with COPD subjects. Many of these studies have focused on the measurement of inflammatory mediators.

Wang et al. [1995] reported that healthy subjects exposed to 752 ug/m³ (400 ppb) NO₂ for 6 hours experienced a significant increase in the amount of eosinophil cationic protein (ECP) found in their nasal lavage fluid after an allergen challenge. NO₂ did not directly affect levels of the other inflammatory mediators tested. Following a 4-hour exposure to 3,760 ug/m³ (2,000 ppb) NO₂, Blomberg et al. [1997, 1999] reported significant increases in the neutrophils, IL-8 and myeloperoxidase (MPO), found in bronchial lavage fluid. Similarly, Solomon et al. [2000] studied subjects exposed to the same 4-hour concentration for three consecutive days. A significant increase in neutrophils and a significant decrease in T-helper cells were observed.

Azadniv et al. [1998] studied BAL fluids 15 healthy subjects after 6 hours of exposure to 3,760 ug/m³ (2,000 ppb) NO₂. In the first phase the BAL was taken 18 hours after the end of the exposure, and in the second phase it was taken immediately after the exposure. First phase results showed an increase in leukocytes (2.2 to 3.1%) and a small decrease in CD8T lymphocytes and in non CD4/non CD8 T lymphocytes. No significant changes were observed in the second phase of testing.

Jorres et al. [1995] and Avissar et al. [2000] both found that exposure to lower concentrations of 1,880 and 2,820 ug/m³ (1,000 and 1,500 ppb) for 3 hours did not have significant effect on the differential cell counts in the BAL fluid of subjects, both healthy and asthmatic. Finally, Strand et al. [1996] reported an increase in the granulocyte expression of the Mac-1 adhesion molecule in mildly asthmatic subjects 30 minutes after a 30-minute exposure to 488 ug/m³ (260 ppb), but no significant changes in tryptase, ECP or MPO. Kelly et al. [1996] reported that significant decreases in the antioxidants uric and ascorbic acid were detected in both bronchial (upper respiratory tract) and bronchoalveolar (lower) fluid after a 4-hour exposure to 3,760 ug/m³ (2,000 ppb) NO₂. A significant increase in bronchial GSH (reduced glutathione) was also observed. These results suggest an NO₂-induced depletion of respiratory tract antioxidants.

3.5.4 Insight from Published Reviews of Controlled NO₂ Exposures

In the studies described above, there is a great deal of variability in the levels of exposure at which responses are detected. In several cases, studies that are similar in design and
execution have produced discordant results. To more clearly understand and interpret this literature, two meta analyses and a key review paper were consulted for further information and insight.

The review of Samet and Utell [1990] includes only two of the papers mentioned in this report [Orehek et al., 1976; Goings et al., 1989], however, it also describes inconsistent findings, in studies conducted pre-1990. Possible explanations for the inconsistencies found in pre-1990 papers, probably also relevant to the more recent studies, are discussed in detail. The authors suggest that following factors complicate the interpretation of experimental results:

- Small sample sizes that do not allow for the establishment of general patterns.
- Differences in exposure protocols that make studies difficult to compare. For example, oronasal breathing (chamber exposures) versus oral breathing (mouthpiece exposures) and exercise versus no exercise protocols.
- Failure to recognize normal exposure circumstances of subjects and, therefore, failure to account for possible pre-established tolerances.
- Possible overemphasis on group mean responses. Lumping all individual study subjects into a mean analysis may result in some patterns and sensitivities being missed.
- Although the major site of NO\textsubscript{2} injury is the terminal bronchioles, most studies focus on tests of the upper airways, which may be relatively insensitive to any deleterious effects.

Despite these challenges to interpretation, Samet and Utell [1990] argue that that many of these studies have shown evidence that individual asthmatics and groups of asthmatics do respond to levels of NO\textsubscript{2} that induce no response in healthy volunteers.

Given the inconsistencies in responses to NO\textsubscript{2} exposure in controlled experimental studies, two meta analyses were conducted in attempts to quantitatively assimilate the information derived from the various studies. In 1992 Folinsbee published a meta-analysis of 25 studies (published and unpublished) that asked the question “Does NO\textsubscript{2} exposure increase airways responsiveness?” Raw data was collected for all of the study subjects (703 asthmatics; 131 health normal) so that individuals could be assessed on a case-by-case basis. Results of airway responsiveness tests before and after exposure to NO\textsubscript{2} were reviewed, and cases were simply labelled as “increased” or “decreased”. If the results for a particular individual could not be assessed with confidence, the data was excluded from further analysis. The number of asthmatic and normal subjects that showed increased airway responsiveness was calculated and tested for statistical significance with a sign test. It was determined that 70% of asthmatics showed increased airway responsiveness during resting exposure, but only 50% showed an increase during exposure with intermittent exercise. 47% of normal subject had increased responsiveness.
with exposures less than 1,880 ug/m\(^3\) (1,000 ppb), and 80% showed increased responsiveness with exposures to higher concentrations. This meta analysis confirmed the increased sensitivity of asthmatics and suggested that a significant proportion of non-asthmatic subjects also experience airway responsiveness at concentrations of approximately 1,880 ug/m\(^3\) (1,000 ppb.).

Rasmussen and colleagues [1992] performed a similar meta-analysis on studies published between 1980 and 1989 that involved 10 or more subjects (healthy and/or asthmatics) and followed a randomized, blinded design. FEV\(_1\), SR\(_{aw}\) and AR were used as indicators of NO\(_2\) impact. Significant effects were seen in the airway resistance and responsiveness of asthmatics at concentrations between 600 and 1,200 ug/m\(^3\) (320–638 ppb), and in the airway responsiveness of healthy subjects at concentrations greater than 2,000 ug/m\(^3\) (1,063 ppb). These findings are in good agreement with the meta analysis of Folinsbee [1992], again indicating adverse effects of exposures to concentrations above approximately 2,000 ug/m\(^3\), and the roughly 2- to 3-fold enhanced sensitivity of asthmatics.

It is important to note that the controlled exposure studies described above have, by design, focused only on acute exposures and responses. Exposures have generally been for periods of 1-6 hours and outcomes were typically evaluated immediately post-exposure. It is therefore not possible from these studies to determine the potential impacts of repeated exposures or the possibility of delayed or chronic responses.

### 3.6 Discussion of LOAELs for Chronic and Acute Exposure to NO\(_2\)

#### 3.6.1 Chronic Exposure

Epidemiological studies are best suited to evaluate the impact of chronic exposures and to serve as the basis for chronic exposure guidelines. The epidemiological studies that were reviewed largely fail to indicate associations between NO\(_2\) exposure and a wide range of health outcomes, although there are several notable exceptions that allow broad conclusions to be made. Overall, the epidemiological studies support the results from chamber studies indicating that asthmatics exhibit increased susceptibility to the effects of NO\(_2\) exposure. While asthma may be exacerbated by NO\(_2\) exposure, there is little evidence to support a relationship between NO\(_2\) exposure and development of asthma. For example, a large infant birth cohort study designed specifically to evaluate the association between respiratory illness incidence and NO\(_2\) exposure from gas stove use showed no association [Samet et al., 1993]. One exception is a Canadian study in which asthma incidence was associated with exposure to NO\(_2\) in a small subset of the study population in which exposures were measured [Infante-Rivard, 1993]. In contrast there is more consistent evidence associating NO\(_2\) exposure with respiratory symptom prevalence in children, but not specifically in infants. This relationship is noteworthy since children were not frequently studied in the controlled exposure investigations.
Given the inconsistencies in results amongst the studies, we focus on the larger studies with measured exposures to recommend a LOAEL. In one of the larger prospective cohort studies of childhood respiratory illness, Neas et al. [1991] report that a 15 ppb increase in long-term NO$_2$ exposure was significantly associated with a 40% increase in the increased cumulative incidence of lower respiratory symptoms (shortness of breath, wheeze, chronic cough, chronic phlegm, bronchitis). Based on this relationship, the results of other studies reporting associations between long term exposure to NO$_2$ and similar lower respiratory symptoms in children, and supported by acute impacts observed in controlled exposure studies, a LOAEL for chronic exposures of 25 ppb (47 ug/m$^3$) is recommended. This value is based upon the increased indoor NO$_2$ concentrations associated with major indoor sources for which health effects have been observed in epidemiological studies. Application of this LOAEL as a standard will be complicated in locations where ambient NO$_2$ concentrations are close to or exceed 25 ppb. This LOAEL is somewhat lower than the World Health Organization (WHO) air quality guideline (40 ug/m$^3$) and the North American outdoor air standard (the U.S. National Ambient Air Quality Standard and the Canadian Maximum Acceptable Air Quality Guideline), an annual mean of 53 ppb (100 ug/m$^3$).

3.6.2 Acute Exposure

To address an acute exposure LOAEL, the numerous controlled exposure studies provide insight and several relatively consistent findings are evident. As with the epidemiological literature, the review of controlled exposure studies suggests that asthmatics exhibit enhanced sensitivity to the effects of NO$_2$ exposure. Whereas healthy adults experience bronchial hyperresponsiveness following 3-hour exposures to approximately 1,000 ppb (1,880 ug/m$^3$) NO$_2$, there is a relatively consistent asthmatic response to levels as low as 300 ppb (564 ug/m$^3$) for 1-hr exposures, with a limited number of studies reporting reduced lung function (3-hr exposure) or bronchial hyperresponsiveness (1-hr exposure) to concentrations as low as 100 ppb (188 ug/m$^3$). These findings are also supported by two meta-analyses. There are some suggestions that individuals with COPD also exhibit enhanced susceptibility to the effects of NO$_2$, although this has only been explored in a limited number of studies and findings were inconsistent. The studies of clinical indicators of response are supported by numerous studies demonstrating associations between NO$_2$ exposure and production of a (sub-clinical) enhanced inflammatory response. None of the studies of biochemical and cytological markers were conducted at exposures below those of the studies with lung function or bronchial responsiveness as endpoints. Therefore it is not possible to determine whether sub-clinical responses are measurable at even lower levels of exposure.

