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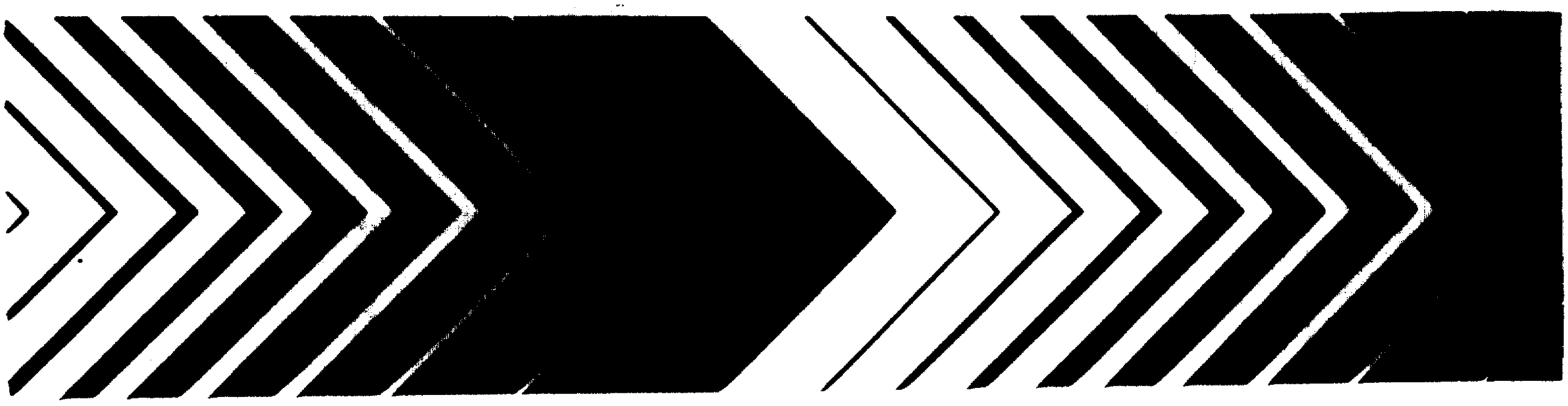
Supplement to the Second Addendum (1986) to Air Quality Criteria for Particulate Matter and Sulfur Oxides (1982)

Assessment of New Findings on Sulfur Dioxide Acute Exposure Health Effects in Asthmatic Individuals



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SUPPLEMENT TO THE SECOND ADDENDUM (1986) TO AIR QUALITY CRITERIA FOR PARTICULATE MATTER AND SULFUR OXIDES (1982):

Assessment of New Findings on Sulfur Dioxide Acute Exposure Health Effects In Asthmatic Individuals

Environmental Criteria and Assessment Office
Office of Health and Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Research Triangle Park, NC 27711

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ABSTRACT

The present Supplement to the Second Addendum (1986) to the document Air Quality Criteria for Particulate Matter and Sulfur Oxides (1982) focuses on evaluation of newly available controlled human exposure studies of acute ($\leq$1 h) sulfur dioxide (SO_2) exposure effects on pulmonary function and respiratory symptoms in asthmatic subjects. The Supplement more specifically: (1) incorporates by reference and concisely summarizes the most important key findings on the same topic from the previous criteria reviews in the 1982 Criteria Document and its 1986 Second Addendum, as they pertain to derivation of health criteria for a possible new "acute exposure" ($<$1 h) primary SO_2 National Ambient Air Quality Standard (NAAQS); and (2) provides an updated assessment of new information that has become available since completion of the 1986 Second Addendum and is of likely importance for derivation of health criteria for any such short-term SO_2 NAAQS. Thus, this Supplement is not intended as a comprehensive detailed review of all new information on SO_2 effects, but rather is targeted explicitly on those human studies thought to provide key information useful to U.S. EPA decision making regarding a $\leq$1-h SO_2 NAAQS.

SUPPLEMENT TO THE SECOND ADDENDUM (1986) TO AIR QUALITY CRITERIA FOR PARTICULATE MATTER AND SULFUR OXIDES (1982): Assessment of New Findings on Sulfur Dioxide Acute Exposure Health Effects in Asthmatic Individuals

1.0 INTRODUCTION

The United States Clean Air Act and its Amendments (1977, 1990) mandate that the U.S. Environmental Protection Agency (U.S. EPA) periodically review criteria for National Ambient Air Quality Standards (NAAQS) and revise such standards as appropriate. Earlier periodic review of the scientific bases underlying the NAAQS for particulate matter (PM) and sulfur oxides (SO_x) culminated in the 1982 publication of the U.S. EPA document Air Quality Criteria for Particulate Matter and Sulfur Oxides (U.S. EPA, 1982a), an associated PM staff paper (U.S. EPA, 1982b) that examined implications of the revised criteria for review of the PM NAAQS, an addendum to the criteria document assessing further information on health effects (U.S. EPA, 1982c), and another staff paper relating the revised scientific criteria to the review of the SO_x NAAQS (U.S. EPA, 1982d). Based on the criteria document, addendum, and staff papers, revised 24-h and annual-average standards for PM were proposed (Federal Register, 1984a) and public comments on the proposed revisions received both in written form and orally at public hearings (Federal Register, 1984b). Subsequently, a Second Addendum to the 1982 PM/SO_x Criteria Document was prepared and published in 1986. The Second Addendum (U.S. EPA, 1986) included evaluation of numerous new studies that had become available since completion of the earlier PM/SO_x criteria document, its addendum, and associated staff papers (U.S. EPA, 1982a,b,c,d), emphasizing assessment of those key new studies likely to have important bearing on development of criteria to support decisionmaking on PM or SO_x NAAQS revisions.

The evaluations contained in the foregoing criteria document, addenda, and staff papers ultimately provided scientific bases for establishment (Federal Register, 1987) of new 24-h and annual average PM NAAQS set at: 150 $\mu g/m^3$ (24 h) and 50 $\mu g/m^3$ (annual) for particulate matter less than 10 μm aerodynamic diameter (PM_{10}). In addition, U.S. EPA

published a proposal (Federal Register, 1988) to retain the current primary NAAQS for sulfur dioxide (SO_2) (i.e., 365 $\mu g/m^3$ [24 h] and 80 $\mu g/m^3$ [annual]) along with a call for public comment on possibly adding an even shorter term (1-h) SO_2 NAAQS to protect against health effects in asthmatic individuals associated with very acute exposures to SO_2. The most crucial information supporting consideration of possible setting of an acute exposure standard cited by the 1988 proposal were recent findings from controlled human exposure studies concerning: (1) exposure-response relationships for SO_2-induced bronchoconstriction and respiratory symptoms in asthmatic subjects; (2) the severity of such effects, which might vary in intensity as a function of the preexisting disease severity (mild to severe asthma); and (3) other factors (e.g., medication use) that might alter such SO_2-induced responses.

Since the Second Addendum (1986) was completed, several new controlled human exposure studies have become available that further evaluate acute ($\leq$1-h) SO_2 exposure effects on asthmatic individuals and provide pertinent additional information useful in supporting U.S. EPA decisionmaking on whether a new short-term SO_2 NAAQS is needed and, if so, the appropriate form and level of such a standard. Accordingly, the present supplement: (1) incorporates by reference and summarizes the most important key findings from the above previous criteria reviews (U.S. EPA, 1982a,c, 1986) as they pertain to derivation of health-related criteria for a possible new "acute exposure" ($<$1-h) primary SO_2 NAAQS; and (2) provides an updated assessment of newly available information of potential importance for derivation of health criteria for any such new short-term SO_2 standard.

This document is intended to be considered in conjunction with the extensive 1982 Criteria Document (U.S. EPA, 1982a) and its earlier Addenda (U.S. EPA, 1982c, 1986). Much background material was presented in these previous documents and is not repeated in this supplement; the reader is therefore encouraged to read such background material to become more fully informed. The material presented here focuses mainly on the assessment of selected new information regarding controlled exposure of asthmatic subjects to SO_2, along with concise summarization and discussion of certain information on the "natural history" of asthma in order to place the SO_2 effects in context in relation to variations in respiratory responses otherwise often experienced by asthmatic subjects.

