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SULFUR DIOXIDE
(CAS Reg. No. 7446-09-5)

FINAL ACUTE EXPOSURE GUIDELINE LEVELS
(AEGLs)

May, 2008

PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicologic and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. Three levels AEGL-1, AEGL-2 and AEGL-3 are developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m³]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m³) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m³) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

EXECUTIVE SUMMARY

Sulfur dioxide is a colorless gas at ambient temperature and pressure. It can be detected by taste at concentrations of 0.35-1.05 ppm and has a pungent, irritating odor with an odor threshold of 0.67-4.75 ppm. Sulfur dioxide is used in the production of sodium sulfite, sulfuric acid, sulfuryl chloride, thionyl chloride, organic sulfonates, disinfectants, fumigants, glass, wine, industrial and edible protein, and vapor pressure thermometers. It is also used during the bleaching of beet sugar, flour, fruit, gelatin, glue, grain, oil, straw, textiles, wood pulp, and wood. Sulfur dioxide is also used in leather tanning, brewing and preserving, and in the refrigeration industry. It is a by-product of ore smelting coal, and fuel-oil combustion, paper manufacturing, and petroleum refining (WHO, 1984).

Sulfur dioxide is an irritant of the upper respiratory tract and eyes. Conjunctivitis, corneal burns, and corneal opacity may occur from direct contact with high concentrations of sulfur dioxide. Death from respiratory arrest may occur from acute over-exposure, while survivors may develop bronchitis, bronchopneumonia, and fibrosing obliterative bronchiolitis. Bronchoconstriction accompanied by increased pulmonary resistance may be asymptomatic or may occur with high-pitched rales. Moderate exposure may result in a prolonged expiratory phase. Respirable particles, cold air, dry air, exercise, and mouth-breathing may increase the severity of adverse effects caused by sulfur dioxide (WHO, 1984).

AEGL-1 values were based on the weight-of-evidence from human asthmatic data suggesting that 0.20 ppm may be a NOEL for bronchoconstriction in exercising asthmatics. No treatment-related effects were noted in asthmatics exposed to 0.2 ppm for 5 min (Linn et al., 1983b), 0.25 ppm for 10-40 min (Schacter et al., 1984), 0.25 ppm for 75 minutes (Roger et al., 1985), 0.5 ppm for 10-40 min (Schacter et al., 1984), or 0.5 ppm for 30 minutes (Jorres and Magnussen, 1990). However, an increase in airway resistance (S_{Raw}) of 134-139% was observed in exercising asthmatics exposed to 0.25 ppm for 5 minutes (Bethel et al., 1985); the increase in S_{Raw} in this study, but not in the other studies, may be attributed to the lower relative humidity (36%) in the Bethel et al. (1985) study compared to the other studies (70-85%). No uncertainty factors were applied because the weight of evidence approach utilized studies from a sensitive human population, exercising asthmatics. The role of exposure duration to the magnitude of SO₂-induced bronchoconstriction in asthmatics appears to decrease with extended exposure. For example, asthmatics exposed to 0.75 ppm SO₂ for 3-hours exhibited increases in S_{Raw} of 322% 10-min into exposure, 233% 20-min into the exposure, 26% 1-hr into the exposure, 5% 2-hours into the exposure, and a decrease of 12% at the end of the 3-hour exposure period. These data suggest that a major portion of the SO₂-induced bronchoconstriction occurs within 10-minutes and increases minimally or resolves beyond 10-minutes of exposure. Therefore, AEGL-1 values for SO₂ were held constant across all time points. Exposure to concentrations at the level of derived AEGL-1 values is expected to have no effect in healthy individuals, but are consistent with the definition of AEGL-1 for asthmatic individuals.

AEGL-2 values were based on the weight-of-evidence from human asthmatic data suggesting that 0.75 ppm induces moderate respiratory response in exercising asthmatics for exposure durations of 10-minutes to 3-hours (Hackney et al., 1987; Schacter et al., 1984). No uncertainty factors were applied because the weight of evidence approach utilized studies from a sensitive human population, exercising asthmatics. The role of exposure duration to the

magnitude of SO₂-induced bronchoconstriction in asthmatics appears to decrease with extended exposure. For example, asthmatics exposed to 0.75 ppm SO₂ for 3-hours exhibited increases in SRaw of 322% 10-min into exposure, 233% 20-min into the exposure, 26% 1-hr into the exposure, 5% 2-hours into the exposure, and a decrease of 12% at the end of the 3-hour exposure period. These data suggest that a major portion of the SO₂-induced bronchoconstriction occurs within 10-minutes and increases minimally or resolves beyond 10-minutes of exposure. Therefore, AEGL-2 values for SO₂ were held constant across all time points. Exposure to concentrations at the level of derived AEGL-2 values is expected to have no effect in healthy individuals, but are consistent with the definition of AEGL-2 for asthmatic individuals.

The AEGL-3 values were based on a calculated BMLC₀₅ in rats exposed to SO₂ for 4-hours (573 ppm) (Cohen et al., 1973). An uncertainty factor of 10 was applied for intraspecies extrapolation due to the wide variability in response to SO₂ exposure between healthy and asthmatic humans. An uncertainty factor of 3 was applied for interspecies variability; this factor of 3 was considered sufficient because no deaths were reported in guinea pigs exposed to 750 ppm SO₂ for 1 hour (Amdur, 1959), in dogs exposed to 400 ppm SO₂ for 2 hours (Jackson and Eady, 1988), or in rats exposed to 593 ppm for 4-hours (Cohen et al., 1973). Furthermore, a median lethal exposure time (Lt₅₀) of 200 minutes was reported for mice exposed to 900 ppm SO₂ (Bitron and Aharonson, 1978) and three of eight rats died when exposed to 965 ppm for 240 minutes (Cohen et al., 1973), suggesting limited interspecies variability. Data are not sufficient to ascertain whether a maximal response to SO₂ for a lethal endpoint is obtained within 10 minutes. Therefore, time scaling will be utilized in the derivation of AEGL-3 values. It has been shown that the concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al., 1986). Data were unavailable for an empirical derivation of n for sulfur dioxide. Therefore, an n of 3 was applied to extrapolate to the 1-hour time period, and n of 1 was used for extrapolation to the 8-hour time period to provide AEGL values that would be protective of human health (NRC, 2001). The 1-hour AEGL-3 value was also adopted as 10-minute and 30-minute values because asthmatic humans are highly sensitive to sulfur dioxide at short time periods.

The calculated values are listed in Table 1 below.

TABLE 1. Summary of AEGL Values For Sulfur Dioxide						
Classification	10-min	30-min	1-h	4-h	8-h	Endpoint (Reference)
AEGL-1 (Nondisabling)	0.20 ppm (0.52 mg/m ³)	0.20 ppm (0.52 mg/m ³)	0.20 ppm (0.52 mg/m ³)	0.20 ppm (0.52 mg/m ³)	0.20 ppm (0.52 mg/m ³)	NOEL for bronchoconstriction in exercising asthmatics (Linn et al., 1983b; Schacter et al., 1984; Roger et al., 1985; Jorres and Magnussen, 1990; Bethel et al., 1985)
AEGL-2 (Disabling)	0.75 ppm (1.95 mg/m ³)	0.75 ppm (1.95 mg/m ³)	0.75 ppm (1.95 mg/m ³)	0.75 ppm (1.95 mg/m ³)	0.75 ppm (1.95 mg/m ³)	Moderate bronchoconstriction in exercising asthmatics (Schacter et al., 1984 Hackney et al., 1984)
AEGL-3 (Lethality)	30 ppm (78 mg/m ³)	30 ppm (78 mg/m ³)	30 ppm (78 mg/m ³)	19 ppm (49 mg/m ³)	9.6 ppm (25 mg/m ³)	Calculated BMCLC05 in the rat after a 4-h exposure (Cohen et al., 1973)

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1. INTRODUCTION

Sulfur dioxide is a colorless gas at ambient temperature and pressure. It can be detected by taste at concentrations of 0.35-1.05 ppm and has a pungent, irritating odor with an odor threshold of 0.67-4.75 ppm. It is soluble in water and forms sulfurous acid which is slowly oxidized to sulfuric acid by dissolved oxygen. In the gaseous state, sulfur dioxide may react with oxygen to form sulfur trioxide which then reacts with moisture to form sulfuric acid. Sulfuric acid may also be associated with airborne particles and react with the particles to form other sulfur compounds (WHO, 1984).

Sulfur dioxide is produced by burning sulfur or iron pyrites in air and is used in the production of sodium sulfite, sulfuric acid, sulfuryl chloride, thionyl chloride, organic sulfonates, disinfectants, fumigants, glass, wine, industrial and edible protein, and vapor pressure thermo-meters. It is also used during the bleaching of beet sugar, flour, fruit, gelatin, glue, grain, oil, straw, textiles, wood pulp, and wood. Sulfur dioxide is also used in leather tanning, brewing and preserving, and in the refrigeration industry. It is a by-product of ore smelting, coal and fuel-oil combustion, paper manufacturing, and petroleum refining (WHO, 1984).

Sulfur dioxide is an irritant of the upper respiratory tract and eyes. Conjunctivitis, corneal burns, and corneal opacity may occur from direct contact with high concentrations of sulfur dioxide. Death from respiratory arrest may occur from acute over-exposure, while survivors may develop bronchitis, bronchopneumonia, and fibrosing obliterative bronchiolitis. Bronchoconstriction accompanied by increased pulmonary resistance may be asymptomatic or may occur with high-pitched rales. Moderate exposure may result in a prolonged expiratory phase of the respiratory cycle. Co-exposure to respirable particles may increase the severity of adverse effects caused by sulfur dioxide (WHO, 1984).

The chemical structure is depicted below, and the physicochemical properties of sulfur dioxide are presented in Table 2.

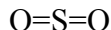


TABLE 2. Physical and Chemical Data		
Characteristic/Property	Data	Reference
Synonyms	Sulfurous anhydride, sulfur oxide, sulfurous oxide, sulfurous acid anhydride	ATSDR, 1998
CAS Registry No.	7446-09-5	ATSDR, 1998
Chemical Formula	SO ₂	ATSDR, 1998
Molecular Weight	64.07	ATSDR, 1998
Physical State	Gas (or liquid)	ATSDR, 1998
Odor	Pungent, irritating	ATSDR, 1998
Vapor Pressure	2477 mm Hg at 20°C	ATSDR, 1998
Specific Gravity	2.927 g/L (gas) (air = 1)	ATSDR, 1998
Melting/Boiling/Flash Point	-72.7°C/-10°C/no data	ATSDR, 1998
Solubility	Soluble in water and organic solvents	ATSDR, 1998
Conversion factors in air	1 ppm = 2.6 mg/m ³ 1 mg/m ³ = 0.38 ppm	NRC, 1984

2. HUMAN TOXICITY DATA

2.1 Case-Reports

2.1.1 Acute Lethality

Charan et al. (1979) described an industrial accident in a paper mill resulting in the deaths of two of five exposed workers. Two maintenance workers (ages 56 and 59 years, non-smokers) were repairing a digester partially filled with wooden chips. The digester was in a large shed where the temperature was 70° F. The valve of a line containing SO₂ and steam was accidentally opened by another worker and the digester was immediately filled with concentrated SO₂ under pressure. Both workers climbed out using a rope ladder suspended in the digester. Both workers died of respiratory arrest within 5 minutes of escape from the digester.

Post-mortem examination revealed a "coagulated appearance" of the pharynx and larynx, frequent denudation of superficial columnar epithelium accompanied by retention of basal cells, and pink edema fluid in the airways. Histologic examination of the lungs showed extensive sloughing of the mucosa of the large and small airways and hemorrhagic alveolar edema. Three additional workers, presumably exposed to lower concentrations of SO₂, survived the accident; these include a worker who helped the trapped workers escape, an individual wearing a dual-cartridge mask ascending to the top of the digester by an open elevator, and a fireman who responded to the accident. The acute symptoms in the 3 survivors included ocular, nasal, and throat irritation and soreness, chest tightness, and intense dyspnea.

The eyes had severe conjunctivitis and superficial corneal burns and the pharyngeal mucosa was hyperemic but free of ulcerations. Pulmonary function tests performed at regular intervals showed that one survivor was asymptomatic, one survivor developed asymptomatic mild obstructive and restrictive disease, and the third survivor developed symptomatic severe airway obstruction unresponsive to bronchodilators. No SO₂ exposure concentrations were provided.

In another report, Galea (1964) describes an accident in a pulp and paper mill where two men were exposed to an undetermined concentration of SO₂ for 15 to 20 minutes. One worker was a 45-year-old man who was a heavy smoker. He survived the accident but exhibited a delayed chronometric vital capacity, prolonged expiratory phase, and marked respiratory fatigue four months after the accident. The second worker was a 35-year-old man who was a non-smoker. He presented with slight ocular irritation and pain on deep breathing.

He was released from the hospital a few days after the accident since his clinical condition had improved. Ten days later, he was readmitted complaining of a dry, irritable cough, dyspnea, and mucous. He had rales at both lung bases and required a tracheotomy on the seventh day of his readmission. He died the following day, seventeen days after the date of the accident. Extensive peribronchiolar fibrosis and bronchiolitis obliterans was assumed to be responsible for the acute emphysematous changes consistent with the immediate cause of death.