Despite the inability of others to reproduce their findings, Orehek and colleagues [1976] found that 13 of 20 asthmatic volunteers were prone to increased airway responsiveness after a 1-hour exposure to 188 ug/m$^3$ (100 ppb) NO$_2$. Considering the variable degree of respiratory impairment between asthmatic subjects and the consequent variability in responses to NO$_2$, the more consistent findings of effects at 300 ppb (564 ug/m$^3$) and the evidence of responses in at least some study subjects to 1-hour exposures of 188 ug/m$^3$. 
(100 ppb), a concentration of 200 ug/m$^3$ (106 ppb) is suggested as an acute exposure LOAEL. This level is consistent with the WHO Air Quality Guideline of 200 ug/m$^3$ (1 hour) and only slightly lower than the 1-hour ambient quality standard for Australia (229 ug/m$^3$). The recommended LOAEL is somewhat lower than the Canadian 1-hour Maximum Acceptable Ambient Air Quality Guideline value of 400 ug/m$^3$ (212 ppb) and the California 1-hour of standard of 480 ug/m$^3$ (255 ppb). There is no short-term NO$_2$ ambient air quality standard for the U.S.
4 Sulfur Dioxide (SO₂)

4.1 Properties and Sources

Information in this section has been drawn from the following sources:


Sulfur dioxide is a colourless gas with a pungent, irritating odour characteristic of burning sulfur. This very reactive weak acid exists as a gas at normal ambient temperatures and pressures. It exists as a colourless liquid below -10°C. Contact with water forms sulfurous acid. The pH of an aqueous solution is slightly acidic. Certain metals and organic substances glow, burn or explode in SO₂ atmospheres. Table 4.1 summarizes the physical and chemical properties of this compound.

Table 4.1 Summary of the Chemical and Physical Properties of Sulfur Dioxide

<table>
<thead>
<tr>
<th>PROPERTY</th>
<th>VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS #</td>
<td>7446-09-5</td>
</tr>
<tr>
<td>Synonyms</td>
<td>bisulfite; sulfur oxide; sulfurous oxide; sulfurous acid anhydride; sulfurous anhydride</td>
</tr>
<tr>
<td>Molecular Formula</td>
<td>SO₂</td>
</tr>
<tr>
<td>Structural Formula</td>
<td>O=S=O</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>64.06 g/mol</td>
</tr>
<tr>
<td>Air Concentration</td>
<td>1 mg/m³ = 0.38 ppm at 101.3 kPa</td>
</tr>
<tr>
<td>Units Conversion</td>
<td>Colourless in both liquid and gaseous forms.</td>
</tr>
<tr>
<td>Odour</td>
<td>Pungent, irritating odour, similar to burning sulfur. Odour thresholds of 0.1-5 ppm have been reported.</td>
</tr>
<tr>
<td>Melting Point</td>
<td>-72.2°C at 101.3 kPa</td>
</tr>
<tr>
<td>Boiling Point</td>
<td>-10.0°C at 101.3 kPa</td>
</tr>
<tr>
<td>Critical Temperature</td>
<td>157.6°C</td>
</tr>
<tr>
<td>Vapour Pressure</td>
<td>339 kPa at 21.1°C</td>
</tr>
<tr>
<td>Vapour Density</td>
<td>2.26 (air = 1)</td>
</tr>
<tr>
<td>Specific Gravity</td>
<td>Liquid: 1.43 at 0°C (water = 1)</td>
</tr>
<tr>
<td>Solubility in Water</td>
<td>Very soluble in water (11.28 g/100 mL at 20°C). Rapidly converted to sulfurous acid (H₂SO₃), which is a dibasic acid with pH less than 3.</td>
</tr>
<tr>
<td>Solubility in Other Liquids</td>
<td>Acetone and other ketones, methanol, ethanol, acetic acid, diethyl ether, chloroform and sulfuric acid.</td>
</tr>
<tr>
<td>Flammability</td>
<td>Does not burn.</td>
</tr>
</tbody>
</table>
4.1.1 Sources of SO$_2$

The average atmospheric residence time for SO$_2$ is 1-5 days. Ambient air concentrations of SO$_2$ range from 1-5 ug/m$^3$ in remote areas to 400 ug/m$^3$ in polluted urban areas.

Volcanoes and geysers are sporadic but possibly significant natural sources of SO$_2$. It is also thought that hydrogen sulfide from the natural decay of vegetation on land and in the oceans is oxidized to SO$_2$ within hours. Most of the sulfur in fossil fuel is converted into SO$_2$ during combustion, and fossil fuel combustion accounts for the greatest proportion of anthropogenic releases globally. Petroleum refining, metal smelting, paper manufacturing and the fabrication of rubber products are other major anthropogenic sources. Unvented kerosene space heaters and coal burning are significant indoor sources of SO$_2$.

Atmospheric SO$_2$ can be oxidized photochemically or catalytically to SO$_3$ then react with water vapor to form sulphuric acid (H$_2$SO$_4$). Other substances can react with sulfate ions to form salts which are washed out by rain. Although wet deposition is a significant route of removal from the atmosphere, direct surface uptake of SO$_2$ is the most significant removal process. The global sulfur cycle involves an atmospheric flux of 140-350 x 10$^6$ tons per year, approximately 40-60 x 10$^6$ tons of which are from anthropogenic sources in the form of SO$_2$, sulfuric acid and sulfate. In the US, 65% of anthropogenic emissions are from coal combustion, and 13% are from oil combustion.

4.2 Toxicologic Characteristics

Section 4.5 reviews the large number of clinical experiments which have exposed human volunteers to sulfur dioxide. As for NO$_2$, human exposure trials are considered more relevant to human health outcomes than animal studies, therefore the toxicology literature is only briefly summarized here using the following reviews as a basis.


Once again, emphasis has been placed on the results of experimental animal studies conducted at exposure concentrations considered to be most relevant to human populations, 5 ppm (13,000 ug/m³) or less.

4.2.1 Absorption and Biochemistry

The ready solubility of sulfur dioxide in water forms the basis for its physiological and toxicological effects. Gaseous SO₂ dissolves in fluids found in the upper respiratory tract to form bisulfite, sulfite, and hydrogen ions that are quickly absorbed by the blood and distributed throughout the body. Studies have shown that the efficiency of this process is affected by the concentration of inhaled SO₂, where high concentrations (≥ 100 ppm) result in absorption of ≥ 90% of the pollutant, and low concentrations (≤ 2 ppm) result in 5-40% absorption. Inspiratory rate and route of inhalation further affect efficiency such that exercising individuals engaged in oronasal breathing absorb more SO₂ (≥ 80%) than those at rest.

Once absorbed, sulfite ions in the blood can be oxidized to sulfates and excreted in the urine, or they can react with proteins to form S-sulfonate, which has been found at elevated levels in the plasma and aorta of SO₂-exposed experimental animals. The biochemical significance of these findings is not yet understood, but they provide evidence for the possibility of toxicological effects in non-pulmonary target organs.

Once absorbed, bisulfite ions in the blood might be responsible for inducing the bronchoconstriction generally associated with sulfur dioxide exposure. By disrupting the disulfide bonds present in tissue proteins, bisulfite may lead to the alteration of neurotransmitter receptors and the subsequent contraction of smooth muscle tissue in the lungs.

4.2.2 Pulmonary Effects

The primary physiological response to sulfur dioxide exposure is bronchial constriction leading to increased airway resistance and decreased pulmonary function. Acute exposures to SO₂ at concentrations greater than 1 ppm (2630 ug/m³) have led to increased airway resistance (8.5-150%) in resting laboratory animals, while effects in exercising animals have been seen at concentrations as low as 0.5 ppm. No significant increases in airway resistance have been reported for animals chronically (> 26 weeks) exposed to sulfur dioxide concentrations between 0.13-5.7 ppm (340-15,000 ug/m³). This result appears to be congruent with the rapid recovery of pulmonary function reported in studies of acute exposure.

On the other hand, chronic exposure in the same range of concentrations has resulted in significant thickening of the tracheal mucous layer, which dampens the effect of ciliary beating and slows mucociliary clearance. Removal of foreign materials from the respiratory tract becomes less efficient as a result, and the primary defence against inhaled infectious agents is compromised. These symptoms, similar to those of chronic
bronchitis in humans, faded over a period of 1 to 3 months after the discontinuation of exposure.

As with nitrogen dioxide, SO₂ has been shown to disrupt the structure and function of the cilia and of alveolar macrophages. These effects have only been seen in animals at concentrations significantly higher than those generally associated with ambient air pollution (> 5 ppm), and are not considered relevant to this review. However, it should be noted that humans with hyperreactive airway conditions are known to be much more sensitive to the effects of SO₂ than those with normal lung function, and that animal study results may need to be considered in a different light when extrapolated to sensitive populations.

4.2.3 Immune Response

The literature investigating how SO₂ affects the immune response of exposed individuals is limited. Significant depression of antibody production has been observed at concentrations of 5 ppm (13,150 μg/m³) and greater, but not at concentrations of 0.5 ppm (1,300 μg/m³) or less. It is important to note that these results may be linked to the dose-absorption relationship discussed above, and that absorption efficiency may have some impact the magnitude of the immune response.