2.0 BACKGROUND INFORMATION ON ASTHMA

The information discussed below on the health effects of SO_2 in asthmatic individuals is derived from controlled human exposure studies which are often used to study the effects of single (or multiple) inhaled pollutants such as SO_2. Such studies may be performed in environmental chambers where the subjects are free to breathe as they would in the ambient environment or studies may be conducted using mouthpiece or facemask systems where the subjects are required to breathe through the mouthpiece or facemask. In addition to the concentration of SO_2, these studies also permit accurate determination of the duration of exposure and the volume of inspired air containing SO_2. Other factors such as exercise and air temperature and humidity, which can alter responses, can also be controlled.

Exercise alone may have some important confounding effects, particularly in the case of exercise-induced bronchoconstriction in asthmatic individuals, which can be indexed by significant decrements in spirometric variables or increments in airway resistance. Exercise-induced bronchoconstriction is followed by a refractory period of several hours during which asthmatic individuals are less susceptible to bronchoconstriction (Edmunds et al., 1978). This period of refractoriness can alter the subject's responsiveness to SO_2 or other inhaled substances. The major external determinants of the exposure "dose" of a pollutant are the concentration of pollutant, the duration of the exposure, and the volume of air breathed (specifically, the route, depth, and frequency of breathing) during the exposure. Further information is necessary to determine the actual dose delivered to the various "target" regions of the respiratory tract (i.e., total respiratory uptake) and is not discussed in this document.

In controlled human exposure studies, the methods used for assessment of respiratory effects primarily involve "noninvasive" procedures. Lung function tests such as spirometric measures of lung volumes, measures of resistance of lung or nasal airways, ventilation volume (volume of air inhaled into the lung), breathing pattern (frequency and depth of breathing), and numerous other "breathing" tests have been utilized (Bouhuys, 1974). These tests provide useful information about some of the basic physiological functions of the lung. Dynamic spirometry tests (forced expiratory tests such as forced expiratory volume in 1 s [FEV_1], maximal and partial flow-volume curves, peak flow measurements, etc.) and specific airway resistance/conductance measurements (SR_{aw}, SG_{aw}) provide information primarily about large airway function. These "standard pulmonary function" tests are relatively simple

to administer, provide a good overall index of lung function, and have a relatively low coefficient of variation (CV). For FEV_1, the CV is about 3% and for SR_{aw}, the CV is about 10 to 20% for normal healthy subjects[1].

Measurements of spirometry (FEV_1, etc.) and peak flow are also commonly used in clinical practice to assess lung function, especially in patients with respiratory disease such as asthma. Measurements of airway resistance with a body plethysmograph may be used in clinical evaluations but, because of the cost, complexity, and size of the equipment required, they are more often conducted in research laboratories or major medical centers. The coefficient of variation for SR_{aw} measurements tends to be somewhat higher in patients with lung disease than in healthy individuals (Skoogh, 1973; Pelzer and Thompson, 1966). Both asthmatic and healthy patients experience a circadian variation in lung function, with the poorest function (i.e., lowest FEV_1 and highest SR_{aw}) being experienced in the early morning hours (4 to 6 AM) and the best function (i.e., highest FEV_1 and lowest SR_{aw}) occurring in the mid-afternoon (2 to 4 PM). The oscillations can vary by ±5 to 10% about the daily mean in asthmatic subjects (this means that FEV_1 could be as much as 20% higher at mid-afternoon as opposed to early morning although the typical range is about 10%), but are typically smaller in healthy subjects. Similar variations in SR_{aw} may result in SR_{aw} being about 40% higher in early morning than at mid-afternoon in asthmatic subjects (Smolensky et al., 1986).

Circadian variations in lung function in asthmatic individuals have been reviewed by Smolensky et al. (1986). They discuss that the chronobiology of asthma is, in part, associated with other body rhythms having a circadian periodicity, such as cortisol, catecholamines, vagal tone, etc. Daily variability of lung function is a typical feature of asthma and has been used as a predictor of airway hyperresponsiveness (Higgins et al., 1992). For a group of subjects selected because they had ever experienced wheezing, the 90th percentile for variability in peak flow (expressed as the [lowest PEF − highest PEF] ÷ mean PEF) was 17.6%. The mean amplitude of variability for those who had wheezed in the past week was 10%.

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[1]CV is the average coefficient of variation for a number of subjects tested multiple times. CV = S.D./mean × 100% for each individual. These are calculated for tests conducted at the same time of day so that circadian variations should not be included.

2.1 DEFINITION AND INCIDENCE OF ASTHMA

The Expert Panel Report from the National Asthma Education Program of the National Heart Lung and Blood Institute (NIH, 1991) has recently defined asthma as:

Asthma is a lung disease with the following characteristics: (1) airway obstruction that is reversible (but not completely so in some patients) either spontaneously or with treatment, (2) airway inflammation, and (3) increased airway responsiveness to a variety of stimuli.

About 10 million people or 4% of the U.S. population are estimated to have asthma (NIH, 1991). The prevalence is higher among African Americans, older (8- to 11-year-old) children, and urban residents (Schwartz et al., 1990). The true prevalence of asthma may be somewhat higher than determined by epidemiologic surveys since some individuals with mild asthma who have never been treated by a physician may be unaware of the fact that they have asthma (Voy, 1984). Depending upon the definition of asthma, some estimates of prevalence may be as high as 7 to 10% of the U.S. population (Evans et al., 1987).

There is a broad range of severity of asthma ranging from mild to severe (see Table 1, reproduced from NIH, 1991). Common symptoms include cough, wheezing, shortness of breath, chest tightness, and sputum production. A positive response (skin test) to common inhalant allergens and an increased serum immunoglobulin E are common features of asthma. However, not all asthmatic individuals have allergies (although estimates range as high as 80%) and a large number of healthy individuals who have allergies (approximately 30 to 40% of healthy individuals) do not develop asthma (Weiss and Speizer, 1993). Asthma is characterized by an exaggerated bronchoconstrictor response to many physical challenges (e.g., cold or dry air; exercise) and chemical and pharmacologic agents (e.g., histamine or methacholine). Notably, however, bronchial hyperresponsiveness is not synonymous with asthma (Weiss and Speizer, 1993). Asthma is typically associated with airway inflammation and epithelial injury (NIH, 1991; Beasley et al., 1989; Laitinen et al., 1985; Wardlaw et al., 1988). Based on laboratory findings (Deal et al., 1980) asthma symptoms are expected to be exacerbated by cold dry weather, although such an effect of ambient cold on asthma morbidity has not been clearly demonstrated. Approximately 50% of childhood asthmatic

TABLE 1. CLASSIFICATION OF ASTHMA BY SEVERITY OF DISEASE[a]