Rabinovitch et al. (1989) described an accident in an underground copper mine where three healthy male workers were exposed to high concentrations of SO₂ as the result of a copper iron sulfide dust explosion. One miner died within minutes. The other two survived by covering their heads with rubber pants and using compressed air to provide adequate ventilation. They were rescued 3.5 hours after the explosion at which time the measured SO₂ concentration was greater than 40 ppm. No other toxic gases were identified and particles of copper and iron were at background levels for the mine. The survivors presented with intense

burning of the eyes, nose, and throat, dyspnea, diffuse precordial and retro sternal chest pain, nausea, vomiting, and urinary incontinence. One of the workers had skin irritation resulting in first degree burns. Two weeks after the accident, all of their symptoms except the dyspnea had resolved. Within three weeks of the accident, both workers had severe airway obstruction, hypoxemia, markedly decreased exercise tolerance, ventilation-perfusion mismatch, and evidence of active inflammation (positive gallium scan). Progressive improvement was observed over the next year; however, ventilation-perfusion scans remained abnormal.

In another mining accident, nine workers were descending into a mine in a cage of a hoist at which time a pyrite (FeS_2) explosion occurred (Harkonen et al., 1983). The workers were exposed to gases, primarily an undetermined concentration of SO_2 , for 20 to 45 minutes. At the mining level, the workers tried to rescue themselves by breathing from compressed air vents. One of the workers died and the others were injured. The lung function of the survivors was followed for 4 years. The largest decreases in forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and maximal midexpiratory flow were observed 1 week after the accident. Pyrometer indicated obstructive findings in 6 workers and restrictive findings in 1 worker. After three months, no further lung function decrement occurred; however, four years after the accident, bronchiolar obstruction was still present in three workers.

2.1.2 Nonlethal Toxicity

Wunderlich et al. (1982) described an accident where a 12-year-old boy fell into a pit (4 m deep; 2.45 x 1.45 m area) containing SO_2 on the grounds of a chemical manufacturing plant. He was not able to free himself and remained in the pit for approximately 4 hours until he was found and rescued. Several days later, the measured concentration of SO_2 in the pit was 4.8 ppm; thus, it is possible that the concentration was higher at the time of the accident. He presented with acute irritation of the eyes and mucous membranes of the upper airways, rhinopharyngitis, laryngitis, bronchitis, conjunctivitis, and corneal lesions. These effects persisted for five days and were followed by a symptom-free period of three days. Bronchitis, bronchiolitis, alveolitis, emphysema of the lung, and bronchiectasis then developed and persisted for 12 months in spite of aggressive therapy. Thereafter, lung emphysema and continuous partial respiratory insufficiency, accompanied by ventilatory obstruction were observed for 4 years. No follow-up beyond four years was reported.

Charan et al. (1979), Galea (1964), Rabinovitch et al. (1989), and Harkonen et al. (1983) describe cases where both non-lethal and lethal effects were observed. These case-reports are described in Section 2.1.1.

2.2. Epidemiologic Studies

2.2.1 Occupational Exposure

Lung function and sputum cytology were compared between copper smelter workers chronically exposed to 0.3 to 4 ppm SO_2 and a control group of mine repair shop workers (Archer et al., 1979). All subjects were white males and exposed and control subjects were paired by age and smoking habits. Measurements of FVC, FEV_1 , FEF_{50} , and closing volume were made both before and after the work shift for both exposed and control workers. Sputum samples for cytological analysis were also collected from both groups of workers. Mean FEV_1

and FVC values were significantly ($p < 0.05$) decreased after a work shift in the smelter compared to controls and significantly more smelter workers had decreased FEV₁ and FEF₅₀ values during the day when compared to controls. Also, more smelter workers complained of chest tightness compared to the control workers. Smelter workers had a higher percentage of sputum samples with moderate and marked atypical than controls; however, the cytological effects did not reach statistical significance.

Sulfur dioxide is used as a bleaching agent in the production of brooms. In another workplace monitoring study, Savic et al. (1987) compared a group of 190 workers from a broom manufacturing factory with a group of 43 workers not exposed to SO₂ in the workplace (no other information concerning the control groups was provided). Sulfur dioxide concentrations in the broom factory ranged from 0 to 0.285 ppm during the summer (windows were open) and from 6.5 to 56.8 ppm in the winter. Dust concentrations were similar in both summer (0-21 mg/m³) and winter (3-27 mg/m³). The most common subjective symptoms reported by exposed workers included coughing (94.2%), dyspnea (91.0%), burning of the nose, eyes, and throat (74.7%), tearing (64.7%), and substernal pain (75.3%). Sulfate concentration in the urine and methemoglobin concentration in the blood of exposed workers was significantly increased ($p < 0.01$) compared to controls. No difference was found in sulfhemoglobin concentrations.

2.2.2 Community Exposure: Ambient Air Pollution

Many studies concerning the relationship between SO₂ exposure in polluted air and human health have been conducted; however, these studies are confounded by the presence of particulate matter and other air pollutants. Perhaps the most notable example of increased mortality from SO₂ and particulate matter exposure occurred in London in the 1950's (WHO, 1979). The London episode lasted 5 days. The number of deaths was approximately 4000 more (a three-fold increase) than would have been expected under normal circumstances. Most deaths occurred in the elderly and in people with preexisting cardiac or respiratory disease. Peak SO₂ concentrations were 1.3 ppm while particulate matter concentrations were too high to be monitored (4.5 mg/m³ was provided as a conservative estimate). The excess deaths were attributed to bronchitis or to other impairments of the respiratory tract. Increased mortality from cardiac effects was also observed. The effects observed from this incident are attributed to the combination of SO₂ and extremely high concentration of particulate matter. Direct attribution of effects to SO₂ is toxicologically questionable because of the exceptionally high concentrations of particulate matter. (See Section 4.4).

More recently, Touloumi et al. (1994) examined the effects of air pollution on mortality in Athens, Greece from 1984-1988. Mean SO₂ levels (averaged over 2 recording stations) for the 5-year period ranged from 0.014 to 0.027 ppm. Total mortality was associated with SO₂, smoke, and CO, with both SO₂ and smoke being independent predictors of daily mortality. The strongest association was found for mortality lagged for 1 day. However, this study is of limited use due to the confounding pollutants and long exposure period (up to 5 years). In another study, Rahlenbeck and Kahl (1996) examined the relationship between mortality and air pollution in East Berlin for the winters of 1981-1989. When controlling for temperature and humidity, both SO₂ and suspended particles were found to be contributors to excess mortality, the strongest association found for mortality lagged for 2 days. The mean SO₂ concentration over the 9-year period was 0.063 ppm.

Rao et al. (1973), Castellsague et al. (1995), and Goldstein and Weinstein (1986) found no relationship between air pollution sulfur dioxide peaks and asthma attack rates in children. In another study, Partti-Pellinen et al. (1996) found increased incidences of cough, respiratory infections, and headache in residents living near a pulp mill compared with a reference community. The average SO₂ concentrations were 0.00038 ppm in the reference community and 0.00076-0.0011 ppm in the exposed community. However, in view of the existing experimental database, it is likely that confounding pollutants, and not solely SO₂, contributed to the observed effects.

Many other reports have shown an association between sulfur dioxide exposure and respiratory symptoms such as decreased lung function, coughing, chest tightness, and increased incidences of respiratory infections (Braback et al., 1994; Higgins et al. 1995; Braun-Fahrlander et al., 1997; Hoek and Brunekreef, 1993; Peters et al., 1997; Saric et al., 1981; Schwartz et al., 1994; Soyseth et al., 1995; Stebbings and Hayes, 1976; Vedal et al., 1987). However, these epidemiological studies are of limited usefulness to define a precise cause-effect relationship since other air pollutants, especially particulate matter, ozone, and nitrogen oxides, are also present.

2.3 Experimental Studies

Many controlled human studies examining the effects of SO₂ are available and indicate that the respiratory system is the principal target after acute exposure. Data show that asthmatics are particularly sensitive to the effects of SO₂ and that effects are enhanced (in both healthy individuals and asthmatics) by exercise. Since it would not be feasible to include all available human SO₂ data, the studies summarized below are considered sufficient to be quantitatively representative of data describing effects from acute exposure to SO₂. Selected data from controlled exposures to SO₂ in non-asthmatic individuals are presented in Table 3 and data from asthmatic individuals are presented in Table 4.

2.3.1 Non-asthmatic Subjects

Amdur et al. (1953) exposed 14 healthy males (ages 28-58 years) to varying concentrations of SO₂ through a face mask for 10 minutes. At 5 ppm most subjects complained of dryness in the throat and upper respiratory passages. Decreased respiratory volume and increased respiratory rate were noted at 1-8 ppm SO₂.

Stacy et al. (1981) examined the effect of SO₂ exposure on healthy nonsmoking males between the ages of 18 and 40 years. A total of 31 subjects were studied. Sixteen subjects were exposed to 0.75 ± 0.04 ppm SO₂ and 15 were exposed to air for 2 hours. All subjects had intradermal skin tests for 16 allergens common to the geographical area where the study was performed. Relative humidity in the exposure chamber was maintained at 60% and temperature at 21°C. Recirculation and reconditioning of chamber air through HEPA filters kept total particle mass to $< 3 \mu\text{g}/\text{m}^3$ and particle count at 1×10^5 particles/ m^3 , thus, creating unfavorable conditions for sulfate formation. Each subject exercised on a treadmill at 6.4 kmph and 10% incline beginning 45 minutes after entry into the chamber. Only parameters related to air flow resistance were significantly affected by SO₂ exposure, although spirometric parameters exhibited a similar trend. At the end of the first hour of exposure,

airway resistance (S_{Raw}) was increased between 2 and 55% in 14 of 16 subjects exposed to SO₂. The average increase was 14.6% compared with a mean decrease of 10.3% in air-exposed subjects. The SO₂-exposed subjects positive for allergen skin-tests appeared to be more reactive to SO₂ than those negative for allergen skin-tests. A component of this study examining nasal mucosa was published later (Carson et al. 1987). Nasal epithelium was obtained from 7 of the subjects and showed increases in the incidence of compound cilia accompanied by abnormal ciliary membrane ultrastructure in 4 of the 7 subjects.

In another study, Sandstrom et al. (1988) exposed eight healthy, nonsmoking subjects (ages 21-29 years, sex not specified) to 0, 0.4, 2, or 4 ppm SO₂ for 20 minutes. During the first 5 minutes of exposure, the electrodes on the subjects were adjusted by a technician. The subjects then worked on a bicycle ergometer at a work load of 75 W for the remaining 15 minutes. The exposure chamber was made of anodized aluminum and had a volume of 14.1 m³. During exposure the chamber temperature was 20°C, relative humidity was approximately 50%, and there was one air exchange every 2 minutes. The SO₂ atmosphere in the chamber was produced by addition of a gas stream from a 1% SO₂ gas tube to the chamber air inlet. The chamber air was analyzed continuously by color metric titration. There were no treatment-related effects on heart rate, breathing rate, FEV_{1.0}, FEF₂₅₋₇₅, FVC, gas distribution, or closing volume. Five of eight subjects reported nasal irritation at 4 ppm only. Unpleasant odor was reported more frequently (p<0.05) at the end of the exposure to 4 ppm SO₂ than before exposure at the beginning of this exposure period. Throat irritation was significantly (p<0.05) increased during exposure to 2 ppm SO₂. It was also reported more frequently during and at the end of 4 ppm SO₂ exposure than before exposure (p<0.02) and was also more common (p<0.05) at the end of exposure to 4 ppm compared to the end of the 0.4 ppm exposure period.

Sandstrom et al. (1989a) also examined the effects of SO₂ exposure on broncho-alveolar lavage fluid (BAL) parameters. Healthy subjects (ages 22-30 years, sex not specified) were exposed to 4 (10 subjects) or 8 ppm (4 subjects) SO₂ for 20 minutes while exercising on a bicycle ergometer with a work load of 75 W. The exposure chamber and test atmosphere generation were the same as that described above in Sandstrom et al. (1988). An increase in alveolar macrophage activity was observed 24 hours after exposure to 4 ppm SO₂ as evidenced by an increase in lysozyme positive macrophages. Twenty-four hours after exposure to 8 ppm of SO₂ a further increase (2 to 4 times higher than pre-exposure values) was observed and was accompanied by an increase in total numbers of macrophages and lymphocytes. Seventy-two hours post-exposure, the BAL fluid from subjects exposed to 8 ppm had returned to baseline values.

In another report, Sandstrom et al. (1989b) exposed 22 healthy males (ages 22-27 years) to 8 ppm SO₂ for 20 minutes. The exposure chamber, atmosphere generation, and exercise regimen were identical to that described above. BAL was analyzed from 8 subjects at each of the following time intervals: 2 weeks before exposure, and 4, 8, 24, and 72 hours after exposure. Increased numbers of lysozyme positive macrophages, lymphocytes, and mast cells were observed 4 hours after exposure. Lymphocytes, lysozyme-positive macrophages, total alveolar macrophage counts, and total cell number reached a peak at 24 hours post-exposure and had returned to pre-exposure values by 72 hours. Sandstrom et al. (1989c) also exposed 22 healthy males (ages 22-37 years) to 4, 5, 8, or 11 ppm SO₂ for 20 minutes. Exposure conditions were the same as those described above; however, no exercise period was included.

Mast cells, lymphocytes, lysozyme positive macrophages, and the total number of macrophages were increased in BAL fluid 24 hours post-exposure. The effects were concentration dependent at 4, 5, and 8 ppm, but no further increase was detected at 11 ppm.