4.2.4 Other Effects

The oxidative effects of sulfur dioxide on red blood cells have been demonstrated in numerous animal studies. Reduced erythrocyte flexibility has been associated with SO₂ concentrations ranging from 0.9-10 ppm (2400-26300 μg/m³), which can lead to increased fragility and decreased lifespan of mature cells. Although the experimental results of well designed studies have been consistent, further study is needed to understand the health implications of this outcome. Very few studies have investigated the carcinogenicity of sulfur dioxide in animals and, due to poor study design, the results have been inconclusive. Chronic exposure to concentrations of 500 ppm (1,300 mg/m³) and greater have been associated with increased incidence of lung tumours, but small study populations bring the statistical significance of the results into question. There is no evidence to support the possible carcinogenicity of SO₂ at ambient concentrations, and the International Agency for Research on Cancer (IARC) has placed it in Group 3: Unclassifiable as to carcinogenicity to humans.

4.3 Indoor Exposure to SO₂

4.3.1 Overview of Studies

Table 4.2 (located at the end of this report) summarizes the results of 14 studies reporting concentrations of SO₂ in non-industrial indoor conditions. All reported results of area
(stationary) sampling; none reported personal exposure monitoring. Most included
measurements made inside and outside homes [Biersteker et al., 1965; Spengler et al.,
1979; Stock et al., 1985; Méranger and Brulé, 1987; Yuhui et al., 1991; Lee et al., 1997;
Bailie et al., 1999; Sanyal and Maduna 2000; Chao, 2001; Kiendzierski and Sembaluk,
2001], including an army tent [Zhou and Cheng, 2000], and a few included measurements
in offices and public places such as recreation or entertainment facilities and shopping
malls [Spengler et al., 1979; Kulkadia and Palmer 1998; Camuffo et al., 1999; Lee et al.,
1999]. Although the studies spanned the years 1964 to 1998, all but 5 were conducted in
the last 10 years. Four studies were conducted in China (including three in Hong Kong),
two in South Africa, three in Europe (Britain, Italy and the Netherlands), and five in
North America (three in the US and two in Canada).

4.3.2 SO_2 Concentrations Indoors

Concentrations of SO_2 were reported in various units: mg/m³, ug/m³, ppm (or uL/L), and
ppb (or nL/L). In Table 4.2, these are listed as reported in the articles, but in this
discussion, to facilitate comparisons, all measurements are converted to ug/m³.

The concentrations reported in the South African studies were extremely high, with mean
levels in the range of 9,500 to 60,000 ug/m³ in living and cooking areas of very low to
middle income homes [Sayal and Maduna, 2000], and of 1,400 ug/m³ in homes with no
chimneys [Bailie et al., 1999]. The only other study reporting such high levels was an
experiment conducted in an army tent, attempting to simulate living conditions of US
Gulf War soldiers [Zhou and Cheng, 2000]. Here the highest levels measured were about
4,000 ug/m³ with tent flaps closed and after several hours of burning kerosene or jet fuel
in convection heaters. Two other studies reported indoor concentrations over 100 ug/m³.
A study in eastern China in 1987-8 measured high levels in kitchens using coal as fuel
(71 to 860 ug/m³) and in some kitchens using gas in the winter time (65 to 163 ug/m³)
[Yuhui et al., 1991]. In a study in the Netherlands in 1964 where coal and high-sulfur
gas was used for heating some homes, seven of 60 homes had average concentrations
greater than 100 (up to 246 ug/m³) [Biersteker et al., 1965].

In the remaining studies, mean indoor SO_2 concentrations ranged from 0.5 to 32 ug/m³,
over the most recent 20 years and throughout locations in North America, Europe and
Asia [Spengler et al., 1979; Stock et al., 1985; Méranger and Brulé, 1987; Lee et al.,
1997; Kulkadia and Palmer 1998; Camuffo et al., 1999; Lee et al., 1999; Chao, 2001;
Kiendzierski and Sembaluk, 2001].

North American studies are the most relevant to the Canadian situation because of the
common heating methods (usually central heating using gas or oil furnaces and water or
forced-air heat circulation) and cooking practices (usually electric, with some gas, usually
vented) used in this area of the world. Spengler et al. [1979] reported results from about
60 locations in 6 eastern to mid-western US cities, taken over a one-year period. Indoor
levels ranged from “zero” to 26 ug/m³, generally following the pattern of concentrations
outdoors in these locales. Stock et al. [1985] measured SO_2 concentrations in 12 houses,
and found an average of 5.1 ug/m³ (standard deviation = 5.3). Méranger and Brulé [1987]
studied the effects of outdoor air on indoor air quality in one house in central Antigonish, Nova Scotia. Levels indoors were usually less than 10 ug/m$^3$, with an average of about 8 ug/m$^3$ over the 8 weeks of sampling. Indoor SO$_2$ did not appear to correlate with outdoor sulphate episodes. In the most recent study, Kendzierski and Sembaluk [2001] studied indoor SO$_2$ levels in one urban and one rural Alberta community in winter and summer. Indoor concentrations of SO$_2$ ranged from 0.2 to 2.3 ug/m$^3$ in the rural community and from 0.9 to 5.2 ug/m$^3$ in the urban community, reflecting the relative levels of outdoor concentrations.

4.3.3 Factors Associated with SO$_2$ Indoors

Many of the studies compared SO$_2$ concentrations indoors and outdoors. Most found that indoor levels were lower than levels outdoors, with indoor:outdoor ratios ranging from about 0.1 to 0.9 [Biersteker et al., 1965; Spengler et al., 1979; Méranger and Brulé, 1987; Lee et al., 1997; Kulkadia and Palmer 1998; Camuffio et al., 1999; Lee et al., 1999; Kendzierski and Sembaluk, 2001]. Four studies found situations in which indoor levels were higher, though the average indoor:outdoor ratios were all below 1.8 and most were still below 1 [Biersteker et al., 1965; Stock et al., 1985; Lee et al., 1999; Chao, 2001]. Results of several studies suggested that indoor concentrations tracked outdoor concentrations, but with lower levels indoors, suggesting that a source of indoor exposure is outdoor pollution and that materials indoors act as a sink for the gas [Biersteker et al., 1965; Spengler et al., 1979; Kendzierski and Sembaluk, 2001].

Only one study conducted inferential analyses of the factors related to indoor SO$_2$ levels. Biersteker et al. [1965] used multiple regression to examine potential determinants of exposure. They found that concentrations increased in older homes, with oil, coal and gas heating (in increasing order), with increasing smoking in the home, and with increasing SO$_2$ outdoors. Only the first factor was statistically significant.

The descriptive statistics reported in other studies are suggestive. Coal heating and cooking appear to be associated with increased SO$_2$ [Yuhui et al., 1991]. Lack of venting of cooking and heating sources appears to increase concentrations [Biersteker et al., 1965; Bailie et al., 1999; Zhou and Cheng, 2000]. Similarly, season may affect indoor levels. In the winter, when windows are closed and use of heaters increases, higher indoor levels were measured [Yuhui et al., 1991; Sanyal and Maduna, 2000]. In one South African study, SO$_2$ levels increased with decreasing socio-economic status [Sanyal and Maduna, 2000].

4.3.4 Factors Associated with SO$_2$ Outdoors

Given that indoor levels appeared to be associated with outdoor levels in these studies, it is useful to consider potential sources of outdoor sulfur dioxide. Note that the literature on outdoor sources was not independently reviewed; these observations are drawn from the indoor studies reported here.
The highest outdoor SO\textsubscript{2} concentrations reported were measured in European cities: from 73 to 384 ug/m\textsuperscript{3} in Rotterdam in 1964 [Biersteker et al., 1965]; and from 52 to 105 ug/m\textsuperscript{3} in Venice in 1996 [Camuffo et al., 1999]. Two cities (Steubenville, Ohio and St. Louis, Missouri) in the US six-cities study had levels in the range of 28 to 60 ug/m\textsuperscript{3} [Spengler et al., 1979]. Other studies in Canada, the US, UK, and Hong Kong reported levels ranging from “zero” to 30 ug/m\textsuperscript{3} [Spengler et al., 1979; Stock et al., 1985; Méranger and Brulé, 1987; Lee, 1997; Kukadia and Palmer, 1998; Lee et al., 1999; Chao, 2001; Kindzierski and Sembaluk, 2001].

Three studies measured outdoor levels in urban and rural areas of the same country [Spengler et al., 1979; Lee et al., 1999; Kendzierski and Sembaluk, 2001]. All found that more densely populated urban areas had higher outdoor SO\textsubscript{2} levels. Industrial, home heating, and vehicular traffic emissions are potential sources related to population density. Chao [2001] reported that ambient levels in Hong Kong have been reduced considerably since the introduction of government restrictions on sulfur content in fuel.

4.3.5 Limitations

Surprisingly few studies have examined SO\textsubscript{2} concentrations in indoor air, perhaps because non-industrial indoor levels are usually (though not always) lower than ambient concentrations outdoors.

Studies conducted to date have used a wide array of sampling and analytical methods; the comparability of these methods is difficult to assess, since many of the reports describe the methods used very briefly and without reference to standard quality assurance techniques, including limits of detection, calibration, and use of blanks.

Some of the studies collected an impressive number of samples under widely varying conditions (e.g., different seasons, building types, population densities, heating types, socioeconomic conditions, and levels of tobacco smoking) and collected descriptive information about these conditions [Biersteker et al., 1965; Spengler et al., 1979; Yuhui et al., 1991; Lee et al., 1997; Bailie et al., 1999; Sanyal and Maduna 2000; Chao, 2001; Kindzierski and Sembaluk, 2001]. Unfortunately, only the earliest study [Biersteker et al., 1965] included inferential analyses to allow reasonable confidence in the interpretation of which factors influence SO\textsubscript{2} concentrations after adjusting for other potential determinants.