Characteristics	Mild	Moderate	Severe
A. Pretreatment			
Frequency of exacerbations	Exacerbations of cough and wheezing no more often than 1-2 times/week.	Exacerbation of cough and wheezing on a more frequent basis than 1-2 times/week. Could have history of severe exacerbations, but infrequent. Urgent care treatment in hospital emergency department or doctor's office <3 times/year.	Virtually daily wheezing. Exacerbations frequent, often severe. Tendency to have sudden severe exacerbations. Urgent visits to hospital emergency departments or doctor's office >3 times/year. Hospitalization >2 times/year, perhaps with respiratory insufficiency or, rarely, respiratory failure and history of intubation. May have had cough syncope or hypoxic seizures.
Frequency of symptoms	Few clinical signs or symptoms of asthma between exacerbations.	Cough and low grade wheezing between acute exacerbations often present.	Continuous albeit low-grade cough and wheezing almost always present.
Degree of exercise tolerance	Good exercise tolerance but may not tolerate vigorous exercise, especially prolonged running.	Exercise tolerance diminished.	Very poor exercise tolerance with marked limitation of activity.
Frequency of nocturnal asthma	Symptoms of nocturnal asthma occur no more often than 1-2 times/month.	Symptoms of nocturnal asthma present 2-3 times/week.	Considerable, almost nightly sleep interruption due to asthma. Chest tight in early morning.
School or work attendance	Good school or work attendance.	School or work attendance may be affected.	Poor school or work attendance.
Pulmonary function			
• Peak Expiratory Flow Rate (PEFR)	PEFR > 80% predicted. Variability[b] <20%.	PEFR 60-80% predicted. Variability 20-30%.	PEFR < 60% predicted. Variability > 30%.
• Spirometry	Minimal or no evidence of airway obstruction on spirometry. Normal expiratory flow volume curve; lung volumes not increased. Usually a >15% response to acute aerosol bronchodilator administration, even though baseline near normal.	Signs of airway obstruction on spirometry are evident. Flow volume curve shows reduced expiratory flow at low lung volumes. Lung volumes often increased. Usually a >15% response to acute aerosol bronchodilator administration.	Substantial degree of airway obstruction on spirometry. Flow volume curve shows marked concavity. Spirometry may not be normalized even with high dose steroids. May have substantial increase in lung volumes and marked unevenness of ventilation. Incomplete reversibility to acute aerosol bronchodilator administration.
• Methacholine sensitivity	Methacholine PC_{20} > 20 mg/mL.[c]	Methacholine PC_{20} between 2 and 20 mg/mL.	Methacholine PC_{20} < 2 mg/mL.
B. After optimal treatment is established			
Response to and duration of therapy	Exacerbations respond to broncodilators without the use of systemic corticosteroids in 12-24 h. Regular drug therapy not usually required except for short periods of time.	Periodic use of bronchodilators required during exacerbations for a week or more. Systemic steroids usually required for exacerbations as well. Continuous around-the-clock drug therapy required. Regular use of anti-inflammatory agents may be required for prolonged periods of time.	Requires continuous, multiple around-the-clock drug therapy including daily corticosteroids, either aerosol or systemic, often in high doses.

[a]Characteristics are general; because asthma is highly variable, these characteristics may overlap. Furthermore, an individual may switch into different categories over time.

[b]Variability means the difference either between a morning and evening measure or among morning peak flow measurements each day for a week.

[c]Although the degree of methacholine/histamine sensitivity generally correlates with severity of symptoms and medication requirements, there are exceptions.

Source: National Institutes of Health (1991).

individuals later experience remission of their disease as adults, although, an early age of onset and the presence of atopy make this less likely (Weiss and Speizer, 1993).

In a group of child and adolescent moderate asthmatics studied over a period of 22 mo (Van Essen-Zandvliet et al., 1992), approximately half of those on beta-agonist therapy alone experienced one or more exacerbations of their asthma requiring treatment with prednisolone. The incidence of exacerbations was much less (about 15%) for those on a combined regimen of inhaled corticosteroids and beta-agonist. Weitzman et al. (1992) reported that 10% of a national sample of children (<18 years) with asthma (U.S. National Health Interview Survey, 1988; total n = 17,100; asthmatic n = 735) were hospitalized within the past year. Based on a total of 450,000 hospitalizations for asthma and an estimated U.S. population of 10,000,000 asthmatics, the incidence of hospitalization for all asthmatic subjects is about 45 per 1,000 asthmatics (≈4.5%/year) (NIH, 1991). Attendance at hospital emergency rooms for asthma in Vancouver, Canada, averaged 350 per 100,000 population or 350 per 4,000 asthmatics (≈8.9%/year) based on an estimated prevalence of 4% and accounted for 1.2% of all emergency room visits.

For asthmatic individuals who experienced an asthma attack causing them to seek treatment by a physician, the rate of hospitalization based on the National Asthma Attack Audit in the United Kingdom (1991 to 1992) was 12% (Neville et al., 1993). Asthma attack rates in general practice in the United Kingdom suggest an incidence of asthma attacks (requiring medical intervention) of <1/asthmatic patient-year (Ayres, 1986). Although asthma attacks occurred throughout the year, there was a tendency for the highest rates to follow the seasonal elevation of grass pollen. Schwartz et al. (1993) found fall and spring peaks for hospital admissions for asthma in Seattle. However, rates did not differ for summer and winter, as also shown by Bates and Siszto (1986) in Ontario, Canada. Based on the Los Angeles asthma panel data (EPRI, 1988), only 15% of mild asthmatics see a physician annually for their asthma compared to about 67% of the moderate asthmatics. The United Kingdom national asthma attack audit reported an attack rate of 14 per 1,000 patients (or 14 per 40 asthmatics), suggesting an attack rate of <1 asthmatic patient/year (Nevill et al., 1993). A similar attack incidence was estimated by Van Essen-Zandvliet et al. (1992) and Lebowitz et al. (1985) for U.S. asthma patients.

Schoettlin and Landau (1961) reported an asthma attack frequency among a group of asthmatic patients currently under a physician's care for asthma. The daily asthma attack rate was 25% of all person-days. However, 95% of all attacks were classified as mild, and 40 of 137 patients had fewer than 4 attacks in 14 weeks. Only 4% of all attacks were attributed to exertion. Zeidberg et al. (1961) also reported that, for 85 asthmatic patients followed for 43 days, the mean asthma attack rate was 0.133 per patient day or an average of just less than once a week.

Death due to asthma is a rare event; about two to four deaths annually occur per 1,000,000 population or about one per 10,000 asthmatic individuals. Mortality rates are higher among males and are at least 100% higher among nonwhites. Indeed, in two large urban centers (New York and Chicago) mortality rates from asthma among nonwhites may exceed the city average by up to five-fold and exceed the national average by an even larger factor (Sly, 1988; Evans et al., 1987; NIH, 1991; Weiss and Wagener, 1990; Carr et al., 1992). The mortality rate from asthma in the East Harlem neighborhood of Manhattan (49 per million population) was approximately 10-fold greater than the national average.

The economic impact of asthma is substantial. McFadden (1988) estimates that asthma results in 27 million patient visits, 134,000 hospital admissions, 6 million lost work days, and 90 million days of restricted activity. In 1975, a cost of $292 million was estimated for medication alone. In 1987, there were 450,000 hospital admissions for asthma, a rate of approximately 45 per 1,000 asthmatics (NIH, 1991).

Asthmatic persons who participate in controlled human exposure studies typically have mild allergic asthma. In many cases, these individuals can go without medication altogether or can discontinue medication for brief periods of time if exposures are conducted outside their normal allergy season. The most common participants are young adult white male and female college and high school students. Black and Hispanic adolescents and young adults have not been studied systematically. The extent to which groups of asthmatic individuals who participate in controlled exposure studies reflect the characteristics of the asthmatic population at large is not known. Subjects who participate in controlled exposure studies are generally self-selected and this could conceivably introduce some bias. However, the high degree of consistency among studies suggests that the subjects are generally representative of

the population at risk or that any selection bias is consistently present across a diverse group of laboratories.

2.2 MEDICATION USE BY ASTHMATIC INDIVIDUALS

The extent to which asthmatic individuals, especially the mild asymptomatic individuals who constitute the majority of asthmatics and who often serve as subjects in these studies, may use prophylactic medication prior to exercising outdoors is unknown. Most mild asthmatic persons only use medication when symptoms arise. National Heart Lung and Blood Institute guidelines (NIH, 1991) for treatment of chronic mild asthma recommend use of beta-agonists on an as needed (prn) basis. The results of an analysis of activity patterns, symptoms, and medication use of a panel of 52 asthmatic subjects in Los Angeles are in accord with these recommendations (Roth et al., 1988). One third of the mild asthmatic patients studied had not used any asthma medication within the past year, and fewer than half used an inhaled bronchodilator at least once during the past year. Furthermore, only 20% of the moderate asthmatic patients studied used an inhaled bronchodilator on a regular basis. Thus the frequency of use of beta-agonist bronchodilator medication varies widely among asthmatic individuals and is related, at least in part, to the severity of their disease. For example, in a rural community in Australia, Marks et al. (1992) reported that 12% of the asthmatic residents had never used a beta-agonist and that only 38% had used a beta-agonist at least once in the preceding week. Thus, for more than half the asthmatic individuals in the community, beta-agonist use was infrequent and would be unlikely to be used in temporal proximity to an environmental exposure. Furthermore, NIH guidelines recommend additional treatment if beta agonists are used on a daily basis.