Kulle et al. (1984) exposed twenty healthy, nonsmoking adults (10 males and 10 females) ages 20 to 35 years-old to filtered air or 1 ppm SO₂ for 4 hours. Each subject served as his own control and exercised for 15 minutes at both 1 and 3 hours into the exposure period. The exercise consisted of riding a bicycle ergometer at a work load of 100 watts at 60 RPM and was designed to ensure a short period of increased ventilation and to simulate the type of activity engaged in by many city dwellers. The exposures were conducted in a 22.2 m³ exposure room with a ventilation rate of 8.49 m³/min, allowing for a complete air change every 2.6 minutes. Temperature was maintained at 22.2°C and relative humidity at 60%. Air entering the room was passed through HEPA filters and activated carbon fibers to remove contaminants. Sulfur dioxide was metered into the room by an air input diffuser and the concentration continuously monitored by a pulsed fluorescent analyzer and a flame photometric analyzer. There were no treatment-related effects on lung function as measured by spirometry, body plethysmography, and methacholine inhalation challenge. Four subjects reported upper respiratory irritation and one reported ocular irritation during SO₂ exposure. Seven subjects perceived the presence of the SO₂ due to odor and/or taste.

Eleven healthy male adults were exposed to 0, 1, 5, or 13 ppm SO₂ for up to 30 minutes (most exposures were for 10 minutes) (Frank et al., 1962). Exposures were spaced 1 month apart and subjects were seated in a volume displacement body plethysmograph, breathing through the mouth while respiratory measurements were made with an esophageal catheter. The SO₂ was administered by occlusion of one port of a wide T-tube that led to room air through which the subjects had been breathing, and by opening the other port leading to the SO₂ source. Subjects were blind to the SO₂ concentration administered, with the exception of one subject who was an author of the study. Pulmonary flow resistance was increased an average of 39% above controls at 5 ppm (p<0.01) and an average of 72% above control at 13 ppm (p<0.001). Within one minute of exposure, flow resistance increased (p<0.001), with a greater increase observed after 5 minutes (p<0.05). No further increase occurred after 10 minutes, and the authors concluded that the peak response occurred between 5 and 10 minutes. Cough, irritation, and increased salivation were also observed at 5 ppm. No treatment-related effects were observed at 1 ppm.

In another study, Frank et al. (1964) administered SO₂ alone or in combination with a physiologically inert NaCl aerosol to 6 healthy non-smoking adult males. The SO₂ concentrations were 1-2, 4-6, or 14-17 ppm; NaCl aerosol concentration averaged 18 mg/m³ (range 10-30 mg/m³). Techniques of exposure and measurement were similar to those described above in Frank et al., (1962). Changes in pulmonary flow resistance induced by SO₂ and the SO₂-NaCl aerosol mixture were similar. No significant effect was observed at 1-2 ppm SO₂ with or without NaCl. A concentration-dependent increase in pulmonary flow resistance was observed at 4-6 and 14-17 ppm SO₂ with or without NaCl. Exposures lasted 30 minutes and as in the previous study, maximum effect was observed after 10 minutes and receded partially thereafter. In another study, Frank et al. (1964) compared oral and nasal SO₂ administration. Oral exposures were performed similarly to those described above, while nasal exposures were accomplished through a hard plastic mask fitted over the bridge of the nose and lower face. Concentrations of SO₂ were 15 or 29 ppm. Pulmonary flow resistance increased maximally at

10 minutes and was approximately 20% for 15 ppm mouth breathers, 65% for 28 ppm mouth breathers, 3% for 15 ppm nose breathers, and 18% for 28 ppm nose breathers. Cough or chest irritation was common in mouth breathers and rare in nose breathers.

Dautrebrande and Capps (1950) found no subjective nasal or ocular irritation in 11 healthy adults exposed to 0.55 ppm SO₂ for 10 minutes. Douglas and Coe (1987) applied various concentrations of SO₂ to the eyes of healthy adult subjects through close fitting goggles. In a separate set of experiments, various concentrations of SO₂ were administered via a mouthpiece. Ocular irritation was measured subjectively, whereas lung response was measured objectively via a plethysmograph. The threshold for ocular irritation was determined to be 5 ppm and the bronchoconstriction threshold was 1 ppm. Andersen et al. (1974) exposed 15 healthy males (ages 20-28 years) to 0, 1, 5, or 25 ppm SO₂ for 6 hours. Sulfur dioxide was metered through rotameters to the inlet duct for ventilating air to the climate chamber. Thorough mixing was accomplished by two fans upstream in the chamber. The SO₂ concentration was continuously monitored by a conductivity method. Nasal mucous flow was decreased at 5 and 25 ppm but not at 1 ppm. Decreases were concentration-dependent and ranged from 13 to 80% of controls. The decrease was greatest in the anterior portion of the nose; however, the affected area increased with increasing exposure time. An increase in nasal airflow resistance and a decrease in forced expiratory volume in one second were observed at 5 and 25 ppm, with little or no effect at 1 ppm. Five subjects complained about dryness in the nose and pharynx after exposure to 5 ppm SO₂. After the 25 ppm exposure, only two subjects had no complaints of irritative effects; dryness or a slight pain in the nose and pharynx was reported by 10 subjects, rhinorrhoea was reported by two subjects, and slight conjunctival pain was reported by 3 subjects. No subjective effects were reported at 1 ppm.

Rondinelli et al. (1987) exposed 10 healthy men (ages 55-73 years) to 0.5 ppm SO₂ and 1 mg/m³ sodium chloride droplet aerosol, 1 ppm SO₂ and 1 mg/m³ sodium chloride droplet aerosol, or 1 mg/m³ sodium chloride droplet aerosol alone. Subjects were exposed for 20 minutes at rest and 10 minutes during moderate exercise on a treadmill. Significant (p<0.05) decreases in FEV₁ were observed 2-3 minutes post-exercise in all treatment regimens. The decrease observed after sodium chloride aerosol and 1.0 ppm SO₂ was significantly greater than that observed after sodium chloride aerosol alone; however, average decreases were in the range of only 5-8% below baseline values.

TABLE 3. Selected Data from Exposure of Non-asthmatic Humans to SO ₂					
Concentration	Duration	Subjects	Exposure Parameters	Effect	Reference
1-8 ppm	10 min	14	Exposure through facemask	1-8 ppm: ↓Respiratory volume ↑ respiratory rate 5 ppm: dry throat	Amdur et al., 1953
0.75 ppm	2 h	16	21 °C, 60% RH, Treadmill exercise 45 min. after entering chamber	SRaw: ↑ 2-55% (14.6% avg)	Stacy et al., 1981
0.4 ppm 2.0 ppm 4.0 ppm	20 min	8	20 °C, 50% RH, exercise 75 W, last 15 min of exposure	No effects on respiratory function parameters. Nasal irritation: 4 ppm (5/8) Throat irritation: concentration-dependent at 0.4, 2, and 4 ppm	Sandstrom et al., 1988
4.0 ppm 8.0 ppm	20 min	10 4	20 °C, 50% RH, exercise 75 W	Transient concentration-related ↑ alveolar macrophage activity	Sandstrom et al., 1989a
8.0 ppm	20 min	22	20 °C, 50% RH, exercise 75 W	Transient concentration-related ↑ alveolar macrophage activity	Sandstrom et al., 1989b
4.0 ppm 5.0 ppm 8.0 ppm 11.0 ppm	20 min	22	20 °C, 50% RH, at rest	Transient ↑ in alveolar macrophage activity. Concentration-related up to 8 ppm, no further increase at 1 ppm	Sandstrom et al., 1989c
1.0 ppm	4 h	20	22.2 °C, 60% RH, exercise 100 W	No effects on lung function parameters. Upper respiratory irritation (4/20) Ocular irritation (1/20)	Kulle et al., 1984
1 ppm 5 ppm 13 ppm	10-30 min	11	Resting	No effects 39%↑ Pulmonary flow res. 72%↑ Pulmonary flow res. Peak response 5-10 min	Frank et al., 1962
1-2 ppm 4-6 ppm 14-17 ppm	30 min	6	Resting; exposures to SO ₂ alone or in combination with 18 mg/m ³ NaCl	No effects ↑ Pulmonary flow resistance ↑ Pulmonary flow resistance	Frank et al., 1964
15 ppm 29 ppm	10 min	11	Compared nose breathing vs. mouth breathing	↑ Pulmonary flow resistance 15 ppm : 3% Nose; 20% mouth 29 ppm: 18% Nose; 65% mouth	Frank et al., 1964
0.55 ppm	10 min	11		No nasal or eye irritation	Dautebrande and Capps, 1950
1 ppm 5 ppm 25 ppm	6 h	15	Resting	No effects Irritation. ↓FEV ₁ , ↓Nasal mucous flow Irritation. ↓FEV ₁ , ↓nasal mucous flow	Andersen et al., 1974

2.3.2 Asthmatic Subjects

Schachter et al. (1984) examined the effects of SO₂ on ten asthmatic (4 males, 6 females, age 27.3±5.1 years) and ten healthy (5 males, 5 females, age 26.1 ±6.3 years) humans. Subjects were exposed in a 3 x 3.7 x 2.4 m chamber with laminar airflow from floor to ceiling. The vertical flow system provided uniform gas conditions with no stagnant areas. The desired SO₂ concentrations were achieved by mixing concentrated gas (0.5% SO₂, balance nitrogen) with the chamber air in the circulating flow stream. Levels of SO₂ were continuously monitored from all chamber areas using a fluorescent SO₂ analyzer. Exposures were 0, 0.25, 0.50, 0.75, or 1.0 ppm SO₂ for 40 minutes. During the first 10 minutes, subjects exercised on a cycloergometer at 450 kpm/min. On separate days, subjects were exposed to 0 or 1.0 ppm SO₂ for 40 minutes in the absence of exercise. No significant effects were observed in pulmonary function parameters during the exercise or non-exercise protocols in nonasthmatic subjects at any SO₂ concentration. No effects were observed in non-exercising asthmatics or in exercising asthmatics at 0.50 ppm or below. In exercising asthmatics exposed to 0.75 ppm SO₂, effects were observed in airway resistance (150% increase), forced expiratory volume in one second (mean -8%), and maximal expiratory flow (mean -22%). In exercising asthmatics exposed to 1 ppm SO₂, significant (p<0.05) effects were observed in airway resistance (470% increase), forced expiratory volume in one second (mean -14%), and maximal expiratory flow (mean -27%), suggesting a concentration-response relationship. Pulmonary effects had resolved 10 minutes after the end of exercise even though SO₂ was still present in the chamber atmosphere.

Balmes et al. (1987) exposed two female and six male nonsmoking adult asthmatics to humidified air for 5 minutes or 0.5 or 1.0 ppm SO₂ for 1, 3, or 5 minutes during eucapnic hyperpnea (60 L/min). Each exposure occurred at the same time on a separate day. Metered flows of SO₂ from a calibrated tank and air from a compressed air source were mixed in a 3-L glass mixing chamber. The subjects inhaled the SO₂ from a mouthpiece attached and SO₂ concentrations were measured continuously with a pulsed fluorescent SO₂ analyzer just proximal to the mouthpiece. Bronchoconstriction, as indicated by increases in SRaw, increased over baseline with increasing exposure time and concentration. SRaw was increased 46% after exposure to 0 ppm for 5 min, and 34%, 173% and 234%, after exposure to 0.5 ppm for 1-min, 3-min, and 5-min, respectively. SRaw was increased 46% after exposure to 0 ppm for 5 min, and 93%, 395% and 580%, after exposure to 1.0 ppm for 1-min, 3-min, and 5-min, respectively. The effects observed after the 1 minute exposures were confined to 2 subjects who also developed chest tightness. After each 3 and 5 minute exposure, 7 of 8 subjects developed increases in SRaw accompanied by wheezing, chest tightness, or dyspnea and requested bronchodilator therapy.

Linn et al. (1985) exposed 22 young adult asthmatics (13 males and 9 females, ages 18-33 years) to all combinations of 2 atmospheric conditions (purified air and 0.6 ppm SO₂), 2 temperatures (21 and 38 °C), and 2 levels of relative humidity (20 and 80%). Exposure involved exercise on a constant-load bicycle ergometer at a work load sufficient to produce a ventilation rate of 50 L/min. The exercise lasted 5 minutes plus a brief warm-up and cool-down period. Exposure atmospheres were produced from SO₂ in a high-pressure cylinder being metered into a purified air inlet duct in a manner providing uniform stable concentrations inside the chamber. SO₂ levels were continuously monitored with duplicate flame photometric analyzers. Symptom questionnaires and body plethysmographic measurements were completed before and after each exposure. Physiologic changes during

clean air exposures were small under all temperature and humidity conditions. At high temperature with high humidity, no change in SRaw or SGaw were noted. At low temperature with high humidity or high temperature with low humidity, SRaw and SGaw were increased approximately 10%. At low temperature with low humidity SRaw and SGaw were increased approximately 20% during clean air exposure. Bronchoconstrictive responses were more severe in SO₂ exposures compared to clean air exposures, but followed a similar pattern with regard to temperature and humidity. In SO₂ exposures, mean SRaw increased 39% at high temperature and high humidity, 89% at high temperature and low humidity, 157% at low temperature and high humidity, and 206% at low temperature and low humidity. Corresponding decreases in SGaw (specific airway conductance) were 22, 44, 62, and 61%, respectively. Subjective reporting of upper and lower respiratory symptoms increased with exposure to SO₂ and appeared to be mitigated by high temperature.