4.4 Epidemiological Studies of Populations Exposed to SO\textsubscript{2}

4.4.1 Overview of Studies

No epidemiological studies of the effects of non-industrial indoor exposures to SO\textsubscript{2} were found. Our review therefore focussed on two groups of epidemiological investigations:
Studies of employees at work sites where SO₂ was identified as a major contaminant, and where exposure measurements were available.

Studies of populations exposed to ambient air pollution, also where exposure measurements were available. This category was further limited to exclude studies in which the air pollution was likely to include a wide array of other co-pollutants (e.g., typical urban air pollution from vehicle traffic), since the levels of these pollutants tend to be highly correlated, making it difficult or impossible to distinguish the independent effects of SO₂ [Moolgavkov and Luebeck, 1996]. We limited the review to studies of ambient air pollution in which special sources of SO₂ were identified.

Twenty epidemiological studies which met the above criteria were identified. Fifteen focused on SO₂-exposed populations in occupational settings including copper, lead and nickel smelters, pulp mills, sulfuric acid plants, a refrigerator manufacturer, a power station, a silicon carbide plant, an aluminum foundry, and a fertilizer factory [Kehoe et al., 1932; Skalpe, 1964; Ferris et al., 1967; Smith et al., 1977; Archer and Gillam, 1978; Lebowitz et al., 1979; Sorsa et al., 1982; Kangas et al., 1984; Rom et al., 1986; Englander et al., 1988; Broder et al., 1989; Osterman et al., 1989; Meng and Zhang, 1990; Yadav and Kaushik, 1996; Froom et al., 1998]. Five studies investigated populations exposed to ambient SO₂, one in a city in which high sulfur coal was the predominant energy source and the others in areas with point sources – including an active volcano and metal smelters [Dodge et al., 1985; Donaghue and Thomas, 1999; Shinkura et al., 1999; Wang et al., 1999; Smith-Sivertsen et al., 2001].

Most of the studies focused on respiratory health [Kehoe et al., 1932; Skalpe, 1964; Ferris et al., 1967; Smith et al., 1977; Archer and Gillam, 1978; Lebowitz et al., 1979; Kangas et al., 1984; Dodge et al., 1985; Rom et al., 1986; Englander et al., 1988; Broder et al., 1989; Osterman et al., 1989; Meng and Zhang, 1990; Yadav and Kaushik, 1996; Shinkura et al., 1999]. A few examined other health outcomes, including absenteeism, cardiovascular and neurological symptoms, all cause and cancer mortality, neonatal mortality, and genotoxicity [Sorsa et al., 1982; Kangas et al., 1984; Englander et al., 1988; Meng and Zhang, 1990; Yadav and Kaushik, 1996; Shinkura et al., 1999].

4.4.2 Studies of Respiratory Symptoms, Lung Function and Other Respiratory Outcomes

Table 4.3 (located at the end of this report) summarizes the results of epidemiological studies examining respiratory health in relation to sulfur dioxide exposure. Most were cross-sectional in design, and examined respiratory symptoms using standardized questionnaires and lung function measurements, usually including forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV₁). This group of studies will be discussed first.

The first published account of the effects of SO₂ exposure included interviews and physical examinations of 100 refrigerator manufacturing workers who used the gas as a
refrigerant and were exposed to very high concentrations: 10 to 100 ppm (26,300 to 263,000 ug/m$^3$) [Kehoe et al., 1932]. In comparison to 100 controls of similar age from other areas of the same plant, these men experienced more pharyngitis, tonsillitis, dyspnea on exertion, increased sensitivity to other irritants, fatigue, abnormal reflexes, and altered senses of smell and taste.

Four studies examined copper smelter employees. In a cross-sectional study, Archer and Gillam [1978] compared 953 smelter workers exposed to 0.4 to 3 ppm SO$_2$ (1,000 to 6,000 ug/m$^3$) as well as low concentrations of arsenic, copper, manganese and iron, to 262 employees of the nearby mine truck maintenance shop. They found higher frequencies of cough, phlegm, dyspnea, chest tightness, and chronic bronchitis. FVC and FEV$_1$ were significantly lower in the exposed group, an effect that increased with duration of exposure, after controlling for smoking. Early retirements were also twice as frequent in the smelter group, suggesting that employees with respiratory difficulties self-selected out of exposure. Lebowitz et al. [1979] examined 430 smelter employees ranked according to differing levels of SO$_2$ (from less than 2.5 ppm to more than 5 ppm) and dust exposure. They found a slight increase in chronic obstructive pulmonary disease among highly SO$_2$-exposed smokers, and reductions in FEV$_1$ (compared to earlier spirometry results) related to exposure among those with less than 20 years in the plant, but no other appreciable differences in lung function among exposed employees. Smith et al. [1977] and Rom et al. [1986] reported on changes in pulmonary function among workers in the same Utah copper smelter. The first study included repeated lung function testing of 113 employees in 1973 and 1974, the second followed a subset of 66 and 48 of the first study’s subjects in 1980 and 1983, respectively. The earlier study measured personal exposures of the subjects, and found levels in the most exposed group ranging from 1.6 to 45 ppm (4,208 to 118,000 ug/m$^3$). A decline in FEV$_1$ and in FEV$_1$/FVC ratio was associated with exposures greater than 1 ppm SO$_2$, which remained after controlling for respirable dust exposures. The later study did not include personal monitoring, but reported exposure data from company records in the intervening time period of 0.1 to 6.5 ppm (262 to 17,000 ug/m$^3$). Workers who were exposed to greater than 1 ppm SO$_2$ in 1973-74 as well as workers whose initial FEV$_1$ was less than 90% predicted displayed improvements in lung function in 1980. No accelerated decline in lung function was observed between 1980 and 1983. Rom et al. [1986] attributed the differences in results to short expiratory times in the original pulmonary function tests.

In another smelter study, in Sudbury, Broder et al. [1989] compared lung function and respiratory symptoms of 143 nickel smelter workers and 117 civic labourers. Smelter workers’ exposures to SO$_2$ were 40 times those of the controls, averaging 0.67 ppm (1,750 ug/m$^3$), based on personal measurements of study subjects. They were also exposed to metal fumes, including iron, nickel and copper. Smelter employees reported a history of pneumonia more frequently than controls, and had decreased FEV$_1$ and forced expiratory flow rates at 50% and 75% of vital capacity, however these decrements were no longer significant after adjusting for age, height, smoking status, duration of employment, and mask wearing (the latter adjustment factor was associated with exposure). Civic workers, 19% of whom were former smelter workers, had more
shortness of breath. The investigators concluded that there was little evidence of chronic effects of SO\(_2\) exposure, but cautioned that based on data about prior employees, the smelter workers studied may constitute healthy workers able to remain in the job.

Three studies examine pulp and paper workers. Skalpe [1964] examined 54 workers from 4 Norwegian pulp mills, exposed to SO\(_2\) at levels between 2 and 36 ppm (5,200 – 94,000 ug/m\(^3\)), and 56 unexposed controls who worked in a local paper mill. The pulp mill workers reported more cough, expectoration and dyspnea on exertion than controls, especially among those younger than 50. Maximal expiratory flow rate was lower among exposed workers under age 50, but not in older employees. There were no differences in vital capacity between the groups. In a similar study in the US, Ferris et al. [1967] compared 147 pulp mill workers (some exposed to chlorine and some to SO\(_2\)) to 124 paper mill workers. SO\(_2\) levels ranged from the limit of detection of 4 ppm to 31 ppm (10,500 to 81,300 ug/m\(^3\)). Pulp mill workers had slightly higher rates of obstructive lung disease, but not of chronic bronchitis. Pulp mill workers who were smokers had higher rates of lung disease than paper workers who smoked. The investigators noted that many of the paper mill workers had previously worked in the pulp department, but had transferred to avoid the pulp mill exposures. Kangas et al. [1984] conducted a cross-sectional study of 162 Finnish pulp mill employees, with estimated exposures from 0.07 to 7.4 ppm (180 to 19,400 ug/m\(^3\)). No differences in respiratory symptoms were reported by workers considered exposed to organic and inorganic sulfides.

Osterman et al. [1989] studied respiratory symptoms in 145 Quebec silicon carbide plant workers with 3 to 41 years of employment, and with average exposures to SO\(_2\) of 0.12 ppm (315 ug/m\(^3\)), with levels as high as 1.5 ppm (3,900 ug/m\(^3\)). Employees were also exposed to respirable silica, carbon monoxide, and polycyclic aromatic hydrocarbons. Employees were assigned quantitative measures of cumulative exposure and exposure intensity to dust and SO\(_2\), based on measurements in each job. Phlegm, wheeze, and dyspnea increased with increasing SO\(_2\), but not dust, exposure (cumulative and average intensity), after controlling for age and current smoking. A synergistic effect of smoking and SO\(_2\) exposure was observed for most symptoms.

From et al. [1998] conducted a cross-sectional study of 72 power station employees. About half were exposed to SO\(_2\), with concentrations from “zero” to 15 ppm (0 to 39,000 ug/m\(^3\)) with an average of 0.7 ppm (1,800 ug/m\(^3\)), and half were not exposed, because the burning chamber they worked with was under negative pressure. Cough, sputum and shortness of breath were elevated in the exposed group, and those with dyspnea had significant decrements in FEV\(_1\), FVC, and expiratory flow rates. However, there were no differences in pulmonary function overall between the exposed and unexposed workers. There appeared to be a synergistic effect on cough of smoking and SO\(_2\) exposure.