Medication compliance for those on a regular medication regime varies considerably among asthmatic patients (from none to full compliance). Average compliance figures are reported to range from approximately 50 to 70% (Weinstein and Cuskey, 1985; Partridge, 1992; Smith et al., 1984; Smith et al., 1986), although Klingelhofer (1987) reports a range of 2 to 83% among children with moderate to severe asthma, based on his review of eleven studies of medical compliance. Given the infrequent use of medication by many mild asthmatic individuals and the poor medication compliance of 30% to 50% of the "regularly medicated" asthmatic patients, it appears that a substantial proportion of asthmatic subjects

would not likely be "protected" by medication use from impacts of environmental factors on their respiratory health. However, the frequency of use of medication (bronchodilators) specifically prior to engaging in outdoor activity cannot be confidently extrapolated from epidemiologic data on medication compliance. Thus, the relative number of persons who may be protected by medication prior to exercise is unclear.

3.0 SUMMARY OF PREVIOUS FINDINGS ON SO_2 EFFECTS

Key controlled human exposure studies of SO_2 respiratory effects published in the scientific literature from 1982 to 1986, as reviewed in the Second Addendum (U.S. EPA, 1986), are summarized in Appendix Table A-1. Those studies were found to support and extend many of the conclusions reached in the earlier PM/SO_x Criteria Document (U.S. EPA, 1982) and its previous Addendum (U.S. EPA, 1982c).

More specifically, the additional studies evaluated in U.S. EPA (1986) clearly showed that asthmatic subjects are much more sensitive to SO_2 as a group than are nonasthmatic individuals. Nevertheless, it was clear that a broad range of sensitivity to SO_2 existed among asthmatic subjects exposed under similar conditions. Those studies also confirmed that normal healthy subjects, even with moderate to heavy exercise, do not experience effects on pulmonary function due to SO_2 exposure in the range of 0 to 2 ppm. The minor exception may be the annoyance of the unpleasant smell or taste associated with SO_2. The suggestion that asthmatic individuals are about an order of magnitude more sensitive than healthy, nonasthmatic persons was thus confirmed.

The studies reviewed in the Second Addendum (U.S. EPA, 1986) further substantiated that normally breathing asthmatic individuals performing moderate to heavy exercise will experience SO_2-induced bronchoconstriction when breathing SO_2 for at least 5 min at concentrations less than 1 ppm. Durations beyond 10 min do not appear to cause substantial worsening of the effect. The lowest concentration at which bronchoconstriction is clearly worsened by SO_2 breathing depends on a variety of factors.

Exposures to less than 0.25 ppm were found not to evoke group mean changes in responses. Although some individuals may appear to respond to SO_2 concentrations less than 0.25 ppm, the frequency of these responses was not demonstrably greater than with clean air.

The Second Addendum (U.S. EPA, 1986) also noted that, in the SO_2 concentration range from 0.2 to 0.3 ppm, six chamber exposure studies were performed with asthmatic subjects performing moderate to heavy exercise. The evidence that SO_2-induced bronchoconstriction occurred at such concentrations with natural breathing under a range of ambient conditions was equivocal. Only with oral mouthpiece breathing of dry air (an unusual breathing mode under exceptional ambient conditions) were small effects observed on a test of questionable quantitative relevance for criteria development purposes. These findings are in accord with the observation that the most reactive subject in the Horstman et al. (1986) study had a $PCSO_2$ (SO_2 concentration required to double SR_{aw}) of 0.28 ppm.

The Second Addendum (U.S. EPA, 1986), however, went on to note that several observations of significant group mean changes in specific airway resistance (SR_{aw}) had then recently been reported for asthmatic subjects exposed to 0.4 to 0.6 ppm SO_2. Most, if not all of the studies, using moderate to heavy exercise levels (>40 to 50 L/min), found evidence of bronchoconstriction at 0.5 ppm. At a lower exercise rate, other studies (e.g., Schachter et al., 1984) did not produce clear evidence of SO_2-induced bronchoconstriction at 0.5 ppm SO_2. Exposures that included higher ventilations, mouthpiece breathing, and inspired air with a low water content resulted in the greatest responses. Mean responses ranged from 45% (Roger et al., 1985) to 280% (Bethel et al., 1983b) increases in SR_{aw}. At concentrations in the range of 0.6 to 1.0 ppm, marked increases in SR_{aw} were observed following exposure, and recovery was generally complete within approximately 1 h, although the recovery period may be somewhat longer for subjects with the most severe responses.

It is now evident that for SO_2-induced bronchoconstriction to occur in asthmatic individuals at concentrations less than 0.75 ppm, the exposure must be accompanied by hyperpnea (deep and rapid breathing). Ventilations in the range of 40 to 60 L/min have been most effective; breathing at these levels typically involves oronasal ventilation (breathing through mouth and nose). Oral breathing (especially via mouthpiece) clearly caused exacerbation of SO_2-induced bronchoconstriction. New studies reviewed in the Second Addendum (U.S. EPA, 1986) reinforced the concept that the mode of breathing is an important determinant of the intensity of SO_2-induced bronchoconstriction in the following order: oral > oronasal > nasal. A second exacerbating factor implicated in the

then-reviewed new reports was the breathing of dry and/or cold air. It was not clearly established whether exacerbation of SO_2 effects was due to airway cooling, airway drying, or some other mechanism.

The new studies reviewed in the Second Addendum (U.S. EPA, 1986), unfortunately, did not provide sufficient additional information to establish whether the intensity of the SO_2-induced bronchoconstriction depended upon the severity of the disease. The studies available at that time more specifically indicated that, across a broad clinical range from "normal" to "moderate" asthmatic subjects, there clearly existed a relationship between the presence of asthma and sensitivity to SO_2. However, within the asthmatic population, the relationship of SO_2 sensitivity to the qualitative clinical severity of asthma had not been systematically studied. It was noted that ethical considerations (i.e., continuation of appropriate medical treatment) generally prevent the unmedicated exposure of "severe" asthmatic individuals because of their dependence upon drugs for control of their asthma. True determination of sensitivity requires that the interference with SO_2 response caused by such medication be removed. Because of these mutually exclusive requirements, it was thought unlikely that the "true" SO_2 sensitivity of severe asthmatic individuals could be determined, although it was noted that more severe asthmatic patients should be studied if possible. Alternative methods to those used with mild asthmatic individuals, not critically dependant on regular medication, were noted as being required to assess asthmatic individuals with severity of disease ranging to beyond the "mild to moderate" level (i.e., moderate to severe asthmatic persons).

Studies reviewed in the Second Addendum (U.S. EPA, 1986) also indicated that consecutive SO_2 exposures (repeated within 30 min or less) result in a diminished response compared with the initial exposure. It was apparent that this refractory period lasts at least 30 min, but that normal reactivity returns within 5 h. The mechanisms and time course of this effect were not yet clearly established, but the refractoriness did not appear to be related to an overall decrease in bronchomotor responsiveness. These observations suggested that the effects of SO_2 on airway resistance and spirometry tend to be brief and do not tend to become worse with continued or repeated exposure. Nevertheless, the issue of repeated or chronic exposure to SO_2 in asthmatic individuals remained to be more definitively addressed.

Overall, then, based on the review of studies included in the Second Addendum, it was clear that the magnitude of response (typically bronchoconstriction) induced by any given SO_2 concentration was highly variable among individual asthmatic subjects. Exposures to SO_2 concentrations of 0.25 ppm or less, which did not induce significant group mean increases in airway resistance, also did not cause symptomatic bronchoconstriction in individual asthmatic subjects. On the other hand, exposures to 0.40 ppm SO_2 or greater (combined with moderate to heavy exercise), which induced significant group mean increases in airway resistance, did cause substantial bronchoconstriction in some individual asthmatic subjects. This bronchoconstriction was often associated with wheezing and the perception of respiratory distress. In a few instances it was necessary to discontinue the exposure and provide medication. The significance of these observations was that some SO_2-sensitive asthmatic subjects appeared to be at risk of experiencing clinically significant (i.e., symptomatic) bronchoconstriction requiring termination of activity and/or medical intervention when exposed to SO_2 concentrations of 0.40 to 0.50 ppm or greater, when such exposure is accompanied by at least moderate activity.