In another study, Linn et al. (1983a) exposed 23 young adult asthmatics (15 males, 8 females, mean age 23 years) to 0 or 0.75 ppm SO₂ for 10-minutes during bicycle exercise (40 L/min) once while breathing unencumbered and once via a mouthpiece while wearing nose clips. At 0 ppm, SRaw was increased 54% by either exposure route. At 0.75 ppm, SRaw was increased 186% by oronasal breathing and 321% by mouthpiece.

In another study, Linn et al. (1983b) exposed 23 young adult asthmatics (13 males, 10 females, ages 19-31 years) to 0, 0.2, 0.4, or 0.6 ppm SO₂ for 5-minutes while exercising (48 L/min). Exposures were random order at 1-week intervals. At 0.2 ppm, there were no effects on SRaw, FEV₁, FVC or V_{max25-75} compared to controls. At 0.4 ppm, SRaw was increased 69%, and V_{max25-75} was decreased 10%, but there was no effect on FEV₁. At 0.6 ppm, SRaw was increased 120%, V_{max25-75} was decreased 26%, and FEV₁ was decreased 13%. Additionally, 21 of 23 subjects reported increased symptoms (cough, irritation, wheezing, and chest tightness) at 0.6 ppm, and 3 subjects required medication to relieve symptoms. No apparent effects were noted the next day or week.

Linn et al. (1984) also exposed a group of 14 asthmatics (12 males, 2 females, ages 18-33 years) to 0 or 0.6 ppm SO₂ for 6-hour periods on 2 successive days. Subjects exercised (50 L/min) for 5-minutes near the beginning of exposure and for an additional 5-min after 5 hours of exposure. At all other times, they were resting. Increases in SRaw were 136% after the first exercise period on day 1, 120% after the second exercise period on day 1, and 147% after the first exercise period on day 2, 100% after the second exercise period on day 2.

Bethel et al. (1983a) exposed ten asthmatics (8 males, 2 females, ages 22-36 years) to 0 or 0.5 ppm SO₂ for 5 minutes during moderately heavy bicycle exercise (60 L/min). Subjects were allowed to breathe freely. Mean SRaw was increased 238% after the exposure period. Bethel et al. (1983b) also exposed nine asthmatics (3 males, 5 females, ages 20-37 years) to 0 or 0.5 ppm SO₂ during low (27 L/min), moderate (41 L/min), or high exercise (61 L/min) via a mouthpiece while wearing a nose clip (oral breathing) or via a face mask (ornasal breathing). Each exposure was 5 min in duration. No SRaw effects were noted with low- or moderate exercise rates; however, SRaw was increased 219% compared to baseline at the high exercise rate.

In another study, Bethel et al. (1985) exposed 19 asthmatic adults (16 males, 3 females, ages 22-46 years) to 0 or 0.25 ppm SO₂ for 5 minutes while performing vigorous exercise

(60 L/min). SRaw increased 77% in the 0 ppm group and 134% in the 0.25 ppm group. Nine (7 males, 2 females) of these original 19 subjects then repeated the exposure, with more vigorous exercise (89-90 L/min); SRaw increased 102% in the 0 ppm group and 139% in the 0.25 ppm group.

Fourteen asthmatics (12 male, 2 female, ages 19-50 years) were exposed to 0, 0.5, or 1.0 ppm SO₂ for 10 minutes during light, medium, or heavy exercise (average ventilation 30, 36, and 43 l/min, respectively) (Gong et al., 1995). The ventilation rates were targeted to bracket a typical adult switching point from nasal to oronasal breathing. Exposures were conducted in a double-walled insulated cubical plexiglass chamber (2.2 m³). Air was supplied at a rate of 15 air changes/hour with no recirculation. SO₂ was metered into the air supply from a cylinder containing 5% SO₂ in nitrogen; concentration was continuously monitored with a pulsed fluorescent analyzer. At 0.5 ppm SO₂ during light exercise, mild to moderate (subjective ratings on a 1 to 10 scale) respiratory effects were reported by subjects, while at 1.0 ppm and heavy exercise, effects were rated as moderate to severe. Effects included shortness of breath, wheezing, and chest tightness. Both FEV₁ and SRaw showed significant ($p>0.05$) exposure-related effects; however, the exact magnitude is difficult to ascertain from the format of the reported data.

Roger et al. (1985) exposed 28 male asthmatics (ages 19-34) to 0, 0.25, 0.50, or 1.0 ppm SO₂. Each 75-minute exposure period included three 10-minute periods of moderate treadmill exercise. Exposures were in a random order at approximately the same time of day and day of the week, with at least 1 week between exposures. Exposures were conducted in a 4 x 6 x 3.2 m stainless steel chamber with continuous reconditioning and recirculation of the air. The SO₂ concentrations were continuously monitored with pulsed fluorescent analyzers. There was no significant effect on SRaw after the 0.25 ppm SO₂ exposure. SRaw was increased two- and three-fold after exposures of 0.5 and 1.0 ppm, respectively. Increases were greatest after the first 10 minute exercise periods and less after the latter two 10-minute periods (with the exception of one subject whose bronchoconstriction increased with increasing exercise and who was unable to complete the protocol). Shortness of breath and chest discomfort were reported ($p<0.001$) after 10 minutes of 1.0 ppm SO₂ exposure. Wheezing, deep breathing discomfort, and cough were also reported.

Horstman et al. (1986) exposed 27 male asthmatics (ages 18-35 years) to 0, 0.25, 0.50, or 1.0 ppm SO₂ for periods of 10-minutes, each on separate days. The test chamber and exposure conditions were similar to those described above (Roger et al., 1985). During exposures, subjects breathed normally and performed moderate exercise (42 L/min). Before and three minutes after each exposure SRaw was measured by body plethysmography. Those subjects whose SRaw was not doubled by exposure to 1.0 ppm were exposed to 2.0 ppm SO₂ for 10 minutes. Concentration-response curves of relative change in SRaw vs. SO₂ concentration were constructed for each subject to determine the concentration of SO₂ producing a 100% increase in SRaw over exercise in clean air. Substantial variation was observed: 25% of subjects experienced a 100% increase in SRaw at <0.5 ppm, 20% of subjects experienced a 100% increase only at concentrations >1.95 ppm. The median concentration for a 100% increase in SRaw was 0.75 ppm.

Horstman et al. (1988) exposed 12 male asthmatics (ages 22-37) to 0 or 1.0 ppm SO₂ for 0, 0.5, 1.0, 2.0, or 5.0 minutes (in random order on separate days) to determine the shortest

duration of exposure sufficient to induce bronchoconstriction significantly greater than that observed by exposure to clean air. The test chamber and exposure conditions were similar to those described above (Roger et al., 1985). The subjects exercised (40 L/min) on a treadmill during exposure. SRaw and symptom ratings increased with increased exposure duration, with significance ($p < 0.025$) being achieved at 2.0 min (121% increase) and 5.0 min (307% increase) exposures. Half of the subjects reported moderate or severe shortness of breath, chest discomfort, and/or wheezing after the 2- or 5-min exposures, and four subjects required bronchodilator therapy.

Sheppard et al. (1983) exposed eight asthmatic adults (4 males, 4 females, ages 22-36 years) to 0.5 ppm SO₂ via mouthpiece for 3 sets of 3-minute intervals while hyperventilating. Each exposure period was separated by a 30-minute rest period. The exposure protocol was repeated 24-hours and 1-week after the initial set of exposures. SRaw was increased 104% after the first 3-minute exposure, 35% after the 30-minute rest, and 30% after the third exposure. An increase in SRaw of 83% was observed at the 24-hr exposure, and 129% one week later.

Hackney et al. (1984) exposed 17 young adult asthmatics (13 males, 4 females, mean age 25 years) to 0.75 ppm SO₂ for a 3-hour period, exercising vigorously (45 L/min) for the first 10-min and resting thereafter. SRaw and symptoms were reported preexposure, immediately post-exercise, and after 1, 2, and 3-hours of exposure. On separate occasions, comparable exposures were performed and FEV₁ was measured after 15-min of exposure, in addition to the other tests. The exposure techniques are similar to those of Linn et al. (1985) described above except that relative humidity was 85%. In the exposure without spirometry, SRaw was increased 263% immediately after exercise (10-min into exposure), 200% at 20-minutes, 34% at 1-hr, 0% at 2-hr and was decreased 12% at 3-hr compared to preexposure values. In the exposure with spirometry, SRaw was increased 322% immediately after exercise (10-min into exposure), 233% at 20-minutes, 26% at 1-hr, 5% at 2-hr and was decreased 9% at 3-hr compared to preexposure values. FEV₁ was decreased 20% after 15-min of exposure. "Symptom scores" for low- and upper-respiratory irritation and nonrespiratory (headache, fatigue) symptoms were significantly ($p < 0.01$) increased after 10-min of exposure, and had returned to pre-exposure values at 1-, 2-, and 3-hr time points. These data suggest that effects peak within 10-minutes into the exposure and then subside within 1-hr.

Kehrl et al. (1987) exposed ten male asthmatics (ages 25-33 years) to 0 or 1.0 ppm SO₂ while performing 3 sets of 10-minute treadmill exercise (41 L/min) separated by 15-minute rest periods. The test chamber and exposure conditions were similar to those described above (Roger et al., 1985). SRaw was measured by whole body plethysmography before each exposure and after each exercise. Total mean SRaw was increased 172% after the first exercise, 137% after the second exercise, and 106% after the third exercise. A separate portion of the study involved exposure to 0 or 1.0 ppm SO₂ for a continuous 30 minute period while exercising, with mean SRaw increasing 233% at the end of the 30-min exposure period.

Fourteen asthmatics (10 males, 4 females, ages 20-55 years) were exposed to 0 or 0.5 ppm SO₂ for 30 minutes while at rest (Jorres and Magnussen, 1990). Subjects breathed the test atmosphere through a mouthpiece that was attached to a two-way valve and an air delivery bag. SO₂ concentration was continuously monitored by a fluorescent analyzer. No increase in SRaw was observed and no exposure-related subjective symptoms were noted.

Magnussen et al. (1990) exposed 46 adult asthmatics (21 males, 25 females, ages 16-62 years) to 0 or 0.5 ppm SO₂ for 20 minutes. During, the first 10-min of the exposure period, the subjects were at rest. The subjects then performed 10-min of isocapnic hyperventilation at a level of 30 L/min. Subjects breathed the test atmosphere through a mouthpiece, and SO₂ concentration was monitored by a fluorescent analyzer. A 45% increase in SRaw was observed after exposure to air, whereas a 163% increase in SRaw was observed after exposure to 0.5 ppm SO₂.

Koenig et al. (1980) exposed nine adolescent asthmatics (7 males, 2 females, ages 14-18 years) to filtered air, 1 ppm SO₂ and 1 mg/m³ sodium chloride droplet aerosol, or 1 mg/m³ sodium chloride droplet aerosol alone. Seated subjects breathed the test atmospheres by mouth through a rubber facemask. Exposures lasted 60 minutes and were divided into 30-minute sections with a brief (5 to 7 minute) interruption at the end of the first 30 minutes for functional measurements. Maximal flow at 50 and 75% of expired vital capacity were decreased with exposure to the SO₂-sodium chloride droplet aerosol. The mean change for V_{max75} was -14% after 30 minutes and -12% after 60 minutes of exposure. All nine subjects had a decrease after 30 minutes, and 7 were decreased after 60 minutes. The mean change for V_{max50} was -8% after 30 minutes, with effects noted in all 9 subjects. There was no effect after 60 minutes exposure. No other pulmonary function effects were noted in any exposure group. No subjective symptoms were reported.

Koenig et al. (1983) studied nine adolescent asthmatics (6 males, 3 females, ages 12-16 years). Exposures via mouthpiece were to 0.5 ppm SO₂ and 1 mg/m³ sodium chloride droplet aerosol, or 1 ppm SO₂ and 1 mg/m³ sodium chloride droplet aerosol, or 1 mg/m³ sodium chloride droplet aerosol alone. Exposures were 40-minutes in duration, which included 30-minutes at rest followed by 10-minutes exercising on a treadmill. No effects were noted in the sodium chloride aerosol alone group. FEV₁₀ decreased 15% at 0.5 ppm SO₂ and 23% at 1.0 ppm SO₂. Total respiratory resistance increased 47% at 0.5 ppm and 71% at 1.0 ppm and V_{max50} and V_{max75} were decreased 30 and 35%, respectively at 0.5 ppm and 51 and 61%, respectively at 1.0 ppm. Seven of the subjects then similarly inhaled 0.5 ppm SO₂ and 1 mg/m³ sodium chloride droplet aerosol via a face mask. No pulmonary function effects were noted.

Koenig et al. (1985) studied ten adolescent asthmatics (5 males, 5 females, ages 14-18 years). Exposures were both via mouthpiece or facemask to 0.5 ppm SO₂ and were 50 minutes in duration, which included 30-minutes at rest followed by 20-minutes exercising on a treadmill (43 L/min). After mouthpiece exposures, nasal resistance increased 32%, FEV₁ decreased 24%, and V_{max50} and V_{max75} were decreased 46 and 56%, respectively. Total respiratory resistance increased 60%. Facemask exposure resulted in an increase in nasal resistance of 30%, a decrease in FEV₁ of 16%, and V_{max50} and V_{max75} were decreased 26%.