Three of the cross-sectional studies were large studies of residents of areas with high levels of ambient SO\(_2\). Wang et al. [1999] studied 420 men and 676 women (all non-smokers and non-coal users) in China’s largest city, Chongqing. Mean urban SO\(_2\) levels were 0.08 ppm (213 ug/m\(^3\)). High sulfur coal was the main fuel used in the city’s industries and homes. Rural SO\(_2\) levels in the region were about half the urban levels at
0.04 ppm (103 ug/m$^3$). Though particulate levels were also high, there was little
difference between urban and rural concentrations. FVC, FEV$_1$, and FEV$_1$/FVC ratio
were significantly reduced in subjects living within one km of the two urban air
monitoring stations, compared to those living within the same radius of the rural station.
The differences remained after removing those with occupational exposures from the
analysis.

More recently, Smith-Sivertsen et al. [2001] examined lung function and respiratory
symptoms in about 1,600 residents of a nickel smelter town in Russia, and of 3,400
residents of a nearby Norwegian town. Monthly average PM$_{10}$ particulate levels were less
than 0.008 ppm (20 ug/m$^3$) in both places. Monthly average SO$_2$ levels were less than 20
ug/m$^3$ in the Norwegian town, but from 0.008 to 0.06 ppm (20 to 150 ug/m$^3$) in the
Russian town. No differences in lung function were observed with ambient exposures to
SO$_2$ on the day before or the day of screening. Russian subjects reported exposure-
associated persistent cough and phlegm, but the analysis did not control for cigarette
smoking (which was also somewhat associated with exposure) or employment at the
smelter (~11% of male subjects and ~3% of females).

Dodge et al. [1985] conducted repeated measurements 3 years apart of 678 3$^{rd}$ to 5$^{th}$
grade children living in areas near an Arizona smelter town with varying mean ambient
SO$_2$ levels: from a low of less than 0.002 ppm (< 4 ug/m$^3$) to a high of 0.04 ppm (103
ug/m$^3$). Cough prevalence was significantly associated with SO$_2$ concentration, but no
other respiratory symptoms or lung function measures were related to exposure.

Two studies examined respiratory effects other than lung function and respiratory
symptoms. Englander et al. [1988] conducted a small retrospective cohort study of 400
sulfuric acid factory workers followed for up to 24 years. This study found an excess of
respiratory cancers (5 observed compared to 2.5 expected, p = 0.11), but no increase in
non-malignant respiratory disease. The median SO$_2$ concentration in the breathing zone
of the workers was estimated to be 1.4 ppm (3,600 ug/m$^3$).

Donoghue and Thomas [1999] conducted a time series analysis of presentations and
admissions to hospital for asthma-related complaints in a small Australian city with
copper and lead smelters. No association with peak SO$_2$ exposures measured at any of the
10 monitoring stations, and ranging from “zero” to 3.3 ppm (8,700 ug/m$^3$), was detected.
The effects of other pollutants (particulates, metals, ozone, and nitrogen oxides) were not
examined.

4.4.3 Studies of Other Health Outcomes

Most of the five studies which examined other health effects of SO$_2$ investigated different
effects, so do not form a body of evidence about any of the outcomes. A summary of the
studies is presented in Table 4.4 (located at the end of this report). The following presents
a brief outline of each study, in order of their appearance in the table.
In their cross-sectional study of 162 Finnish pulp mill employees, Kangas et al. [1984] found that workers considered exposed to organic and inorganic sulfides reported significantly more headaches and had a greater number of sick leaves in the previous year. Self-reported neurological symptoms and difficulty in concentrating were also elevated in the exposed group, though not significantly so. There were no differences in cardiovascular symptoms reported. SO$_2$ exposures of pulp mill workers measured by these investigators ranged from 0.07 to 7.4 ppm (180 – 19,400 ug/m$^3$); measurements of hydrogen sulfide and mercaptans were also reported, but not other pulp mill exposures.

In the retrospective cohort study of 400 sulfuric acid factory workers by Englander et al. [1988], standardized mortality ratios (based on local rates in their Swedish county) showed excess overall mortality. The excesses were primarily due to deaths from violence and intoxication, gastrointestinal illnesses, and cardiovascular diseases. There was also a significant excess of bladder tumours, but not other cancers. The observed excesses did not appear to be related to duration of employment. The study had very low power to examine any but the most common causes of death, or to examine subgroups. The median SO$_2$ concentration was 1.4 ppm (3,600 ug/m$^3$).

Meng and Zhang [1990] also studied sulphuric acid factory workers, in Taiyuan City, China. They examined chromosomal aberrations and sister-chromatid exchanges in 40 plant employees, exposed to 0.13 to 4.6 ppm (340 to 11,970 ug/m$^3$) SO$_2$, and in 42 controls from Shanxi University, matched on age, sex, and smoking habits. Both markers were significantly elevated in the exposed workers, including all types of chromosomal aberrations. The increases were not associated with increasing duration of employment in the factory. Yadav and Kaushik [1996] conducted a similar cross-sectional study of 42 fertilizer factory workers, compared to 42 unexposed controls with unspecified employment. The fertilizer plant employees were exposed to average SO$_2$ concentrations of 16 ppm (41,700 ug/m$^3$) for up to 20 years. This group had significantly increased levels of all the markers of genotoxicity studied, including chromosomal aberrations, sister chromatid exchanges, satellite association, and mitotic index. Chromosomal aberrations and sister chromatid exchanges increased with exposure duration, but mitotic index decreased. The markers were also related to smoking and alcohol consumption. Although these lifestyle factors were a basis for matching, there were more smokers and fewer drinkers in the factory employee group. Sorsa et al. [1982] did not find any differences in the frequency of chromosomal aberrations or sister chromatid exchanges among 8 aluminum foundry workers exposed to lower concentrations of SO$_2$, 0.2 to 3 ppm (500 to 7,900 ug/m$^3$), in comparison to 8 clerks of similar age.

Shinkura et al. [1999] examined neonatal mortality in the first 28 days of life among all live births (~ 30,000) in a 10-year period in the health region near Mt. Sakurajima, one of the most active volcanoes in the world. Mortality rate was positively associated with average SO$_2$ concentrations in the month after birth, but not with ash, particulate or maximum hourly SO$_2$ concentrations. Pollutant levels were measured at a single ambient monitoring station and were very low in comparison to industrial levels or levels in some polluted cities, averaging 0.01 ppm (26 ug/m$^3$).
4.4.4 Limitations

The advantage of epidemiological studies is their potential to measure health effects in subjects who span a range of ages and susceptibilities, and who are exposed over a period of time in actual living or working conditions. Unfortunately, the shortcomings described below mean that the epidemiological data about SO\(_2\) can only support limited conclusions for standard setting purposes.

There was a paucity of epidemiological studies of the health effects of sulfur dioxide which met our inclusion criteria. The only studies which examined similar outcomes, thus allowing consideration of the weight of evidence, were cross-sectional studies of respiratory disease symptoms and lung function. Cross-sectional studies are the weakest epidemiological study design, because of the difficulty of determining the temporal relationship between exposure and disease. Those with longitudinal follow-up have the opportunity to examine changes over time, but none of the studies reported here quantitatively addressed the issue of the healthy worker effect by tracing and testing those who left employment in the intervening period. Most of the cross-sectional studies, and the retrospective cohort study, had small study populations, precluding effective analyses by exposure subgroups.

Most of the studies reviewed were conducted in occupational workforces in industrial settings. Most of these studies were conducted among male adults in North American and European communities likely to have baseline health status similar to such populations in Canada. However, it is known that such work groups are likely to be healthier than the population at large, which includes both children and the elderly outside of the working age range, as well as less healthy individuals either unable to work altogether, or unsuitable for industrial employment. Most of the occupational studies reported here involved exposures 10 to 100-fold higher than indoor non-industrial exposures in North America (in exposure studies, the latter ranged from about 0.2 to 30 ug/m\(^3\)). The exposures in community-based epidemiological studies had SO\(_2\) levels closer to those indoors in North America, though still about 3 to 7-fold higher. Unfortunately two of these were conducted in countries where baseline health status may not be comparables to Canada’s, i.e., China and Russia.

To meet our inclusion criteria, epidemiological studies had to use measurements to assign subjects’ exposures. Only a few of the studies (all occupational) included subject-specific measurements. Other occupational studies reported work site measurements which were used to crudely classify workers as exposed or unexposed. Studies of populations exposed to SO\(_2\) air pollution always used data from ambient monitoring stations to classify exposures of subjects or time periods.

Most of the studies grouped subjects into two groups, one less exposed than the other. Without health outcome data over a range of exposure levels, it is difficult or impossible to ascertain an exposure level at which no effect is observed. Occupational studies tended to examine groups with exposures much higher than those expected in the indoor non-industrial environment.
Though we attempted to isolate the independent effects of SO\textsubscript{2} by excluding air pollution studies in which exposures to co-pollutants were likely to be highly correlated, the communities of the air pollution studies included in the review still had other potential exposures. In addition, most of the occupational studies were conducted in work sites where other important exposures are likely to occur, but many of these were not measured or accounted for in the analysis. In these cases it is difficult to determine whether observed outcomes are attributable to the independent effect of SO\textsubscript{2}, to other exposures, or to the joint effects of SO\textsubscript{2} and the other agents.