The Second Addendum (U.S. EPA, 1986), therefore, clearly supported the premise that asthmatic individuals are substantially more responsive to sulfur dioxide (SO_2) exposure than individuals without airways hyperresponsiveness. The extensive exposure-response information presented in the Addendum indicated that exercising asthmatic subjects may respond to brief exposures to SO_2 concentrations greater than 0.40 ppm, but little (if any) response is observed with resting exposures at concentrations less than 1.0 ppm SO_2. Exposure durations of 5 to 10 min were found to be sufficient to stimulate a near maximal bronchoconstrictive response. The median concentration, to which a large group of asthmatic subjects responded by doubling their specific airway resistance (over and above that caused by air exposure and exercise alone), was 0.75 ppm (Horstman et al., 1986) as depicted in Figure 1. Responses to SO_2 are amplified by oral breathing of SO_2, by breathing cold dry air in combination with SO_2, and by the magnitude of either voluntary or exercise-induced hyperpnea. However, repeated exposures to SO_2 result in a period of diminished responsiveness, also called a refractory period. In addition to SO_2-induced changes in respiratory function indicative of bronchoconstriction (namely increased airway resistance and decreased FEV_1) there were increased symptoms, most notably wheezing and a perception of

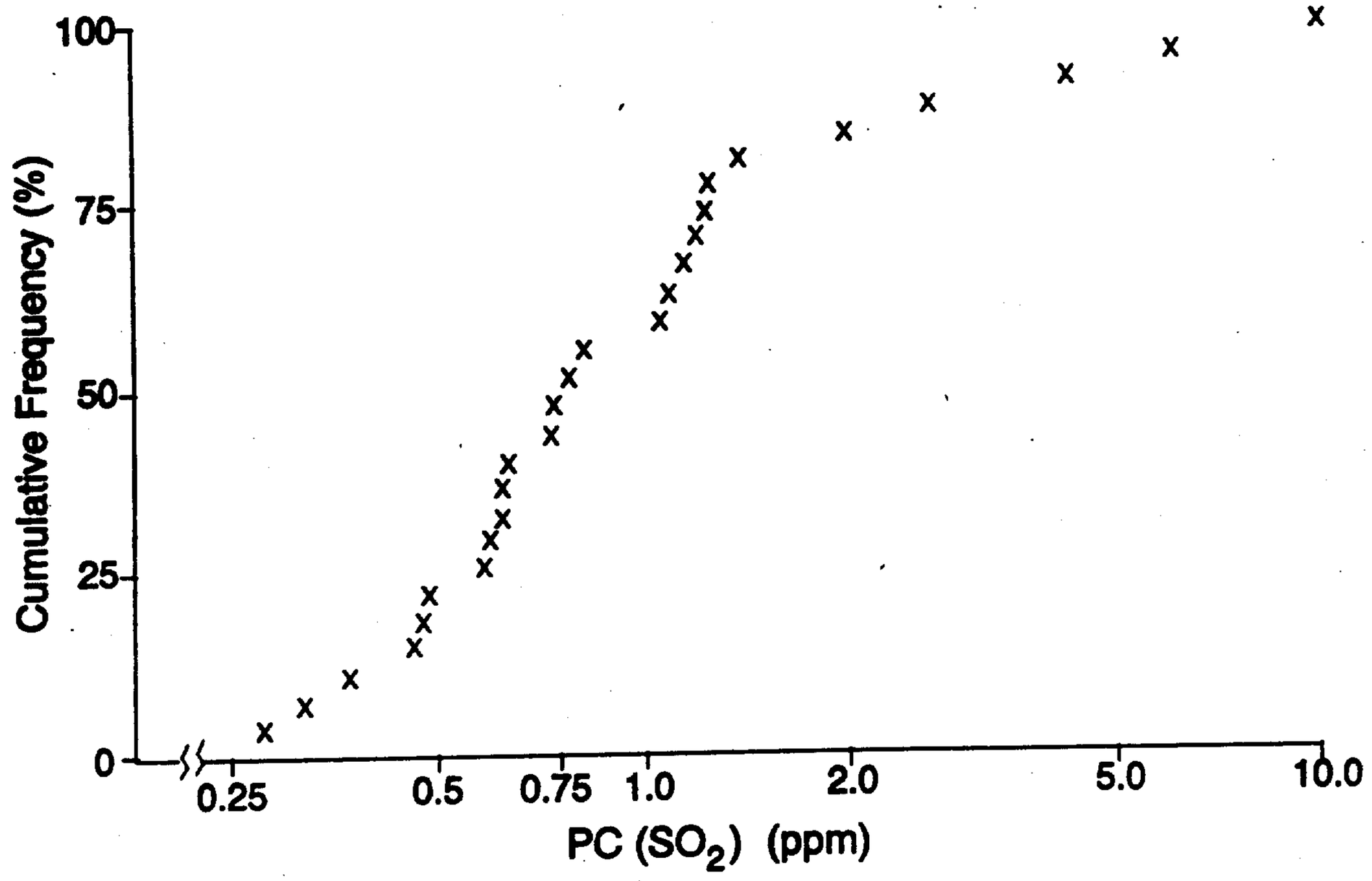

Figure 1. Distribution of individual airway sensitivity to SO_2, ($PC[SO_2]$). $PC(SO_2)$ is the estimated SO_2 concentration needed to produce doubling of SR_{aw} in each subject. For each subject, $PC(SO_2)$ is determined by plotting change in SR_{aw}, corrected for exercise-induced bronchoconstriction, against SO_2 concentration. The SO_2 concentration that caused a 100% increase in SR_{aw} is determined by linear interpolation. Cumulative percentage of subjects is plotted as a function of $PC(SO_2)$, and each data point represents $PC(SO_2)$ for an individual subject (see also the discussion of $PC[SO_2]$ in Section 3.3).

Source: Horstman et al. (1986).

respiratory distress. A small number of studies noted increased medication usage among SO_2-exposed asthmatic subjects, although no studies were specifically designed to study medication use. The effects of some asthma medications on response to SO_2 were also studied. It was shown that cromolyn sodium inhibited SO_2-induced bronchoconstriction (SIB) in a dose-related manner (Myers et al., 1986a). Also, albuterol, a β-sympathomimetic drug, was shown to inhibit the response to SO_2 (Koenig et al., 1987).

4.0 KEY NEW FINDINGS ON FACTORS AFFECTING RESPIRATORY RESPONSES TO SULFUR DIOXIDE IN ASTHMATIC SUBJECTS

Since completion of the earlier Second Addendum (1986), a number of additional studies have become available that provide further information with regard to various aspects related to the induction by acute SO_2 exposure of respiratory effects in asthmatic subjects, and the most salient findings from such studies are concisely discussed below. Key new studies yielding important new information on SO_2 exposure-response relationships for asthmatic subjects and factors affecting such relationships are summarized in Table 2.