TABLE 4.* Selected Data from Exposure of Asthmatic Humans to SO₂

Concentration	Duration	Subjects	Exposure Parameters	Effect	Reference
0.2 ppm	5 min	8	23 °C, 85% RH, exercise 48 L/min	None	Linn et al., 1983b
0.25 ppm	10-40 min	10	23 °C, 70% RH, exercise 35 L/min	None	Schacter et al., 1984
0.25 ppm	5 min	19	23 °C, 36% RH, exercise 60 L/min	SRaw ↑134%	Bethel et al., 1985
		9	23 °C, 36% RH, exercise 80-90 L/min	SRaw ↑139%	
0.25 ppm	75 min	28	26 °C, 70% RH, exercise 42 L/min intermittent	None	Roger et al., 1985
0.4 ppm	5 min	23	23 °C, 85% RH, exercise 48 L/min	SRaw ↑69% V _{max25-75} ↓10%	Linn et al., 1983b
0.5 ppm	10-40 min	10	23 °C, 70% RH, exercise 35 L/min	None	Schacter et al., 1984
0.5 ppm	5 min	10	23 °C, 41% RH, exercise 60 L/min	SRaw ↑238%	Bethel et al., 1983a
0.5 ppm	5 min	9	23 °C, 80% RH, exercise 27 L/min	None	Bethel et al., 1983b
			23 °C, 80% RH, exercise 41 L/min	None	
			23 °C, 80% RH, exercise 61 L/min	SRaw ↑219%	
0.5 ppm	1 min 3 min 5 min	8	22 °C, 75% RH, exercise 60 L/min	SRaw ↑34% SRaw ↑173% SRaw ↑234%	Balmes et al., 1987
0.5 ppm	20 min	46	23 °C, 92% RH, exercise 30 L/min for 10 min	SRaw ↑131%	Magnussen et al., 1990
0.5 ppm	30 min	14	24 °C, 50% RH, at rest	None	Jorres & Magnussen, 1990
0.5 ppm	50 min	10	22 °C, 75% RH, 30 min rest + 20 min exercise 43 L/min . Facemask	Nasal resistance ↑30% FEV ₁ ↓16% V _{max-50} ↓26% V _{max-75} ↓26%	Koenig et al., 1985
0.5 ppm	50 min	10	22 °C, 75% RH, 30 min rest + 20 min exercise 43 L/min . Mouthpiece	Nasal resistance ↑32% FEV ₁ ↓24% V _{max-50} ↓46% V _{max-75} ↓56%	Koenig et al., 1985
0.5 ppm	75 min	28	26 °C, 70% RH, exercise 42 L/min, intermittent	SRaw ↑100%	Roger et al., 1985
0.5 ppm	3 min x 3	8	23 °C, 82% RH, exercise (hyperventilating) intermittent	SRaw ↑104% (1st) SRaw ↑35% (2nd) SRaw ↑30% (3rd)	Sheppard et al., 1983
0.6 ppm	5 min	22	21 °C, 20% RH, exercise 50 L/min	SRaw ↑206% SRaw ↑157%	Linn et al., 1985

TABLE 4.* Selected Data from Exposure of Asthmatic Humans to SO ₂					
Concentration	Duration	Subjects	Exposure Parameters	Effect	Reference
			21 °C, 80% RH, exercise 50 L/min 38 °C, 20% RH, exercise 50 L/min 38 °C, 80% RH, exercise 50 L/min,	SRaw ↑89% SRaw ↑39%	
0.6 ppm	5 min	23	23 °C, 85% RH, exercise 48 L/min	SRaw ↑120% V _{max25-75} ↓26% FEV ₁ ↓13%	Linn et al., 1983b
0.75 ppm	3 h	17	22 °C, 85% RH, exercise 45 L/min (first 10-min of exposure)	SRaw ↑: 322% (at 10-min) 233% (at 20-min) 26% (at 1-hr) 5% (at 2-hr) FEV ₁ : ↓20% (at 15-min)	Hackney et al., 1984
0.75 ppm	10 min	23	23 °C, 90% RH, exercise 40 L/min Facemask Mouthpiece	SRaw ↑186% SRaw ↑321%	Linn et al., 1983a
0.75 ppm	10-40 min	10	23 °C, 70% RH, exercise 35 L/min	SRaw ↑150% FEF ↓22% FEV ₁ ↓8%	Schacter et al., 1984
1.0 ppm	10-40 min	10	23 °C, 70% RH, exercise 35 L/min	SRaw ↑470% FEF ↓27% FEV ₁ ↓14%	Schacter et al., 1984
1.0 ppm	75 min	28	26 °C, 70% RH, exercise 42 L/min, intermittent	SRaw ↑300%	Roger et al., 1985
1.0 ppm	30 min	10	26 °C, 70% RH, exercise 41 L/min (3- 10 min periods separated by rests of 15 min)	SRaw ↑172% SRaw ↑137% SRaw 106%	Kehrl et al., 1987
1.0 ppm	30 min	10	26 °C, 70% RH, continuous exercise 41 L/min	SRaw ↑233%	Kehrl et al., 1987
1.0 ppm	1 min 3 min 5 min	8	22 °C, 75% RH, exercise 60 L/min	SRaw ↑93% SRaw ↑395% SRaw ↑580%	Balmes et al., 1987
1.0 ppm	0.5 min 1.0 min 2.0 min 5.0 min	12	20 °C, 40% RH, exercise 40 L/min	No SRaw effect No SRaw effect SRaw ↑121% SRaw ↑307%	Horstman et al., 1988

*Adapted from U.S. EPA, 1994

2.4 Developmental/Reproductive Toxicity

Developmental/reproductive data regarding human exposure to SO₂ were not available

2.5 Genotoxicity

Genotoxicity studies regarding acute human exposure to SO₂ were not available. However, the incidence of chromosomal aberrations and sister chromatid exchanges was increased in lymphocytes from workers at an Indian fertilizer plant who were exposed to an average of 15.9 ppm SO₂ (Yadav and Kaushik, 1996) and in workers exposed to 0.13 to 4.57 ppm SO₂ in a Chinese sulfuric acid factory (Meng and Zhang, 1990). The significance of these findings is questionable since no confounding exposures were discussed. Exposure of mammalian cells to SO₂ resulted in toxicity, but not mutagenicity (Thompson and Pace, 1962).

2.6 Carcinogenicity

No information suggesting an increased cancer incidence from SO₂ exposure in humans was located.

2.7 Summary

Although no specific concentrations were reported, case reports suggest that exposure to apparently high concentrations of SO₂ may cause death via asphyxia secondary to pulmonary edema and irreversible airway obstruction. Epidemiological studies from occupational exposures and ambient air pollution also indicate that the respiratory system is the primary target for SO₂ toxicity. With regard to air pollution, the elderly and chronically ill appear to be more sensitive than healthy young adults; however, attributing the observed toxicity to SO₂ is difficult due to the presence of confounding factors such as smoke, particulates, and other air pollutants. Controlled experimental studies show that mild irritation, bronchoconstriction, and lung function changes are observed after exposure to low concentrations of SO₂. Asthmatics are more sensitive than healthy people to the effects of SO₂ and healthy elderly subjects may be more sensitive than healthy young people, but less sensitive than asthmatics. Exercise exacerbates the respiratory effects of SO₂ in both healthy and asthmatic subjects. Data also suggest that cold air, dry air, the presence of other particulates and oral, rather than nasal, breathing may enhance the toxic effects of SO₂. The body of experimental data suggests that 0.25 ppm may be a threshold for bronchoconstriction in asthmatics, and that a significant proportion of asthmatics will experience bronchoconstriction requiring medication or cessation of activity at 0.4-0.5 ppm. Data also suggest that a maximum response is obtained during the first 10-minutes of exposure and that continued or repeated exposures do not enhance the bronchoconstrictive response. Occupational exposures suggest that SO₂ may be clastogenic; however, because confounding factors, such as exposure to other chemicals, were not considered, no definitive conclusions can be made regarding genotoxicity. No information concerning reproductive/developmental toxicity or carcinogenicity was available.

3. ANIMAL TOXICITY DATA

3.1 Acute Lethality

3.1.1 Mice

Hilado and Machado (1977) exposed groups of four Swiss-albino mice to nominal SO₂ concentrations (no analytical data were presented) of 1190 to 14,286 ppm and monitored time to first sign of incapacitation, time to convulsions, and time to death. Animals were exposed

in a 4.2 liter, polymethyl methacrylate chamber. The SO₂ was injected with a 60 ml syringe which had been filled from a gas supply cylinder. Time to first sign of incapacitation was under 3 minutes for 3500 to 14,300 ppm SO₂ and increased to 6 minutes as SO₂ concentration was decreased to 1100 ppm. Average time to staggering increased from 1 to 6 minutes and average time to convulsions increased from 2 to 8 minutes as SO₂ concentration decreased from 14,300 to 3500 ppm. Average time to death increased from 3 to 8 minutes as SO₂ concentration decreased from 14,300 to 4800 ppm. There were no deaths in animals exposed to 1190 ppm SO₂ for 30 minutes.

Bitron and Aharonson (1978) exposed groups of 14 male albino mice (21±1 g, 1 month old) to 900 ppm SO₂ for 25-640 minutes (9 exposure groups), 1400 ppm SO₂ for 15 to 180 minutes (13 exposure groups), or 1900 ppm SO₂ for 10 to 75 minutes (9 exposure groups). Median lethal exposure time (Lt₅₀) for each concentration was calculated to be 200 minutes, 38 minutes, and 10 minutes for the 900, 1400, and 1900 ppm SO₂ concentrations, respectively.

3.1.2 Rats

Groups of eight male CD outbred rats (150 g) were exposed to varying concentrations of SO₂ in a portable stainless-steel chamber for 4 hours and observed for 14 days (Cohen et al., 1973). The test atmospheres were maintained by metering SO₂ directly into the incoming air and were monitored at frequent intervals by an iodometric procedure. The actual SO₂ concentrations were maintained within 5% throughout exposures. Data are summarized in Table 5. An LC₅₀ of 1057 ppm and BMCL₀₅ of 573 ppm were calculated (by the author of this document) using the Litchfield and Wilcoxon method.

SO₂ Concentration (ppm)	Mortality
224	0/8
593	0/8
965	3/8
1168	5/8
1319	8/8

3.2 Nonlethal Toxicity

3.2.1 Rats

Male Swiss Albino rats (250-300 g) were exposed to 0 (51 rats) or 0.87 ppm SO₂ (50 rats) for 24 hours (Baskurt, 1988). The experimental atmosphere was obtained by continuous mixing of filtered ambient air at a flow rate of 30 l/minute with SO₂ gas at a constant rate. Air samples were obtained from the exposure chamber with an impinger and the SO₂ concentration was measured by a hydrogen peroxide-acid titration method. Hematocrit values were increased (p<0.005) in the SO₂ exposed group compared to controls (43.55±0.41% vs. 41.97±0.35%). Sulfhemoglobin values were also increased (p<0.05) in the SO₂ exposed group compared to controls (0.6±0.08% vs. 0.08±0.02%).

In another study, Langley-Evans et al. (1997) examined the effect of a low protein maternal diet on later susceptibility to pulmonary injury from SO₂ exposure. Rats were fed

diets containing 180 g casein/kg diet (control diet), or 120, 90, or 60 g casein/kg diet (experimental diets). After acclimation to the diets for 14 days, the rats were mated and maintained on the same diet until parturition. Within 12 hours of parturition, all dams were transferred to standard diets and the same diet was used to wean the pups. At 7 weeks of age, groups of 4 to 16 male rats were exposed to 0 or 0.11 ppm SO₂, 5 hours/day for 28 days. The exposure chamber had a volume of 0.5 m³ and a flow rate of 7 L/min. The test atmosphere was produced by mixing the contents of SO₂ from cylinders with compressed air. The SO₂ concentration was monitored with an "industrial monitor." Rats exposed to 90 or 60 g/casein/kg diet *in utero* exhibited greater pulmonary injury, as evidenced by broncho-alveolar lavage, than those exposed to control diet *in utero*. Maternal diet or SO₂ exposure influenced liver GSH concentrations. GSH was lower in livers of rats exposed to the 120 g casein/kg maternal diet than in the 180 g/kg diet controls. Rats exposed to 60 g/kg diets had higher hepatic GSH levels than the 120 g/kg rats. SO₂ exposure had no effect on hepatic GSH in the 180 or 90 g/kg diet group. In the 60 g/kg diet group, hepatic GSH was lowered by SO₂ exposure. Conversely, rats exposed to the 120 g/kg diet had greater hepatic GSH in response to SO₂ exposure.

3.2.2 Guinea Pigs

Amdur (1959) exposed groups of 10 to 30 guinea pigs to approximately 2.6, 20, 100, 200, or 750 ppm SO₂ in a dynamic exposure chamber for 1 hour. (SO₂ concentrations are approximations from a graph). The SO₂ atmosphere was generated by metering 1% SO₂ in air from a cylinder into the main air stream. The air sample was collected in hydrogen-peroxide sulfuric acid reagent and the increase in conductivity was measured. Increased airway resistance was observed at all exposure concentrations. Data are summarized in Table 6.

SO ₂ Concentration*	Number of Animals	% Increase in Airway Resistance*
2.6 ppm	16	20%
20 ppm	18	25%
100 ppm	10	70%
200 ppm	30	140%
750 ppm	13	300%

*Approximate values estimated from graph

Amdur (1959) also exposed a group of 6 guinea pigs to 24 ppm SO₂ for 3 hours. Increased airway resistance progressed from 20% at the end of the first hour to 86% at the end of the third hour. Three hours after exposure, the resistance had returned to control levels.