4.5 Studies of Controlled Human Exposures to SO\textsubscript{2}

4.5.1 Overview of Studies

Sixty-two controlled human exposure studies were located; these are summarized in Table 4.5 (located at the end of this report). Of these, most (41) were published in the period from 1980 to 1989, with 14 published after 1989 and 7 prior to 1980. The vast majority (50) were conducted in North America. Ten studies were conducted in Europe and two in Asia.

The majority of the studies involved exposing human subjects to specified concentrations of SO\textsubscript{2} in an environmental chamber. Forty involved unencumbered breathing of test air, 21 involved breathing test air through a mouthpiece or facemask, and one study required subjects to breathe within a head dome. The studies reviewed were almost exclusively of the crossover design, i.e., subjects crossed from one exposure condition to another, so that they served as their own controls.

The ages of subjects ranged from 12 to 73 years. Most of the studies focussed on non-smoking adults, but five focussed on children under the age of 18, and two involved both adults and children. 41 studies included asthmatic subjects, including all five whose focus was children. Of the studies of asthmatics, 10 also included healthy and/or atopic subjects. One study involved healthy and atopic individuals, while 18 focussed on healthy subjects only. One study investigated individuals with chronic obstructive pulmonary disease (COPD), and one study did not provide a subject description.

Outcomes of interest included spirometry parameters (such as FEV\textsubscript{1}, FVC, and expiratory flow rates), airway resistance, respiratory symptoms and various other measures of response. The concentrations of SO\textsubscript{2} to which subjects were exposed ranged from 0.07 to 28 ppm (180 – 73,000 ug/m\textsuperscript{3}). Four studies involved exposures above 5 ppm (13,000 ug/m\textsuperscript{3}), 14 involved exposures between 1 and 5 ppm (2,600 and 13,000 ug/m\textsuperscript{3}), 13 involved exposures up to 1 ppm, and a further 33 involved exposures of 0.75 ppm (2,000 ug/m\textsuperscript{3}) or less. Durations of exposure ranged from 1 minute to 6 hours, but most (48) involved exposures lasting 1 hour or less.
The following sections describe the results, first for adults, then for children. Studies of adults are further categorized by the health outcomes investigated and by the health status of the subjects.

4.5.2 Adults: Studies of Pulmonary Function

Thirty controlled exposure studies investigated pulmonary function effects of SO$_2$ exposure using typical spirometric measures including FVC, FEV$_1$, and expiratory flow rates [Speizer and Frank, 1966; Snell and Luchsinger, 1969; Wolff et al., 1975; Kreisman et al., 1976; Newhouse et al., 1978; Jaeger et al., 1979; von Neiding et al., 1979; Stacy et al., 1981; Linn et al., 1982, 1983a, 1983b, 1984b, 1985b, 1987, 1990; Kagawa, 1983; Bedi et al., 1984; Hackney et al., 1984; Kulle et al., 1984; Schachter et al., 1984; Folinsbee et al., 1985; Witek and Schachter, 1985; Rondinelli et al., 1987; Bedi and Horvath, 1989; Devalia et al., 1994; Heath et al., 1994; Gong et al., 1995; Nowak et al., 1997; Trenga et al., 1999; Tunnicliffe et al., 2001]. In studies of both healthy and asthmatic individuals, oral exposure was observed to have a greater effect on lung function than oronasal or nasal exposure [Snell and Luchsinger, 1969; Linn et al., 1983a].

Healthy Subjects

19 controlled exposure studies investigating effects of SO$_2$ exposure on pulmonary function involved healthy adult subjects. Among these, eleven tested SO$_2$ concentrations of 1 ppm or more, most with very small sample sizes of between 8 and 20 subjects. Three of these studies revealed no change in lung function (FEV$_1$, FVC, expiratory flow rates, or functional residual capacity) following exposure to 1 or 2 ppm (2,600 or 5,200 ug/m$^3$) SO$_2$ with exposures and exercise for 30 minutes to 4 hours [Bedi et al., 1984; Kulle et al., 1984; Bedi and Horvath, 1989]. Newhouse et al. [1978] found small but statistically non-significant differences in FEV$_1$ following 2-hour oral exposure to 5 ppm SO$_2$ with intermittent exercise. von Neiding et al. [1979] measured small but non-significant decreases in respiratory gas exchange on exposure to 5 ppm SO$_2$. A mouthpiece study of healthy older subjects (aged 55 to 73) exposed to 1 ppm SO$_2$ revealed significant reductions in FEV$_1$ following SO$_2$ in combination with NaCl droplet aerosol as compared to exposure to NaCl droplet aerosol alone [Rondinelli et al., 1987]. Speizer and Frank [1966] found that exposures to 15 ppm (39,000 ug/m$^3$) had inconsistent effects on functional residual capacity. Three studies showed significant changes in maximal expiratory flow rates after 5 minutes to 3 hours of at-rest exposure to 1 and 5 ppm SO$_2$ [Snell and Luchsinger, 1969; Wolff et al., 1975; Kreisman et al., 1976]. Snell and Luchsinger [1969] identified a dose-response relationship between SO$_2$ and MEF$_{50}$, and found that changes in pulmonary function parameters following nasal exposure were smaller than those following oral exposure to SO$_2$. In the one large study, Nowak et al. [1997] gave 3-minute exposures of 2 ppm SO$_2$ via isocapnic hyperventilation to 790 subjects aged 22 to 44 years and found that 3.4% of subjects were hypersensitive to SO$_2$ (i.e., the exposure resulted in FEV$_1$ decrements of more than 20%). Of subjects who responded to methacholine, 22.4% were also hypersensitive to SO$_2$. 

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Review of the Health Risks associated with NO$_2$ and SO$_2$ in Indoor Air

University of British Columbia School of Occupational and Environmental Hygiene
Eight controlled studies investigating pulmonary function parameters in healthy subjects involved exposures of 0.75 ppm (2,000 ug/m³) or less. Five of these studies reported no change in pulmonary function parameters (FVC, FEV1, expiratory flow rates) in response to SO₂ concentrations of 0.75, 0.6, 0.5, 0.25, and 0.2 ppm SO₂ [Jaeger et al., 1979; Stacy et al., 1981; Schachter et al., 1984; Linn et al., 1987; Tunnicliffe et al., 2001]. Three studies reported statistically non-significant SO₂-induced impacts on lung function (FVC, FEV1, expiratory flow rates) [Snell and Luchsinger, 1969; Kreisman et al., 1976; Rondinelli et al., 1987].

Asthmatic Subjects

In the 16 studies that examined asthmatic adults, effects were more pronounced than in healthy subjects and were evident at lower concentrations. In one mouthpiece study, 23 asthmatic subjects had non-significant decreases in FEV₁, FVC, and peak expiratory flow rate in response to SO₂ concentrations of 0.75 ppm (2,000 ug/m³) [Linn et al., 1983a]. In a similar study of 40 asthmatic subjects FEV₁ decreased following oral exposure to SO₂ concentrations ranging from 0.2 to 0.6 ppm (520 to 1,600 ug/m³), increasing with exposure level [Linn et al., 1987]. Jaeger et al. [1979] also found decreases in mid-maximal expiratory flow in mouthpiece breathing asthmatics exposed to 0.5 ppm.

Asthmatic subjects exposed to concentrations of 0.75 ppm or higher in an environmental chamber, with exercise for 10 minutes to 3 hours had significant decrements in expiratory flow and FEV₁ [Hackney et al., 1984; Schachter et al., 1984; Witek and Schachter, 1985; Heath et al., 1994]. Two studies observed significant decrements in pulmonary function (FVC, FEV₁, peak expiratory flow rate) at somewhat lower concentrations, 0.5 and 0.6 ppm (1,300 to 1,600 ug/m³) [Linn et al, 1983b; Trenga et al., 1999]. Gong et al. [1995] observed significant dose-response in FEV₁ in asthmatic subjects with 10 minutes of heavy exercise over a concentration range from 0.5 to 1 ppm.

Five studies involving adult asthmatics exposed to 0.1-0.25 ppm SO₂ [Linn et al., 1982, 1983b, 1990; Devalia et al., 1994; Tunnicliffe et al., 2001], and 1 study of adults with COPD exposed to 0.4 ppm SO₂ [Linn et al., 1985b] revealed no changes in pulmonary function attributable to SO₂.

4.5.3 Adults: Studies of Airway Resistance

Gong et al., 1995]. Because of the specialized equipment required for such studies, all were relatively small in size with 6 to 85 subjects (median = 14).

Healthy Subjects

In healthy subjects, airway resistance studies did not display a consistent pattern, though most often no changes in resistance were observed. Exposure of healthy, exercising adults up to 1 ppm in five studies, and 2 ppm in one study revealed no significant changes in airway resistance [Kulle et al., 1984; Schachter et al., 1984; Folinsbee et al., 1985; Linn et al., 1987; Rondinelli et al., 1987; Bedi and Horvath, 1989]. Studies of healthy subjects at rest revealed no change in pulmonary resistance after either a 10-minute exposure to 0.5 ppm or a 2-hour exposure to 5 ppm SO₂ [von Neiding et al., 1979; Magnussen et al., 1990].

Other investigators found increases in resistance at SO₂ concentrations similar to or lower than the previously cited group. A significant increase in airway resistance was seen following exposure of healthy adults to 1 ppm during exercise [Bedi et al., 1984]. Another study revealed significant changes in airway resistance after 2-hour exposures to 0.75 ppm SO₂ during exercise [Stacy et al., 1981]. Airway resistance was also increased following mouthpiece exposures to 0.5 ppm, 5 ppm or 15 ppm SO₂ at rest [Speizer and Frank, 1966; Snell and Luchsinger, 1969; Sheppard et al., 1980].