4.1 EXPOSURE DURATION/HISTORY AS SULFUR DIOXIDE DOSE-RESPONSE DETERMINANTS

Previous studies reviewed in the Second Addendum (U.S. EPA, 1986) found that the bronchoconstrictive response to SO_2 has a rapid onset and reaches a peak response within about 5 to 10 min. Two more recent studies have shown that significant responses can occur in as little as 2 min. Horstman et al. (1988) showed, in a group of 12 SO_2-responsive asthmatic subjects, that with 2 and 5 min of exercise ($\dot{V}_E$ = 40 L/min) exposure to 1.0 ppm SO_2, SR_{aw} increased by 121 and 307%, respectively (percentages corrected for exercise-induced responses during exercise in clean air). Balmes et al. (1987) demonstrated an even more rapid onset of bronchoconstriction in eight asthmatic subjects exposed to 1.0 ppm SO_2 during eucapnic hyperpnea ($\simeq$60 L/min) by mouthpiece. At 1, 3, and 5 min, they reported SR_{aw} increases of 47, 349, and 534%, respectively. They also showed significant increases in SR_{aw} after 3 (127%) and 5 (188%) min of exposure to 0.5 ppm SO_2. In each of these two studies, several subjects requested a bronchodilator to alleviate symptoms induced by the exposures; 7 of 8 subjects did so in the Balmes et al. (1987) study, as did 4 of 12 in the Horstman et al. (1988) study. Additionally, two subjects were unable to complete the 5-min exposures to 1.0 ppm in the Balmes et al. (1987) study.

Linn et al. (1987) concluded that exposure history to SO_2 (over the course of several weeks as opposed to hours) was largely irrelevant. They did, however, observe, as had Kehrl et al. (1987), that bronchoconstriction responses to a first exercise period within an hour-long SO_2 exposure resulted in a diminished response in the second exercise period.

TABLE 2. SUMMARY OF KEY NEW STUDY RESULTS FROM CONTROLLED HUMAN EXPOSURE STUDIES OF ACUTE SULFUR DIOXIDE EXPOSURE EFFECTS IN ASTHMATIC SUBJECTS

SO_2 Concentration	Duration	Number of Subjects	Exposure Mode	Exposure Status	Observations	Comments	References
0.1 ppm	15 min SO_2 after 45 min O_3	13 adolescent asthmatic subjects	Oral mouthpiece 22 °C 75% RH	Intermittent exercise $\dot{V}_E \approx 30$ L/min Exposure sequence: (1) air followed by 0.1 ppm SO_2; (2) 0.12 ppm O_3 followed by 0.12 ppm O_3; (3) 0.12 ppm O_3 followed by 0.1 ppm SO_2	45-min prior exposure to 0.12 ppm O_3 modified response to 15-min exposure to 0.10 ppm SO_2 (FEV_1 decreased 8%; R_T increased 19%; $\dot{V}_{max50}$ decreased 15%). Respiratory symptom scores (57 for air-SO_2; 60 for O_3-O_3; 78 for O_3-SO_2) not significantly different.	Prior O_3 exposure may increase bronchial hyperresponsiveness in asthmatic subjects such that they respond to an ordinarily subthreshold SO_2 concentration with pulmonary function decrements but not necessarily higher respiratory symptom rates.	Koenig et al. (1990)
0.0, 0.2, 0.4, 0.6 ppm	1 h	85 (24 normals; 21 atopics; 16 mild asthmatic subjects; 24 moderate/ severe asthmatic subjects medication dependent)	Chamber 21 °C 50% RH	Included three 10-min periods exercise; pulmonary function tested after first (10-min) and third (50-min) exercises $\dot{V}_E \approx 40$ L/min Exposure sequence: each subject exposed to all SO_2 levels in random order at 1-week intervals and tested twice at each concentration	Normals unresponsive; atopics minimally responsive; asthmatic subjects developed meaningful bronchoconstriction and associated respiratory symptoms. Mild asthmatic subjects showed slight SR_{aw} response at 0.0 ppm (exercise effect), which increased progressively with SO_2 concentrations. Moderate/severe asthmatic subjects reacted more markedly to exercise at 0.0 ppm but response to increasing SO_2 similar to minimal/mild asthmatic subjects. FEV_1 decreased with exercise; decrease greatest in moderate/severe asthmatic subjects. When "exercise effect" subtracted out, response to SO_2 similar in both mild and moderate/severe asthmatic subjects.	Severity of asthma did not influence FEV_1 response to SO_2. Additional drop in FEV_1 caused by SO_2 (above that caused by exercise) similar for mild and moderate/severe asthmatic subjects. Most subjects able to maintain physical activity near own normal levels even at 0.6 ppm SO_2. Some atopic (i.e., nonasthmatic) subjects responded to SO_2. This suggests that population at risk may be larger than just the asthmatic population.	Hackney et al. (1987). Linn et al. (1987

TABLE 2 (cont'd). SUMMARY OF KEY NEW STUDY RESULTS FROM CONTROLLED HUMAN EXPOSURE STUDIES OF ACUTE SULFUR DIOXIDE EXPOSURE EFFECTS IN ASTHMATIC SUBJECTS

SO_2 Concentration	Duration	Number of Subjects	Exposure Mode	Exposure Status	Observations	Comments	References
0.0, 0.25, 0.5, 1.0, 2.0, 4.0 ppm	4 min	9 asthmatic subjects	Chamber 22 °C 55% RH	Intermittent exercise $\dot{V}_E$ = 30 L/min Exposure for 30 min to 0.30 ppm NO_2 or clean air followed by SO_2 challenge (i.e., successive doubling of SO_2 concentration every 4 min during voluntary encapnic hyperpnea at $\dot{V}_E$ = 20 L/min).	No significant effects of NO_2 on lung function (single breath nitrogen washout, SR_{aw}, FVC, FEV_1) or respiratory symptoms. Conc. of SO_2 to increase SR_{aw} by 8 units was 1.25 ± 0.70 ppm after air exposure and 1.31 ± 0.75 ppm after NO_2.	Preexposure to NO_2 did not appear to increase responsiveness to subsequent SO_2 exposure at either subthreshold or superthreshold SO_2 levels.	Rubinstein et al. (1990)
0.5, 1.0 ppm	1, 3, 5 min	8 adult asthmatic subjects	Oral mouthpiece ≈22 °C ≈75% RH	Voluntary eucapnic hyperpnea $\dot{V}_E$ = 60 L/min	Magnitude of bronchoconstrictor response to SO_2 progressively increased with time. After 1, 3, and 5 min with 1.0 ppm SO_2, SR_{aw} increased 47, 349, and 534%; after 3 and 5 min with 0.5 ppm SO_2, SR_{aw} increased 127 and 188% .	Seven of eight subjects required bronchodilator medication after SO_2 exposure. Two subjects unable to complete 5-min exposure to 1.0 ppm SO_2 because of symptomatic bronchoconstriction.	Balmes et al. (1987)
0.5 ppm	20 min	46 adult asthmatic subjects	Oral mouthpiece 23 °C 92% RH	Voluntary eucapnic hyperpnea $\dot{V}_E$ = 30 L/min Exposure sequence: 10 min followed by 10 min isocapnic hyperpnea	Exposure to air increased SR_{aw} 45%; SO_2 increased SR_{aw} 131%.	Weak correlation between histamine and SO_2 responses indicates NSBR response to histamine is a poor predictor of SO_2 response. Results also indicate that large mean change driven by larger changes in small group of subjects.	Magnussen et al. (1990)
0.5, 0.75 ppm	30 min	14 adult mild asthmatic subjects	Oral mouthpiece 24.3 °C 50.5% RH	$\dot{V}_E$ = 45 L/min. Subjects breathed 0.25 ppm NO_2 or 0.5 ppm SO_2 at rest followed by challenge with 0.75 ppm SO_2 during voluntary eucapnic hyperpnea. Ventilation increased in 15-L/min steps, each lasting 3 min.	No difference in response to SO_2 challenge when it was preceeded by breathing SO_2 at rest. Enhanced airway responsiveness to 0.75 ppm SO_2 during hyperventilation following prior 30-min exposure to 0.25 ppm NO_2 at rest.	Prior exposure at rest to SO_2 concentration not causing bronchoconstriction did not alter subsequent magnitude of response to suprathreshold SO_2 exposure; but prior subthreshold exposure to NO_2 did appear to enhance subsequent suprathreshold response to SO_2.	Jörres and Magnussen (1990)
1.0 ppm	60 min	10 young adult mild asthmatic subjects	Chamber 26 °C 70% RH	Intermittent exercise $\dot{V}_E$ = 41 L/min 10-min periods broken by 15-min rest periods or 30 min continuous exercise	SR_{aw} increased with exercise and SO_2 exposure; increase with continuous exercise (233%) significantly greater than with intermittent exercise (106%).	Asthmatic subjects show an attenuated response to repetitive exercise in 1.0 ppm SO_2 atmosphere.	Kehrl et al. (1987)