3.2.3 Rabbits

Groups of 21 rabbits were exposed to 0 or 0.57 ppm SO₂ for 10 minutes (Islam and Oberbarnscheidt, 1994). Respiratory flow was slightly decreased and respiratory resistance was slightly increased in SO₂ exposed animals compared to controls. There were no effects on tidal volume or dynamic compliance. The magnitude of the changes was difficult to assess since all results were presented graphically.

3.2.4 Dogs

Anesthetized, intubated mongrel dogs (20-30 kg) were exposed to 0 (3 dogs) or 500 ppm (7 dogs) SO₂ for 1 hour (Hulbert et al., 1989). The SO₂ atmosphere was generated by mixing pure SO₂ with air using a Matheson dyna blender and flow controller. Four SO₂-exposed dogs were sacrificed, in pairs, at 1 and 6 hours after exposure, and their tracheas removed and fixed for microscopic examination. Three dogs were sacrificed immediately after the SO₂ exposure, their tracheas removed, epithelium isolated and maintained *in vitro* (in buffer) before being fixed for microscopic examination 1 and 6 hours post-exposure. Tracheal epithelial damage was not observed in any controls, but was observed in all dogs exposed to SO₂. Findings were similar whether tissues were obtained fresh or had been maintained *in vitro*. At 1 hour, injury was difficult to assess because the tracheal surfaces were covered with exfoliated cells or were in total disarray. After 6 hours, the lesions were well defined and large flattened cells covered the basement membranes where mucosal cells had exfoliated.

In another study, Jackson and Eady (1988) exposed 8 anesthetized and intubated beagle dogs of both sexes to 400 ppm SO₂ for 2 hours. Each dog was artificially respired with the SO₂-air mixture (12 ml/kg, 20 breaths/minute) which was analyzed with a Drager gas sampling system. Exposure to SO₂ caused an immediate increase in lung reactivity to histamine aerosol. The lungs were most reactive immediately after exposure and lung reactivity had returned to control levels 2 hours after exposure. The total number of cells obtained from BAL fluid increased after SO₂ exposure; initially, the increase was due to an increase in epithelial cells (0.25 and 1 hour) and later by neutrophils (1, 2, 3, and 4 hours). No changes were observed in lymphocyte, macrophage, eosinophils, goblet cells, or mast cells in lavage fluid.

3.3 Developmental/Reproductive Toxicity

Murray et al. (1979) exposed groups of 40 and 32 CF-1 mice to 0 and 23.9 ppm SO₂, respectively, during days 6 through 15 of gestation, and groups of 20 New Zealand white rabbits to 0 or 70 ppm SO₂ from days 6 through 18 of gestation. Animals were exposed under dynamic airflow conditions in stainless steel and glass Rochester chambers with a 4.3 m³ volume. The chamber airflow was 800 L/minute and the SO₂ atmosphere was generated by metering SO₂ at known rates through rotometers into the airstream being drawn into the chamber. Concentrations were analyzed by infrared spectrometry. A marginal, although statistically significant ($p < 0.05$), decrease in mouse fetal body weight was noted (1.05 ± 0.11 g for controls vs 1.00 ± 0.08 g for test animals). No other treatment-related, biologically significant effects were noted in either mice or rabbits.

Pregnant CD-1 albino mice were exposed to 0, 32, 65, 125, or 250 ppm SO₂ from days 7 to 17 of gestation (Singh, 1982). The exposure duration for each day was not reported. Exposures were conducted in plexiglass chambers with a total gas flow rate of 450 mL/minute. The SO₂ concentration was monitored at each chamber inlet via infrared spectrometry. The mice were sacrificed on day 18 of gestation. No signs of maternal toxicity were noted during the exposure period and no treatment related developmental effects were noted. In a similar study, Singh (1989) exposed pregnant CD-1 mice to 0, 32, or 65 ppm SO₂ from days 7 to 18 of gestation. Again, the duration of exposure each day was not reported. Dams were allowed to deliver. Increased time for righting reflex was observed for pups exposed to both SO₂ concen-

trations compared to controls on postnatal day 1. Increased negative geotaxis was noted in exposed offspring on postnatal day 10. Birth weights of 65 ppm pups were 89% of controls. No other effects were noted.

Petruzzi et al. (1996) exposed adult male and female CD-1 mice to 0, 5, 12, or 30 ppm SO₂ for 24 days, from 9 days before the formation of breeding pairs through pregnancy day 12-14. Exposures were near-continuous, covering approximately 80% of the total time and were conducted in stainless steel exposure chambers with a hatch glass in the front door. SO₂ was delivered from aluminum bottles and differing concentrations were obtained by varying the flow and gas pressure from the bottles. SO₂ concentrations were monitored with an ultraviolet SO₂ analyzer. Actual concentrations were within 10% of target concentrations. Within 1 hour of the start of exposure, increased rearing and social interactions were observed and were more evident in males than in females. Observations on days 3, 6, and 9 showed dose-dependent decreased grooming and increased digging. Food and water consumption decreased in treated animals and increased in controls after the formation of breeding pairs. No effects were noted for reproductive performance or neurobehavioral development of the offspring. In another report from the same laboratory, the male CD-1 mice prenatally exposed to 0, 5, 12, or 30 ppm SO₂ from the Petruzzi et al. (1996) study were examined for changes in behavior as adults (Fiore et al., 1998). At adulthood, following a 4 week isolation period, they underwent a 20 minute aggressive encounter with a CD-1 male opponent. Dose-related increases were noted for body sniffing and nonsocial activities, whereas freezing, tail rattling, and defensive behaviors were decreased.

3.4 Genotoxicity

Genotoxic studies regarding animal exposure to SO₂ were not available. However, high bisulfite concentrations formed from SO₂ at nonphysiological pH were positive in assays with phage T₄ (Summers and Drake, 1971), phage T (Hayatsu and Miura, 1970), *E. coli* (Mukai et al., 1970), and *S. cerevisiae* (Dorange and Dupuy, 1972). The biological significance of this mutagenic response is questionable as the effect may be due to the pH shift.

3.5 Carcinogenicity

Peacock and Spence (1967) exposed mice to 0 (41 males, 39 females) or 500 ppm (35 males, 30 females) SO₂ 5 minutes/day, 5 days/week for 2 years. Data suggested possible treatment-related lung tumors; however, since only one concentration was tested these data are of limited use. In females, the incidence of lung adenomas and carcinomas was 13/30 in treated animals and 5/30 in controls. In males, the incidence of lung adenomas and carcinomas was 15/28 in treated animals and 11/35 in controls.

3.6 Summary

Well-conducted animal lethality studies are limited to a mouse study defining median lethal time to death (Lt₅₀) and a rat study yielding a 4-hour LC₅₀ of 1057 ppm and an BMCL₀₅ of 573 ppm SO₂. Non-lethal toxicity studies are more abundant and show that, as in humans, relatively low concentrations of SO₂ induce bronchoconstriction and associated increase in airway resistance in a number of animal species. Respiratory tract pathology is observed at higher SO₂ concentrations. SO₂ was generally not a developmental or reproductive toxicant.

Genotoxic studies regarding exposure to SO₂ are equivocal and the carcinogenicity study, although suggesting a possible increase in pulmonary tumors, is of poor quality and thus of limited use.

4. SPECIAL CONSIDERATIONS

4.1 Metabolism and Disposition

Although the main effects of SO₂ are on the respiratory tract, much of an inhaled dose may be transferred into systemic circulation. During inhalation, SO₂ may react with water in the respiratory tract to form sulfurous acid or may be oxidized to form sulfur trioxide. Sulfur trioxide reacts rapidly with water to form sulfuric acid. Sulfurous acid dissociates to sulfite and bisulfate ions, which are in chemical equilibrium. Bisulfite ions react by sulfonation, auto-oxidation, and by addition to cytosine. Most inhaled SO₂ is detoxified in the liver by the sulfite-oxidase pathway, which forms S-sulfonates that can be found in the plasma and sulfates that are excreted in the urine. The S-sulfonates are long-lived and supply the circulation with bisulfite that may reach many tissues. In rabbits exposed to 10 ppm SO₂, the half-life for clearance of plasma protein S-sulfonates was 4.1 days. Some circulating S-sulfonates may decompose to SO₂ which is exhaled (WHO, 1984).

4.2 Mechanism of Toxicity

SO₂ is a water-soluble irritant which causes upper-airway irritation and may induce increased airway resistance via reflex bronchoconstriction. The exact mechanism responsible for SO₂-induced bronchoconstriction is not known. However, the rapid onset and reversibility of SO₂-induced bronchoconstriction observed in asthmatics is likely due to decreased airway caliber caused by contraction of airway smooth muscle. Constriction of airway smooth muscle in response to environmental stimuli can be induced by intrinsic chemical and/or physical stimuli, acting via neural and/or humoral pathways. SO₂ may act either directly on smooth muscle or may cause the release of chemical mediators from the tissue, especially the release of histamine from mast cells. Other potential pharmacological mediators of SO₂-induced bronchoconstriction are leukotrienes and prostaglandin F₂-alpha, both of which are released in the airways and may cause smooth muscle contraction (Horstman and Folinsbee, 1989).

4.3 Temporal Extrapolation

The impact of exposure duration on the magnitude of low-concentration SO₂-induced bronchoconstriction in asthmatics and healthy humans appears to decrease with extended exposure. For example, asthmatics exposed to 0.75 ppm SO₂ for 3-hours exhibited increases in SRaw of 322% 10-min into the exposure, 233% 20-min into the exposure, 26% 1-hr into the exposure, and 5% 2-hours into the exposure. At the end of the 3-hour exposure period, SRaw was decreased 12%. These, and other data presented in Tables 4 and 5, suggest that a major portion of the SO₂-induced bronchoconstriction occurs within 10-minutes and increases minimally or resolves beyond 10-minutes of exposure. Furthermore, there is no evidence that any other effect is relevant at low sulfur dioxide concentrations; the respiratory response is a first-level, sensitive response to SO₂ exposure. This phenomenon is also observed with healthy humans. For example, maximum pulmonary flow resistance was observed within 5 to 10 minutes when healthy adult males were exposed to 5 or 13 ppm SO₂ for up to 30 minutes

(Frank et al., 1962) or 4-6 or 14-17 ppm SO₂ for up to 30 minutes (Frank et al., 1964). Therefore, time scaling will not be utilized for AEGL values for SO₂.

Data are not sufficient to ascertain whether a maximal response to SO₂ for a lethal endpoint is obtained within 10 minutes. Therefore, time scaling will be utilized in the derivation of AEGL-3 values. It has been shown that the concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al., 1986). Data were unavailable for an empirical derivation of n for sulfur dioxide. Therefore, an n of 3 may be applied to extrapolate to shorter time periods, and n of 1 may be used for extrapolation to the 8-hour time period to provide AEGL values that would be protective of human health (NRC, 2001).

4.4 Concurrent Exposure

As previously stated, the relationship between SO₂ exposure in polluted air and human health effects is confounded by the presence of other air pollutants, especially nitrogen oxides, ozone, smoke and particulate matter. Several controlled human studies have examined the health effects resulting from concurrent exposure to SO₂ and other chemicals. As previously described, inert sodium chloride aerosols had no added effect when administered to healthy subjects in conjunction with SO₂ (Frank et al., 1964; Rondinelli et al., 1987). In human asthmatics, Jorres and Magnussen (1990) demonstrated an amplified response to SO₂ after a 30 minute exposure to 0.75 ppm NO₂. Data from a study by Rigas et al. (1997) suggests that exposure to SO₂ may enhance absorption of ozone in the lungs of healthy adult males. In asthmatic subjects, exposure to a combination of 400 ppb NO₂ + 200 ppb SO₂ enhanced the airway response to an inhaled allergen (*Dermatophagoides pteronyssinus*) (Rusznak et al., 1996).

Amdur (1959) examined the effect of concurrent exposure of SO₂ and sulfuric acid mist or inert sodium chloride aerosol on guinea pigs and found that particle size was a factor in the magnitude of response. When animals were exposed to 0.8 μ sulfuric acid mist particles and SO₂, a synergistic response was observed with regard to bronchoconstriction; however, when 2.5 μ sulfuric acid particles were administered with SO₂, no synergism was observed. The response was actually slightly less than the response to SO₂ alone. When sodium chloride aerosols of 0.04 μ and 2.5 μ were administered in combination with SO₂, a similar response was noted with regard to bronchoconstriction; potentiation was observed with the smaller particles but not by the larger particles.

5. RATIONALE AND PROPOSED AEGL-1

5.1 Human Data Relevant to AEGL-1

Upper respiratory and throat irritation were noted in healthy males (Amdur et al., 1953; Frank et al., 1962) exposed to 5 ppm SO₂ for 10-30 minutes. Throat and nasal irritation were reported in healthy, exercising subjects exposed to 2 or 4 ppm SO₂ for 20 minutes (Sandstrom et al., 1988). Upper respiratory and ocular irritation were noted in healthy adults exposed to 1 ppm SO₂ for 4 hours with intermittent exercise (Kulle et al., 1984). No treatment-related effects were noted in exercising asthmatics exposed to 0.2 ppm for 5 min (Linn et al., 1983b), 0.25 ppm for 10-40 min (Schacter et al., 1984), 0.25 ppm for 75 minutes (Roger et al., 1985),

or 0.5 ppm for 10-40 min (Schacter et al., 1984). An increase in SRaw of 134-139% was observed in exercising asthmatics exposed to 0.25 ppm for 5 minutes (Bethel et al., 1985).