Exercising Asthmatic Subjects

Of the 22 studies that examined airway resistance in exercising asthmatics, all but one revealed increases in airway resistance in association with exposure to SO₂ concentrations ranging from 0.2 to 1 ppm and exposure durations ranging from 5 minutes to 6 hours [Sheppard et al., 1981; Kirkpatrick et al., 1982; Linn et al. 1983a., 1983b, 1984a, 1984b, 1984c, 1985a, 1987, 1990; Bethel et al. 1983a., 1983b, 1985; Schachter et al., 1984; Hackney et al., 1984; Roger et al., 1985; Horstman et al., 1986, 1988; Kehrl et al., 1987; Gong et al., 1995]. Twelve of these studies involved exposure to SO₂ concentrations of 0.5 ppm or less. In one, exposure to 0.1 ppm SO₂ for 10 minutes significantly increased airway resistance in the 2 most responsive subjects [Sheppard et al., 1981]. Numerous studies showed dose-response relationships between SO₂ concentration and airway resistance [Linn et al., 1983b, 1984b, 1984c, 1987; Schachter et al., 1984; Horstman et al., 1986; Gong et al., 1995].

One study of asthmatics exercising intermittently found no variation in airway resistance with separate exposures to 0.25 and 0.5 ppm SO₂ for 1 hour. [Linn et al., 1982]

At-Rest Asthmatic Subjects

Similar to studies of healthy adults, studies of asthmatics at-rest were not consistent. Some showed increased airway resistance with concentrations in the range of 0.5 to 1 ppm SO₂ [Sheppard et al., 1980, 1984b; Balmes et al., 1987; Magnussen et al., 1990], but others did not [Sheppard et al., 1981; Bethel et al., 1984; Schachter et al., 1984].
Sheppard et al. [1980] found that in asthmatic individuals at rest, airway resistance increased after 10 minutes of exposure to 1 ppm SO\(_2\), with greater changes at concentrations of 5 ppm.

Interestingly, two studies indicated that repeated exposure to SO\(_2\) over a short period induces tolerance to the bronchomotor effects of SO\(_2\) [Sheppard et al., 1983; Linn et al., 1984a]. The effect was seen in exposures separated by 30-minute intervals in one study and on successive days in the other. Duration of exposure was also observed to influence the impact of SO\(_2\) on airway resistance [Horstman et al., 1988]. At 1 ppm SO\(_2\), bronchoconstriction was significantly increased after 2- and 5-minute exposures, but not after exposures of shorter duration.

**Eucapnic Hyperventilation**

Four studies involving eucapnic hyperventilation of SO\(_2\) revealed increases in airway resistance at 0.5 ppm SO\(_2\) for 10-, 9- and 3-minute durations, and at 0.6 ppm SO\(_2\) for 5 minutes [Sheppard et al., 1981, 1983; Balmes et al., 1987; Islam et al., 1992]. Subjects were healthy and asthmatic adults and sample sizes ranged from 6 to 26 subjects.

**Temperature and Humidity**

Another study of eucapnic hyperventilation of SO\(_2\) revealed that dry, cold air increased the effect of SO\(_2\) on airway resistance [Sheppard et al., 1984b]. Airway resistance increased from baseline by 100% at 0.51 ± 0.2 ppm in dry cold air, at 0.60 ± 0.41 ppm in dry warm air, and at 0.87 ± 0.41 ppm in dry humidified air, following 3 minute exposures. These findings are supported by other studies of adult asthmatics exposed to SO\(_2\) [Bethel et al., 1984; Linn et al., 1984c, 1985a]. In one, high temperature and humidity mitigated the bronchoconstriction induced by SO\(_2\) exposure [Linn et al., 1985a]. In another study, of exposures from 0.3 to 0.6 ppm SO\(_2\) at temperatures ranging from -6 to 21 °C, the effects of decreasing temperature and increasing SO\(_2\) were additive [Linn et al., 1984c]. The limits of the effect of cold are illustrated by the study of Linn et al. [1984b] which found that decreases in temperature from room temperature to 5 °C only slightly increased airway response to SO\(_2\).

### 4.5.4 Adults: Studies of Respiratory Symptoms

Many of the studies of spirometry and/or airway resistance outcomes also recorded changes in various symptoms. These were generally subject-reported and included respiratory symptoms such as taste, odour, nasal congestion or discharge, cough, sputum production, wheeze, shortness of breath, sore throat, substernal irritation, sore chest, and chest tightness, as well as non-respiratory symptoms including heart rate variability. Twenty-one studies included an examination of respiratory symptoms [Speizer and Frank, 1966; Kreisman et al., 1976; Stacy et al., 1981; Kagawa, 1983; Linn et al., 1982; 1983a, 1983b, 1984a, 1984b, 1984c, 1985a, 1985b, 1987; Kulle et al., 1984; Witek et al., 1985; Hackney et al., 1984; Witek et al., 1985; Horstman et al., 1988; Gong et al., 1995; Tunnicliffe et al., 2001].
Healthy Subjects

Few changes in respiratory symptoms were observed in healthy subjects at low SO\textsubscript{2} concentrations (< 1 ppm). Four studies found no increases in symptoms in 7-31 exercising or at-rest adults exposed to 0.15-0.75 ppm SO\textsubscript{2} for 1-2 hours [Stacy et al., 1981; Kagawa, 1983; Linn et al., 1987; Tunnicliffe et al., 2001]. A study of 10 healthy subjects revealed increasing numbers and severity of symptoms with increasing exposure from 0.25 to 1 ppm [Witek et al., 1985]. A study of 4-hour exposures of 20 healthy, exercising adults to 1 ppm revealed SO\textsubscript{2}-induced symptoms that were most pronounced when SO\textsubscript{2} was administered in combination with (NH\textsubscript{4})\textsubscript{2}SO\textsubscript{4} [Kulle et al., 1984]. Studies of 8 and 18 healthy individuals exposed to between 3 and 28 ppm (7,900 and 74,000 ug/m\textsuperscript{3}) SO\textsubscript{2} for 1 to 10 minutes, revealed symptoms associated with increasing SO\textsubscript{2} concentration [Speizer and Frank, 1966; Kreisman et al., 1976]. The earlier study reported that symptoms were more common during oral rather than nasal exposure.

Asthmatic Subjects

Respiratory symptoms were observed more consistently among asthmatics than healthy subjects. Of 13 investigations of exercising asthmatic subjects, 11 revealed increased respiratory symptoms in association with SO\textsubscript{2} exposure [Linn et al., 1983a, 1983b, 1984a, 1984b, 1984c, 1985a; Hackney et al., 1984; Witek et al., 1985; Horstman et al., 1988; Gong et al., 1995], while 2 reported no consistent changes. [Linn et al., 1987; Tunnicliffe et al., 2001] SO\textsubscript{2} concentrations exhibiting no effect ranged from 0.2-0.6 ppm but concentrations ranging from 0.2 to 1 ppm resulted in increased symptoms. The shortest duration of exposure revealing increased symptomatology was 5 minutes (at 0.6 ppm in 2 studies and 1 ppm in another).

Three of the studies reporting SO\textsubscript{2}-induced increases in symptoms reported that changes tended to be transient, disappearing 1 hour or 1 day following exposure. [Linn et al., 1983b, 1984a; Hackney et al., 1984] One study indicated that the combination of SO\textsubscript{2} and exercise had a synergistic effect on respiratory symptoms [Gong et al., 1995]. In a study of 10 healthy and 10 asthmatic individuals, asthmatics tended to complain of lower respiratory complaints with increasing SO\textsubscript{2} concentration, whereas the healthy subjects complained more frequently of upper airway symptoms [Witek et al., 1985].

4.5.5 Adults: Studies of Other Measures of Response

Other measures of response which have been investigated include lung clearance, respiratory inflammatory response, genetic sensitivity to asthmatic response, and heart rate.

Lung Clearance

Wolff et al. [1975] and Newhouse et al. [1978] examined bronchial clearance in 9 and 10 healthy adults exposed to 5 ppm SO\textsubscript{2}. In at-rest subjects exposed to SO\textsubscript{2} for 3 hours, there was little change in clearance with exposure [Wolff et al., 1975]. Among exercising
subjects exposed to SO$_2$ for 2.5 hours, clearance was significantly faster compared to baseline [Newhouse et al., 1978].

**Cellular Inflammatory Response in the Respiratory System**

Bronchoalveolar lavage (BAL) to recover mast cells, macrophages, and lymphocytes has recently been used to examine inflammatory responses to inhalation exposures. Sandstrom et al. [1989a, 1989b, 1989c] were the first to report such investigations for SO$_2$. They exposed 12 healthy, exercising adults to 4 or 8 ppm SO$_2$ for 20 minutes, and 24 hours later found increased numbers of inflammatory cells in BAL fluid, which increased with increasing exposure levels, and decreased to near normal numbers after 3 days. A subsequent study found very similar results in 22 healthy, at-rest adults exposed to 4, 5, 8, and 11 ppm SO$_2$ for 10 minutes [Sandstrom et al., 1989b]. A third study included BAL 4, 8, 24, and 72 hours post-exposure; it confirmed that the peak response was 1 day after exposure [Sandstrom et al., 1989c]

**Genetic Susceptibility**

Winterton et al. [2000] investigated five genetic polymorphisms linked to asthma to determine whether any might be associated with hypersensitivity to SO$_2$ among asthmatics. They exposed 62 adult at-rest asthmatics to 0.5 ppm SO$_2$ for 10 minutes; of these, 12 were hypersensitive (i.e., they had a decline in FEV$_1$ greater than 12%). All of the sensitive responders had the wild-type allele of the TNF-α gene promoter polymorphism, vs. only 61% of the non-sensitive subjects. No other polymorphism was associated with the SO$_2$ hypersensitivity.