TABLE 2 (cont'd). SUMMARY OF KEY NEW STUDY RESULTS FROM CONTROLLED HUMAN EXPOSURE STUDIES OF ACUTE SULFUR DIOXIDE EXPOSURE EFFECTS IN ASTHMATIC SUBJECTS

SO_2 Concentration	Duration	Number of Subjects	Exposure Mode	Exposure Status	Observations	Comments	References
1.0 ppm	0.0, 0.5, 1.0, 2.0, 5.0 min	12 young adult asthmatic subjects	Chamber 20 °C 40% RH	Exercising $\dot{V}_E \approx 40$ L/min Exposure sequence: each subject exposed to all exposure durations in random order on separate days	Postexposure SR_{aw} and symptom ratings increased with exposure duration in SO_2. Stat. significant bronchoconstriction due to SO_2 observed at 2.0-and 5.0-min exposures, SR_{aw} increased by 121% and 307%.	Approximately half of subjects perceived significant (mod. or severe) SO_2-induced symptoms after 2- or 5-min exposure; 4 of 12 required bronchodilator therapy after exposure.	Horstman et al. (1988)

Note: Voluntary eucapnic hyperpnea is defined as voluntarily maintaining an increased level of ventilation while normal end-tidal CO_2 levels are maintained by addition of CO_2 to the inspired air.

This observation is in support of the concept of a refractory period from repeated SO_2 exposures accompanied by exercise or hyperpnea.

Jörres and Magnussen (1990) examined the effect of 30 min of resting ventilation of 0.5 ppm SO_2 on a subsequent SO_2 ventilatory challenge. The SO_2 challenge involved breathing 0.5 ppm SO_2 at progressively increasing levels of eucapnic hyperpnea. There was no difference in response to the SO_2 challenge when it was preceded by breathing of SO_2 while at rest. This is not surprising since breathing of $\leq$1.0 ppm SO_2 while at rest does not typically cause changes in lung function or symptoms.

Overall, the above new results provide further evidence for the rapid onset of respiratory effects in exercising asthmatics in response to SO_2, demonstrating that such effects can occur within a few minutes (2 to 5 min) of initiation of SO_2 exposure. The results also further confirm a refractory period for SO_2-induced respiratory effects, following prior SO_2 exposure within the immediately preceding few hours that resulted in a physiologically significant increase in airway resistence. This means that repeated SO_2 exposures during a short time period do not lead to any greater manifestation of effects beyond those seen immediately after the first SO_2 exposure. However, other evidence indicates that much earlier SO_2 exposures (days/weeks ago) do not prevent or dampen effects of subsequent SO_2 exposures.

4.2 SULFUR DIOXIDE RESPONSES AND ASTHMA SEVERITY

Another question left unresolved by studies evaluated in the 1986 Second Addendum was the extent to which differential sensitivity might exist among SO_2-sensitive asthmatic individuals (with regard to lowest effective SO_2 exposure levels evoking significantly enhanced bronchoconstriction and/or respiratory symptoms or the magnitude of such effects observed at a given SO_2 exposure level), especially as a function of the severity of the preexisting disease (from mild to severe asthma). Some newly available studies have attempted to address this difficult issue.

Although in most studies of asthmatic individuals exposed to SO_2, a change in specific airway resistance (SR_{aw}) has been used as a measure of response, in other studies, a change in FEV_1 was the response measure. In a few studies, data for both response measures have been obtained. In order to provide an estimate of the comparability of the two response

measures, the data of Linn et al. (1987, 1990) were used (actual data were obtained from two project reports [Hackney et al., 1987, 1988]). In Table 3, the preexposure and postexposure measurements for FEV_1 and SR_{aw} are shown for three different groups of subjects after clean air exposure and after SO_2 exposure. Using these data, the comparability of SR_{aw} and FEV_1 as physiologic measures of response can be estimated. Based on simple linear interpolation, a 100% increase in SR_{aw} roughly corresponds to a 12 to 15% decrease in FEV_1 and a 200% increase in SR_{aw} corresponds to a 25 to 30% decrease in FEV_1.

TABLE 3. COMPARISON OF MEAN SR_{AW} AND FEV_1 RESPONSES TO AIR AND SULFUR DIOXIDE EXPOSURE IN ASTHMATIC SUBJECTS

	$[SO_2]$	Pre-FEV_1	Post-FEV_1	Δ% FEV_1	Pre-SR_{aw}	Post-SR_{aw}	Δ%SR_{aw}
Linn et al., 1990[a]							
low	0.0	1,907	1,634	-14.3	16.0	26.8	+68
normal	0.0	2,270	1,992	-12.2	7.9	14.0	+77
low	0.6	1,914	1,332	-30.0	13.3	40.9	+208
normal	0.6	2,264	1,584	-30.0	7.9	27.6	+249
Linn et al., 1987[b]							
mild	0.0	2,962	2,908	-1.8	5.4	6.9	+29
moderate	0.0	2,473	2,278	-7.9	7.8	13.5	+73
mild	0.6	2,968	2,428	-18.2	5.4	13.7	+153
moderate	0.6	2,430	1,775	-27.0	8.1	24.4	+201

[a] n = 21; low and normal refer to medication level.
[b] n = 16 (mild), n = 24 (moderate), $[SO_2]$ in ppm, FEV_1 in mL, SR_{aw} in cm $H_2O \cdot L^{-1} \cdot s \cdot L$.

Hackney et al. (1987) studied both (a) concentration-response relationships of SO_2 and lung function, as well as (b) differences in response between normal, atopic, mild asthmatic individuals and moderate/severe asthmatic individuals. All groups of subjects were exposed to 0, 0.2, 0.4, and 0.6 ppm SO_2. Each subject was exposed to each level on two different occasions. These results were also reported in the published Linn et al. (1987) report. The 1-h exposures included three 10-min exercise periods. This study supported earlier

investigations (Roger et al., 1985), in that the responses (especially of asthmatic subjects at the highest concentration) tended to be greatest early in exposure (i.e., after the first exercise) and were possibly greater on the first round of exposures than on the second. When the mild asthmatic subjects were compared with the moderate/severe asthmatic subjects, the FEV_1 decrement caused by exercise was greater in the moderate/severe asthmatic subjects, and the combined response to exercise and SO_2 exposure resulted in a greater overall decrease in FEV_1. However, when the "exercise effect" was subtracted from the overall FEV_1 response, the response to SO_2 was similar in the mild versus the moderate/severe asthmatic subjects. Thus severity of asthma, as defined operationally in this study (Hackney et al., 1987), did not influence the FEV_1 response to SO_2.

However, this conclusion must be tempered by the fact that the moderate/severe asthmatic subjects started the exposure with compromised function compared to the mild asthmatic subjects. Thus, it is not clear that similar functional declines beginning from a different baseline have the same biological importance (see Figure 2). Another possible reason that the responses were not greater in the moderate/severe group is that there may have been some persistence of medication, since this group was less able to withhold medication and some of the medication normally used had effects that would persist beyond the brief withholding period prescribed in this study.