5.2 Animal Data Relevant to AEGL-1

Amdur (1959) observed a 20% and 25% increase in airway resistance in guinea pigs exposed to 2.6 and 20 ppm SO₂, respectively, for 1 hour.

5.3 Derivation of AEGL-1

A weight of evidence approach utilizing the human asthmatic data will be utilized to derive AEGL-1 values for SO₂. The body of experimental data suggests that 0.20 ppm may be a NOEL for bronchoconstriction in exercising asthmatics, based on the fact that no treatment-related effects were noted in asthmatics exposed to 0.2 ppm for 5 min (Linn et al., 1983b), 0.25 ppm for 10-40 min (Schacter et al., 1984), 0.25 ppm for 75 minutes (Roger et al., 1985), 0.5 ppm for 10-40 min (Schacter et al., 1984), or 0.5 ppm for 30 minutes (Jorres and Magnussen, 1990). However, an increase in SRaw of 134-139% was observed in exercising asthmatics exposed to 0.25 ppm for 5 minutes (Bethel et al., 1985); the increase in SRaw in this study, but not in the other studies, may be attributed to the lower relative humidity (36%) in the Bethel et al. (1985) compared to the other studies (70-85%). No uncertainty factors will be applied because the weight of evidence approach utilized studies from a sensitive human population, that of exercising asthmatics. The role of exposure duration to the magnitude of SO₂-induced bronchoconstriction in asthmatics appears to decrease with extended exposure. For example, asthmatics exposed to 0.75 ppm SO₂ for 3-hours exhibited increases in SRaw of 322% 10-min into exposure, 233% 20-min into the exposure, 26% 1-hr into the exposure, 5% 2-hours into the exposure, and a decrease of 12% at the end of the 3-hour exposure period. These, and other data presented in Tables 3 and 4, suggest that a major portion of the SO₂-induced bronchoconstriction occurs within 10-minutes and increases minimally or resolves beyond 10-minutes of exposure. Therefore, AEGL-1 values for SO₂ will be held constant across all time points. The AEGL-1 values for SO₂ are presented in Table 7, and the calculations for these AEGL-1 values are presented in Appendix A.

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1	0.20 ppm (0.52 mg/m ³)	0.20 ppm (0.52 mg/m ³)	0.20 ppm (0.52 mg/m ³)	0.20 ppm (0.52 mg/m ³)	0.20 ppm (0.52 mg/m ³)

Exposure to these AEGL-1 values are expected to have no effect in healthy individuals, but are consistent with the definition of AEGL-1 for asthmatic individuals.

6. RATIONALE AND PROPOSED AEGL-2

6.1 Human Data Relevant to AEGL-2

A 72% increase in pulmonary flow resistance accompanied by cough, irritation, and increased salivation was observed in healthy males exposed to 13 ppm SO₂ for 10 minutes (Frank et al., 1962). A 65% increase in pulmonary flow resistance, cough, and chest irritation were observed in healthy male mouth-breathers exposed to 28 ppm SO₂ for 10 minutes (Frank

et al., 1962). Asthmatics developed increased airway resistance of 5- to 322% after exposure to 0.75 ppm SO₂ for up to 3 hours (Hackney et al., 1984). An increase in SRaw of 150%, decrease in FEF of 22%, and decrease in FEV₁ of 8% were observed in exercising asthmatics exposed to 0.75 ppm SO₂ for 10-40 minutes (Schacter et al., 1984).

6.2 Animal Data Relevant to AEGL-2

Amdur (1959) observed a 70% increase in airway resistance in guinea pigs exposed to 100 ppm SO₂ for 1 hour and an increase of 85% in guinea pigs exposed to 24 ppm for 3 hours. Tracheal pathology was observed in anesthetized dogs exposed to 500 ppm SO₂ for 1 hour.

6.3 Derivation of AEGL-2

A weight of evidence approach utilizing the human asthmatic data will be utilized to derive AEGL-2 values for SO₂. Data suggest that 0.75 ppm induces moderate respiratory response in exercising asthmatics for exposure durations of 10-minutes to 3-hours (Hackney et al., 1984; Schacter et al., 1984). No uncertainty factors will be applied because the weight of evidence approach utilized studies from a sensitive human population, that of exercising asthmatics. The role of exposure duration to the magnitude of SO₂-induced bronchoconstriction in asthmatics appears to decrease with extended exposure. For example, asthmatics exposed to 0.75 ppm SO₂ for 3-hours exhibited increases SRaw of 322% 10-min into exposure, 233% 20-min into the exposure, 26% 1-hr into the exposure, 5% 2-hours into the exposure, and a decrease of 12% at the end of the 3-hour exposure period. These, and other data presented in Tables 3 and 4, suggest that a major portion of the SO₂-induced bronchoconstriction occurs within 10-minutes and increases minimally or resolves beyond 10-minutes of exposure. Therefore, AEGL-2 values for SO₂ were held constant across all time points. The AEGL-2 values for SO₂ are presented in Table 8, and the calculations for these AEGL-2 values are presented in Appendix A.

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-2	0.75 ppm (1.95 mg/m ³)	0.75 ppm (1.95 mg/m ³)	0.75 ppm (1.95 mg/m ³)	0.75 ppm (1.95 mg/m ³)	0.75 ppm (1.95 mg/m ³)

Exposure to these AEGL-2 values are expected to have no effect in healthy individuals, but are consistent with the definition of AEGL-2 for asthmatic individuals.

7. RATIONALE AND PROPOSED AEGL-3

7.1 Human Data Relevant to AEGL-3

No human data were relevant to establishing the AEGL-3 values.

7.2 Animal Data Relevant to AEGL-3

No deaths were observed in mice exposed to 1190 ppm (nominal concentration) SO₂ for 30 minutes (Hilado and Machado, 1977). No deaths occurred in rats exposed to 593 ppm SO₂ for 4 hours; an LC₅₀ of 1057 ppm ; and an BMCL₀₅ of 573 ppm were also calculated from the same study (Cohen et al., 1973).

7.3 Derivation of AEGL-3

The AEGL-3 values will be based on a calculated $BMCL_{05}$ in rats exposed to SO_2 for 4-hours (573 ppm) (Cohen et al., 1973). An uncertainty factor of 10 will be applied for intraspecies extrapolation due to the wide variability in response to SO_2 exposure between healthy and asthmatic humans. An uncertainty factor of 3 was applied for interspecies variability; this factor of 3 was considered sufficient because no deaths were reported in guinea pigs exposed to 750 ppm SO_2 for 1 hour (Amdur, 1959), in dogs exposed to 400 ppm SO_2 for 2 hours (Jackson and Eady, 1988), or in rats exposed to 593 ppm for 4-hours (Cohen et al., 1973). Furthermore, a median lethal exposure time (Lt_{50}) of 200 minutes was reported for mice exposed to 900 ppm SO_2 (Bitron and Aharonson, 1978), and three of eight rats died when exposed to 965 ppm for 240 minutes (Cohen et al., 1973), suggesting limited interspecies variability. Data are not sufficient to ascertain whether a maximal response to SO_2 for a lethal endpoint is obtained within 10 minutes. Therefore, time scaling will be utilized in the derivation of AEGL-3 values. It has been shown that the concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al., 1986). Data were unavailable for an empirical derivation of n for sulfur dioxide. Therefore, an n of 3 was applied to extrapolate to the 1-hour time period, and n of 1 was used for extrapolation to the 8-hour time period to provide AEGL values that would be protective of human health (NRC, 2001). The 1-hour AEGL-3 value was also adopted as 10-minute and 30-minute values because asthmatic humans are highly sensitive to sulfur dioxide at short time periods. The AEGL-3 values for SO_2 are presented in Table 9, and the calculations for these AEGL-3 values are presented in Appendix A.

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-3	30 ppm (78 mg/m ³)	30 ppm (78 mg/m ³)	30 ppm (78 mg/m ³)	19 ppm (49 mg/m ³)	9.6 ppm (25 mg/m ³)

8. SUMMARY OF PROPOSED AEGLS

8.1 AEGL Values and Toxicity Endpoints

The derived AEGL values for various levels of effects and durations of exposure are summarized in Table 10. A weight-of-evidence approach from studies in exercising asthmatics was used to derive AEGL-1 (NOEL for bronchoconstriction) and AEGL-2 (moderate respiratory effects) values. A calculated $BMCL_{05}$ in rats was used as the basis for AEGL-3.

Classification	0-min	30-min	1-h	4-h	8-h
AEGL-1 (Nondisabling)	0.20 ppm (0.52 mg/m ³)	0.20 ppm (0.52 mg/m ³)	0.20 ppm (0.52 mg/m ³)	0.20 ppm (0.52 mg/m ³)	0.20 ppm (0.52 mg/m ³)
AEGL-2 (Disabling)	0.75 ppm (1.95 mg/m ³)	0.75 ppm (1.95 mg/m ³)	0.75 ppm (1.95 mg/m ³)	0.75 ppm (1.95 mg/m ³)	0.75 ppm (1.95 mg/m ³)
AEGL-3 (Lethality)	30 ppm (78 mg/m ³)	30 ppm (78 mg/m ³)	30 ppm (78 mg/m ³)	19 ppm (49 mg/m ³)	9.6 ppm (25 mg/m ³)

8.2 Other Exposure Criteria

Standards and guidance levels for workplace and community exposures for sulfur dioxide are listed in Table 11. In addition to the standards listed in Table 11, air quality standards have also been developed for SO₂. The National Ambient Air Quality Standard is 0.14 ppm, with a significant harm level of 1.0 ppm for a 1-hour average (U.S. EPA, 1999).

TABLE 11. Extant Standards and Guidelines for Sulfur Dioxide					
Guideline	Exposure Duration				
	10-min	30-min	1-h	4-h	8-h
AEGL-1	0.20 ppm	0.20 ppm	0.20 ppm	0.20 ppm	0.20 ppm
AEGL-2	0.75 ppm	0.75 ppm	0.75 ppm	0.75 ppm	0.75 ppm
AEGL-3	30 ppm	30 ppm	30 ppm	19 ppm	9.6 ppm
ERPG-1 ^a	0.3 ppm				
ERPG-2 ^a	3 ppm				
ERPG-3 ^a	15 ppm				
NIOSH IDLH ^b	100 ppm				
NIOSH REL ^c					2 ppm
OSHA PEL-TWA ^d					2 ppm
ACGIH TLV-TWA ^e					2 ppm
NIOSH-STEL	5 ppm				
ACGIH TLV-STEL ^f	5 ppm				
NAS EEGL ^g	30 ppm (10 min)	20 ppm (30 min)	10 ppm (60 min)		5 ppm (24 hr)
German MAK ^h					0.5 ppm
Dutch MAC ⁱ					2 ppm
Swedish OEL- LLV ^j					2 ppm
Swedish OEL- CLV ^j	5 ppm				

^a**ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association (AIHA 2002)**

The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor. The ERPG-1 for SO₂ is based on increased airway resistance in exercising asthmatics.

The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protection action. The ERPG-2 for SO₂ is based on bronchoconstriction requiring bronchodilation therapy in asthmatics exposed to 5 ppm for 10-min.

The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing life-threatening health effects. The ERPG-3 for SO₂ is based on potential induction of bronchospasm in asthmatic or sensitive individuals that may trigger cardiopulmonary events in individuals with pre-existing heart disease. As of 2000, the ERPG values for SO₂ are under ballot review and consideration.

^b **IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health) (NIOSH 1994)** represents the maximum concentration from which one could escape within 30 minutes without any escape-impairing symptoms, or any irreversible health effects. The IDLH for SO₂ is based on acute inhalation toxicity data in humans.

^c**NIOSH REL (Recommended Exposure Limits)** (NIOSH 2003) is defined analogous to the ACGIH TLV-TWA.

^d**OSHA PEL-TWA (Occupational Health and Safety Administration, Permissible Exposure Limits - Time Weighted Average)** (OSHA 1998) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 hours/day, 40 hours/week.

^e**ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average)** (ACGIH 2003) is the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect. The value for SO₂ is based on irritation.

^f**ACGIH TLV-STEL (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Short Term Exposure Limit)** (ACGIH 2003). The value for SO₂ is based on irritation.

^g**EEGL (Emergency Exposure Guidance Levels, National Research Council)** (NRC 1984)
The EEGLs for SO₂ are based on concentrations at which people can continue to function in an emergency situation and be unlikely to suffer irreversible respiratory effects. They are intended for specific populations (military and space personnel) and may not be applicable to the general population.

^h**MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration])** DFG [Deutsche Forschungsgemeinschaft] (German Research Association) 2000 is defined analogous to the ACGIH-TLV-TWA.

ⁱ**MAC (Maximaal Aanvaarde Concentratie [Maximal Accepted Concentration])**. SDU Uitgevers (under the auspices of the Ministry of Social Affairs and Employment), The Hague, The Netherlands 2000, is defined analogous to the ACGIH-TLV-TWA.

^jSwedish OEL (Occupational Exposure Limit). IPCS INCHEM, 2000.