**Heart Rate**

Another new train of investigation related to air pollutants is cardiac arrhythmias. Linn et al. [1990] exposed moderate to severe asthmatic subjects to 0.3 and 0.6 ppm SO$_2$ during 10 minutes of exercise and found no change in heart rate. Tunnicliffe et al. [2001] exposed 12 healthy and 12 asthmatic subjects to 0.2 ppm for 1 hour at rest and also found no change in heart rate during exposure. They did find changes in the frequency domains of the electrocardiograms (in opposite directions for healthy and asthmatic subjects), which led them to initial hypotheses about effects on vagal tone induced by bronchoconstriction and bronchodilation of lung airways.

**4.5.6 Studies of Children**

Seven studies included children and adolescents, in the age range of 9 to 18 years [Koenig et al., 1983, 1985, 1990; Huang et al., 1991; Magnussen et al., 1990; Islam et al., 1992; Linn et al., 1997]. No studies of children under 9 or of infants were found. Because the studies of Magnussen et al. [1990] and Islam et al. [1992] included adults and did not entail separate analyses by age, the results of these studies are reported in the previous sections.
Two studies by Koenig et al. [1983, 1985] of asthmatic adolescents exposed at rest or during exercise to 0.5 and 1 ppm for 10 or 50 minutes found significant decrements in pulmonary function (FEV₁, expiratory flow rates), despite the small numbers of subjects in the studies (9 and 10, respectively). Results of both studies also suggested that exposures by mouth exacerbate the effect of SO₂, as they do in adults.

In a study of 13 adolescents, Koenig et al. [1990] examined the joint effect of very low levels of SO₂ (0.1 ppm) and ozone (at 0.12 ppm), and found that this combination resulted in significant decrements in FEV₁, where exposures to either gas alone did not. Two other studies examined the effect of gases in combination. Huang et al. [1991] exposed 6 asthmatic children to road tunnel air with SO₂ and NO₂ concentrations 6 and 20 times (respectively) higher than those of ambient air. Very slight non-significant decrements in FVC, FEV₁, and expiratory flow were observed after 105 breaths of the polluted air. Linn et al. [1997] exposed 26 asthmatic and 15 healthy children to 0.1 ppm SO₂, 0.1 ppm ozone, and 100 ug/m³ sulphuric acid aerosol for 4 hours, with intermittent exercise. They found little change in spirometric measures after the simulated “acid haze” exposures.

4.5.7 Limitations

The controlled human experiments had several advantages compared to the epidemiological studies of the health effects of SO₂. The experimental conditions allowed the exact exposure concentration to be controlled and known. Co-exposures could be eliminated or given under controlled circumstances, so that the independent and joint effects of SO₂ could be more confidently assessed. Of course, controlled exposures are also less realistic, considering the complex mixtures which may occur in ambient or indoor air; a few investigators attempted to reconstruct such exposures in their chambers.

Clinical exposures were always of short duration, ideal for assessing the acute changes which can result from exposure episodes of minutes to hours, but not for assessing the results of chronic low level exposures. This limitation coincides with the fact that the lowest exposures offered to clinical study subjects were about 0.1 ppm (260 ug/m³) considerably higher than levels typically observed in North American homes or ambient air. Acute exposures also limit the range of health outcomes which can be observed; long-term health effects such as cancer, chronic obstructive pulmonary disease, and systemic effects cannot be endpoints in experimental studies of humans, for both practical and ethical reasons.

Another limitation of clinical studies is the very small number of subjects typically included, such that changes in lung function that were not statistically significant may have resulted from power problems. Small studies also limit investigators’ ability to identify at-risk subsets of the population, although asthmatics were certainly considered. Age groups that are often cited as most at risk, infants and the elderly, were not. Only two studies examined subjects beyond middle age, and the eldest was 73 years of age.
4.6 Discussion of LOAELs for Chronic and Acute Exposures to $\text{SO}_2$

4.6.1 Chronic Exposure

Standard setting to protect against chronic exposure to $\text{SO}_2$ is best addressed by the epidemiological literature on the respiratory health of exposed subjects. This literature usually reported long-term averages of 24-hour measurements from ambient monitoring stations or of shift-long (likely 8-hour) measurements of occupational exposures. Although not always explicitly expressed, the outcomes examined tended to be effects expected to develop over a period of years, such as decrements in lung function, or chronic respiratory symptoms.

The only study [Kehoe et al., 1932] which examined truly independent exposures to $\text{SO}_2$ found increases in almost all respiratory symptoms in employees using the gas as a refrigerant; they were exposed to very high concentrations in the range of 10 to 100 ppm. The studies in smelters, pulp mills, and silicon carbide plants which examined average exposures of 0.5 ppm and higher usually found decrements in FEV$_1$, as well as increases in cough, phlegm, dyspnea, and chronic obstructive pulmonary disease in exposed workers. Many reported anecdotal evidence of workers who chose to avoid exposure by either transferring to less exposed jobs or retiring early. Some, but not all of these studies controlled for co-exposures such as dust.

Among studies of populations residing near special ambient sources of $\text{SO}_2$, the study in Chongqing, China [Wang et al., 1999] showed the most convincing difference between the exposed and unexposed group, with significant decrements in lung function with long-term average exposures of 0.08 vs. 0.04 ppm, and little difference in particulate exposure. The study of the smelter city of Nikel, Russia and its region [Smith-Sivertsen et al., 2001], where the highest monthly means were 0.06 ppm showed no differences in lung function related to daily average exposure, but increased cough and phlegm in the more exposed Russian population. However, there was no control for differences in smoking and occupational exposures. Finally, in the Arizona smelter region [Dodge et al., 1985], again no lung function or asthma differences were associated with exposure, but children with the highest exposures (0.02 to 0.04 ppm) had a higher prevalence (but not cumulative incidence) of cough. There was no control for concurrent particulate exposures which did differ between the study groups, but not to the same extent as $\text{SO}_2$ exposures.

This evidence suggests that $\text{SO}_2$ has a chronic effect on lung function and respiratory symptoms and disease. The lowest observable adverse effect level (LOAEL) for lung function decrements appears to be about 0.08 ppm, averaged over about one year. The LOAEL for cough may be lower (0.02 to 0.04 ppm), but other explanations for the evidence in this regard cannot be ruled out.

Table 4.6 lists current exposure guidelines set in North America and by the World Health Organization (WHO). The annual air quality guidelines are in the range of the more tenuous LOAELs reported above: 0.01 to 0.03 ppm.
The epidemiological data reviewed in this report does not adequately address asthmatics, children, or the elderly as potential susceptible sub-populations. In occupational studies, several investigators noted an excess risk of respiratory disease or symptoms among SO$_2$-exposed subjects who were also smokers, implying a synergistic relationship between these two exposures.

The three studies which examined chromosomal damage and the one which found excess bladder and lung cancer risk, all included subjects exposed at levels higher than the above LOAELs. Genetic changes including cancer is a research area which deserves ongoing attention, as does the emerging area of reproductive outcomes and infant mortality. To date, most studies of the latter outcomes have been conducted in regions where the source of SO$_2$ exposure is typical mixed urban air pollution.

4.6.2 Acute Exposure

The studies of controlled human exposures provide the best evidence about the dose-related acute effects of SO$_2$. In healthy adults, few studies found changes in lung function or symptoms at exposures below 1 ppm, although bronchoconstriction did result at concentrations in the range of 2 to 5 ppm. Among the exceptions was a study of older adults (55 to 73 year of age) which found decrements in FEV$_1$ after exposure to 0.5 and 1 ppm for 30 minutes with exercise [Rondinelli et al., 1987].

Asthmatic adults and children were considerably more likely to react to lower concentrations of SO$_2$, with exposures over 0.5 ppm consistently resulting in decrements in FEV$_1$. Increases in airway resistance were consistently observed in exercising asthmatics, at even lower concentrations, including exposure-duration combinations as low as 0.2 ppm for 5 minutes and 0.1 ppm for 10 minutes. Reductions in FEV$_1$ were also observed at these low levels when adolescents and adults were exposed to SO$_2$ either during or after exposure to similar concentrations of ozone.

This evidence suggests that asthmatics, especially when breathing through the mouth, are sensitive to low concentrations of SO$_2$ even with very short durations of exposure. The lowest observable adverse effect level (LOAEL), though not consistently replicated, was 0.1 ppm during 10-minute exposures.

Among the acute exposure guidelines set in Canada, the US and the WHO (Table 4.6, overleaf), only the WHO guideline recognizes the potential speed of asthmatic response to this gas, with a 10-minute guideline of 0.175 ppm.
**Table 4.6 Ambient Air Standards for SO₂ (in ppm)**

<table>
<thead>
<tr>
<th>Type of Standard</th>
<th>Canadian Air Quality Objectives</th>
<th>United States National Ambient Air Quality Standards</th>
<th>World Health Organization Health-Based Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maximum Desirable</td>
<td>Maximum Acceptable</td>
<td>Maximum Tolerable</td>
</tr>
<tr>
<td>Annual</td>
<td>0.011</td>
<td>0.023</td>
<td>0.030</td>
</tr>
<tr>
<td>24 hours</td>
<td>0.057</td>
<td>0.115</td>
<td>0.306</td>
</tr>
<tr>
<td>3 hours</td>
<td>0.172</td>
<td>0.344</td>
<td></td>
</tr>
<tr>
<td>1 hour</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 minutes</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5 References


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