8.3 Data Adequacy and Research Needs

The data base for human exposure for effects defined by AEGL-1 and AEGL-2 is relatively good as controlled chamber studies with both asthmatic and otherwise healthy volunteers are available. These studies, when considered together, provide good threshold-response information and are appropriate for derivation of AEGL-1 and AEGL-2 values. Case reports of accidental human exposure to sulfur dioxide leading to effects consistent with the definitions of AEGL-3 did not include concentration or duration parameters adequate for derivation of values. Studies sufficient for derivation of AEGL-3 values were limited to animal data.

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APPENDIX A: TIME SCALING CALCULATIONS FOR SULFUR DIOXIDE

DERIVATION OF AEGL-1 VALUES

Key study: Weight-of-evidence approach suggests 0.20 ppm is NOEL for bronchoconstriction in exercising asthmatics (see table below)

Concentration	Duration	Subjects	Exposure Parameters	Effect	Reference
0.2 ppm	5 min	8	23 °C, 85% RH, exercise 48 L/min	None	Linn et al., 1983b
0.25 ppm	10-40 min	10	23 °C, 70% RH, exercise 35 L/min	None	Schacter et al., 1984
0.25 ppm	5 min	19 9	23 °C, 36% RH, exercise 60 L/min 23 °C, 36% RH, exercise 80-90 L/min	SRaw ↑134% SRaw ↑139%	Bethel et al., 1985
0.25 ppm	75 min	28	26 °C, 70% RH, exercise 42 L/min intermittent	None	Roger et al., 1985
0.4 ppm	5 min	23	23 °C, 85% RH, exercise 48 L/min	SRaw ↑69% V _{max25-75} ↓10%	Linn et al., 1983b
0.5 ppm	10-40 min	10	23 °C, 70% RH, exercise 35 L/min	None	Schacter et al., 1984

Toxicity endpoint: NOEL for bronchoconstriction in exercising asthmatics

Scaling: Data suggest that a major portion of the SO₂-induced bronchoconstriction occurs within 10-minutes and increases minimally or resolves beyond 10-minutes of exposure. Therefore, AEGL-1 values for SO₂ will be held constant across all time points.

Uncertainty factors: None: subjects were exercising asthmatics

10-min., 30-min., 1-h., 4-h., and 8-h. AEGL-1 = 0.20 ppm

DERIVATION OF AEGL-2 VALUES

Key study: Weight-of-evidence approach suggests 0.75 ppm induces moderate respiratory response in exercising asthmatics for exposure durations of 10-minutes to 3-hours ppm (see table below)

0.75 ppm	10-40 min	10	23 °C, 70% RH, exercise 35 L/min	SRaw ↑150% FEF ↓22% FEV ₁ ↓8%	Schacter et al., 1984
0.75 ppm	3 h	17	22 °C, 85% RH, exercise 45 L/min (first 10-min of exposure)	SRaw ↑: 322% (at 10-min) 233% (at 20-min) 26% (at 1-hr) 5% (at 2-hr) FEV ₁ : ↓20% (at 15-min)	Hackney et al., 1984
1.0 ppm	10-40 min	10	23 °C, 70% RH, exercise 35 L/min	SRaw ↑470% FEF ↓27% FEV ₁ ↓14%	Schacter et al., 1984
1.0 ppm	75 min	28	26 °C, 70% RH, exercise 42 L/min, intermittent	SRaw ↑300%	Roger et al., 1985
1.0 ppm	30 min	10	26 °C, 70% RH, exercise 41 L/min (3- 10 min periods separated by rests of 15 min)	SRaw ↑172% SRaw ↑137% SRaw 106%	Kehrl et al., 1987
1.0 ppm	30 min	10	26 °C, 70% RH, continuous exercise 41 L/min	SRaw ↑233%	Kehrl et al., 1987
1.0 ppm	1 min 3 min 5 min	8	22 °C, 75% RH, exercise 60 L/min	SRaw ↑93% SRaw ↑395% SRaw ↑580%	Balmes et al., 1987
1.0 ppm	0.5 min 1.0 min 2.0 min 5.0 min	12	20 °C, 40% RH, exercise 40 L/min	No SRaw effect No SRaw effect SRaw ↑121% SRaw ↑307%	Horstman et al., 1988

Toxicity endpoint: Moderate, but reversible, respiratory effects in exercising asthmatics

Scaling: Data suggest that a major portion of the SO₂-induced bronchoconstriction occurs within 10-minutes and increases minimally or resolves beyond 10-minutes of exposure. Therefore, AEGL-2 values for SO₂ were held constant across all time points.

Uncertainty factors: None: subjects were exercising asthmatics

10-min., 30-min., 1-h., 4-h., and 8-h. AEGL-2 = 0.75 ppm

DERIVATION OF AEGL-3 VALUES

Key study: Cohen et al., 1973

Toxicity endpoint: $BMCL_{05}$ in rats exposed for 4 h (573 ppm)

Scaling: $C^3 \times t = k$
 $(573 \text{ ppm})^3 \times 4 \text{ h} = 752530068 \text{ ppm}\cdot\text{h}$

$C^1 \times t = k$
 $(573 \text{ ppm})^1 \times 4 \text{ hr} = 2292 \text{ ppm}\cdot\text{h}$

Uncertainty factors: 10 for intraspecies variability
3 for interspecies variability

10-min AEGL-3 1-h AEGL-3 value adopted as 10-min value because asthmatic humans are highly sensitive to sulfur dioxide at short time periods

30-min AEGL-3 1-h AEGL-3 value adopted as 30-min value because asthmatic humans are highly sensitive to sulfur dioxide at short time periods

1-hr AEGL-3

$C^3 \times 1 \text{ h} = 752530068 \text{ ppm}\cdot\text{h}$
 $C^3 = 752530068 \text{ ppm}$
 $C = 909$
1-h AEGL-3 = $909 \text{ ppm}/30 = 30 \text{ ppm}$

4-hr AEGL-3

4-hr AEGL-3 = $573 \text{ ppm}/30 = 19 \text{ ppm}$

8-hr AEGL-3

$C^1 \times 8 \text{ hr} = 2292 \text{ ppm}\cdot\text{hr}$
 $C^1 = 287 \text{ ppm}$
 $C = 287$
8-hr AEGL-3 = $287 \text{ ppm}/30 = 9.6 \text{ ppm}$

APPENDIX B: DERIVATION SUMMARY TABLES FOR SULFUR DIOXIDE

**ACUTE EXPOSURE GUIDELINES FOR SULFUR DIOXIDE
(CAS NO. 7446-09-5)**

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AEGL-1 VALUES				
10 min	30 min	1 h	4 h	8 h
0.20 ppm	0.20 ppm	0.20 ppm	0.20 ppm	0.20 ppm
Weight-of-evidence approach suggests 0.20 ppm is NOEL for bronchoconstriction in exercising asthmatics				
Time Scaling: Data suggest that a major portion of the SO ₂ -induced bronchoconstriction occurs within 10-minutes and increases minimally or resolves beyond 10-minutes of exposure. Therefore, AEGL-1 values for SO ₂ will be held constant across all time points.				
Data adequacy: Robust data base of controlled studies in both healthy and asthmatic humans.				

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Weight-of Evidence for AEGL-1					
Concentration	Duration	Subjects	Exposure Parameters	Effect	Reference
0.2 ppm	5 min	8	23 °C, 85% RH, exercise 48 L/min	None	Linn et al., 1983b
0.25 ppm	10-40 min	10	23 °C, 70% RH, exercise 35 L/min	None	Schacter et al., 1984
0.25 ppm	5 min	19 9	23 °C, 36% RH, exercise 60 L/min 23 °C, 36% RH, exercise 80-90 L/min	SRaw ↑134% SRaw ↑139%	Bethel et al., 1985
0.25 ppm	75 min	28	26 °C, 70% RH, exercise 42 L/min intermittent	None	Roger et al., 1985
0.4 ppm	5 min	23	23 °C, 85% RH, exercise 48 L/min	SRaw ↑69% V _{max25-75} ↓10%	Linn et al., 1983b
0.5 ppm	10-40 min	10	23 °C, 70% RH, exercise 35 L/min	None	Schacter et al., 1984

1 **ACUTE EXPOSURE GUIDELINES FOR SULFUR DIOXIDE**
2 **(CAS NO. 7446-09-5)**
3

AEGL-2 VALUES				
10 min	30 min	1 h	4 h	8 h
0.75 ppm	0.75 ppm	0.75 ppm	0.75 ppm	0.75 ppm
Weight-of-evidence approach suggests 0.75 ppm induced moderate bronchoconstriction in exercising asthmatics.				
Time Scaling: The role of exposure duration to the magnitude of SO ₂ -induced bronchoconstriction in asthmatics appears to decrease with extended exposure. Data suggest that a major portion of the SO ₂ -induced bronchoconstriction occurs within 10-minutes and increases minimally or resolves beyond 10-minutes of exposure. Therefore, AEGL-2 values for SO ₂ were held constant across all time points.				
Data adequacy: Robust data base of controlled studies in both healthy and asthmatic humans.				

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WEIGHT-OF EVIDENCE FOR AEGL-2					
0.75 ppm	3 h	17	22 °C, 85% RH, exercise 45 L/min (first 10-min of exposure)	SRaw ↑: 322% (at 10-min) 233% (at 20-min) 26% (at 1-hr) 5% (at 2-hr) FEV ₁ : ↓20% (at 15-min)	Hackney et al., 1984
0.75 ppm	10-40 min	10	23 °C, 70% RH, exercise 35 L/min	SRaw ↑150% FEF ↓22% FEV ₁ ↓8%	Schacter et al., 1984
1.0 ppm	10-40 min	10	23 °C, 70% RH, exercise 35 L/min	SRaw ↑470% FEF ↓27% FEV ₁ ↓14%	Schacter et al., 1984
1.0 ppm	75 min	28	26 °C, 70% RH, exercise 42 L/min, intermittent	SRaw ↑300%	Roger et al., 1985
1.0 ppm	30 min	10	26 °C, 70% RH, exercise 41 L/min (3- 10 min periods separated by rests of 15 min)	SRaw ↑172% SRaw ↑137% SRaw 106%	Kehrl et al., 1987
1.0 ppm	30 min	10	26 °C, 70% RH, continuous exercise 41 L/min	SRaw ↑233%	Kehrl et al., 1987
1.0 ppm	1 min 3 min 5 min	8	22 °C, 75% RH, exercise 60 L/min	SRaw ↑93% SRaw ↑395% SRaw ↑580%	Balmes et al., 1987
1.0 ppm	0.5 min 1.0 min 2.0 min 5.0 min	12	20 °C, 40% RH, exercise 40 L/min	No SRaw effect No SRaw effect SRaw ↑121% SRaw ↑307%	Horstman et al., 1988

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ACUTE EXPOSURE GUIDELINES FOR SULFUR DIOXIDE (CAS NO. 7446-09-5)

AEGL-3 VALUES				
10 min	30 min	1 h	4 h	8 h
30 ppm	30 ppm	30 ppm	19 ppm	9.6 ppm
Reference: Cohen, H.J., Drew, R.t., Johnson, J.L., and Rajagopalan, K.V. 1973. Molecular basis of the biological function of molybdenum. The relationship between sulfite oxidase and the acute toxicity of bisulfite and SO ₂ . PNAS. 70: 3655-3659.				
Test Species/Strain/Sex/Number: CD outbred rats/ 8 males/ concentration				
Exposure Route/Concentrations/Durations: Rats/Inhalation: 224, 593, 965, 1168, or 1319 ppm/4 hour (BMCL ₀₅ of 573 ppm, was determinant for AEGL-3)				
Endpoint/Concentration/Rationale: BMCL ₀₅ / 573 ppm/ threshold for death for 4 hour exposure in rats				
Effects:	Concentration	Mortality		
	224 ppm	0/8		
	593 ppm	0/8		
	965 ppm	3/8		
	1168 ppm	5/8		
	1319 ppm	8/8		
Uncertainty Factors/Rationale: Total uncertainty factor: 30 Intraspecies = 10: due to the wide variability in response to SO ₂ exposure between healthy and asthmatic humans. Interspecies = 3: considered sufficient because no deaths were reported in guinea pigs exposed to 750 ppm SO ₂ for 1 hour (Amdur, 1959), in dogs exposed to 400 ppm SO ₂ for 2 hours (Jackson and Eady, 1988), or in rats exposed to 593 ppm for 4-hours (Cohen et al., 1973). Furthermore, a median lethal exposure time (Lt ₅₀) of 200 minutes was reported for mice exposed to 900 ppm SO ₂ (Bitron and Aharonson, 1978) and three of eight rats died when exposed to 965 ppm for 240 minutes (Cohen et al., 1973), suggesting limited interspecies variability.				
Modifying Factor: NA				
Animal to Human Dosimetric Adjustment: Insufficient data				
Time Scaling: Data are not sufficient to ascertain whether a maximal response to SO ₂ for a lethal endpoint is obtained within 10 minutes. Therefore, time scaling was utilized in the derivation of AEGL-3 values. An n of 3 was applied to extrapolate to the 1-hour time period, and n of 1 was used for extrapolation to the 8-hour time period to provide AEGL values that would be protective of human health (NRC, 2001). The 1-hour AEGL-3 value was also adopted as 10-minute and 30-minute values because asthmatic humans are highly sensitive to sulfur dioxide at short time periods.				
Data adequacy: Well-conducted study with appropriate endpoint for AEGL-3.				

APPENDIX C: CATEGORY PLOTS FOR SULFUR DIOXIDE

Chemical Toxicity - TSD Animal Data Sulfur Dioxide