Based on an analysis similar to that of Horstman et al. (1986) (i.e., an analysis of the median concentration at which the SR_{aw} was doubled, PC_{100} SR_{aw}), Hackney et al. (1987) estimated that the median $PC_{100}SR_{aw}$ was greater than 0.6 ppm. Pooling the data for mild and moderate/severe asthmatic subjects and using only the first round of exposures, only 15 of 40 subjects showed a doubling of SR_{aw} at $\leq$0.60 ppm SO_2. Based on Horstman et al.'s (1986) cumulative frequency plot of $PC_{100}SR_{aw}$ against SO_2 concentration, approximately 35% of asthmatic subjects would be expected to reach the $PC_{100}SR_{aw}$ at a concentration of 0.60 ppm. Thus the 37.5% incidence (15/40) observed by Linn et al. (1987) is consistent with Horstman et al.'s observations (see Table 4), despite the fact that Linn et al.'s subject group included asthmatic individuals with more severe disease.
In comparing responses to SO_2 among asthmatic subjects of varying severity, the health significance of the observed lung function responses would have been considered to be greater had these responses persisted for several hours or days after exposure or if there had

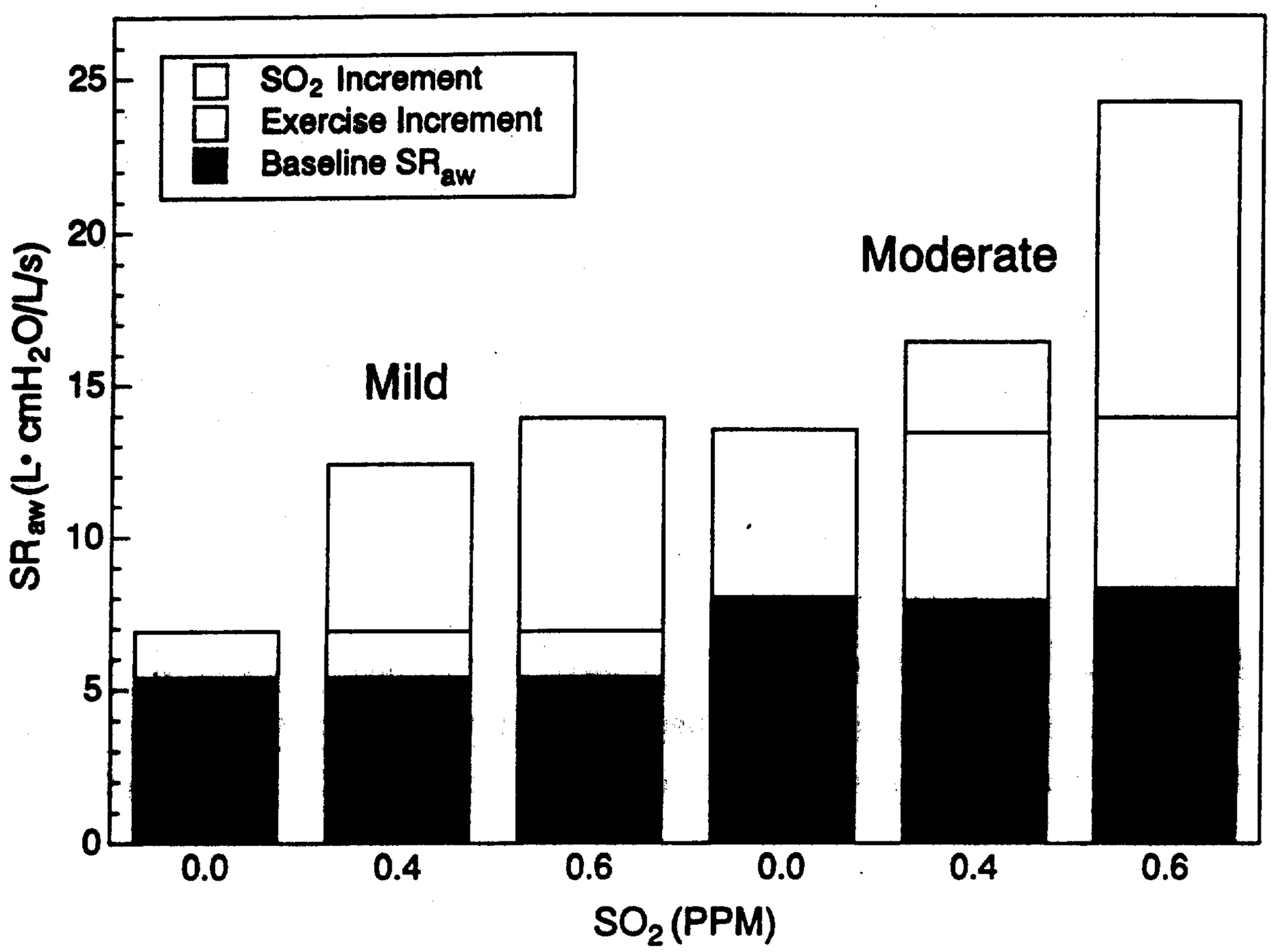

Figure 2. **Redrawn from Linn et al. (1987). SR_{aw} of 16 mild (10 M, 6 F) and 24 moderate (10 M, 14 F) asthmatic subjects exposed to 0.0, 0.4, and 0.6 ppm SO_2. The bottom segment of the bar illustrates the baseline SR_{aw}; the middle segment, the response to exercise; and the upper segment, the increase in SR_{aw} due to SO_2 exposure. Overall bar height indicates SR_{aw} after SO_2 exposure. At 0.6 ppm, after adjustment for SR_{aw} increase due to exercise in 0.0 ppm, the percentage change in SR_{aw} as a result of SO_2 exposure is 124% in mild asthmatic subjects and 128% in moderate asthmatic subjects, expressed as:** $\left[\frac{SO_2 \text{ increment}}{\text{baseline } SR_{aw}} \times 100\%\right]$.

been a persistent change in airway responsiveness. However, it was concluded in the Hackney et al. (1987) report that there were no persistent functional or symptom effects and that SO_2 did not alter airway responsiveness.

Linn and coworkers (1990) examined the effects of different levels of medication in a group of moderate asthmatic individuals dependent on regular medication for normal lung

TABLE 4. ESTIMATES OF SULFUR DIOXIDE RESPONSES IN ASTHMATIC SUBJECTS

	Asthma[a]	L/min[b]	Fraction[c]	$PCSO_2$[d]
Horstman (1986)	Mild	Chamber 40	14/27	0.75
Linn (1987)	Mild/moderate	Chamber 40	15/40	0.60
Magnussen (1990)	Mild/moderate	Mouth 30	16/45	0.50

[a]Asthma is the rating of asthma severity.
[b]L/min is the ventilation and exposure method.
[c]Fraction is the number of subjects with 100% increase.
[d]$PCSO_2$ is the $[SO_2]$ at which SR_{aw} was doubled.

function. These subjects had a similar response to 0.6 ppm SO_2 as observed in moderate asthmatic subjects in a previous study (Linn et al., 1987). The somewhat greater increase in SR_{aw} (approximately fourfold versus approximately threefold) in the more recent study may be due to the slightly higher exercise ventilation rate (about 50 L/min versus 40 L/min). There was a weak correlation of the baseline SR_{aw} with the response to SO_2 ($r = 0.35$) when the subjects from the 1987 and the 1990 studies were combined. Therefore, baseline function may not be a good predictor of response to SO_2. Subjects were exposed to three levels of SO_2 in this study: 0.0, 0.3, and 0.06 ppm. These exposures occurred under three different medication levels: (1) normal; (2) reduced or "low" medication (normal medications withheld for 48 h for antihistamines, 24 h for oral bronchodilators, and 12 h for inhaled bronchodilators), and (3) enhanced medication (an additional dose of metaproterenol [i.e., 0.3 mL of 5% Alupent]). The responses are illustrated in Figure 3 and Table 3. When medication was withheld, baseline lung function deteriorated (e.g., FEV_1 fell about 350 mL). Exercise alone caused slightly less than a 300 mL decrease in FEV_1, and 0.6 ppm SO_2 caused a significant further decline in FEV_1. Although the absolute FEV_1 was lower after SO_2 exposure in the low medication condition, the decrement caused by SO_2 was similar to that seen in the normal medication state.[2] The lower absolute level of FEV_1 in

[2]Based on a previously released project report [Hackney et al., 1988], baseline FEV_1 fell from about 2,270 mL in the normal medication state to about 1,910 mL in the low medication state. The average decrease in FEV_1 resulting from exercise in clean air was similar in the two conditions: −273 and −278 mL in the low and normal states, respectively. The overall decrease in FEV_1 was −582 and −680 mL, respectively, in the two conditions, leaving an SO_2 effect (total FEV_1 decrease − exercise in clean air effect) of −309 and −402 mL, respectively.

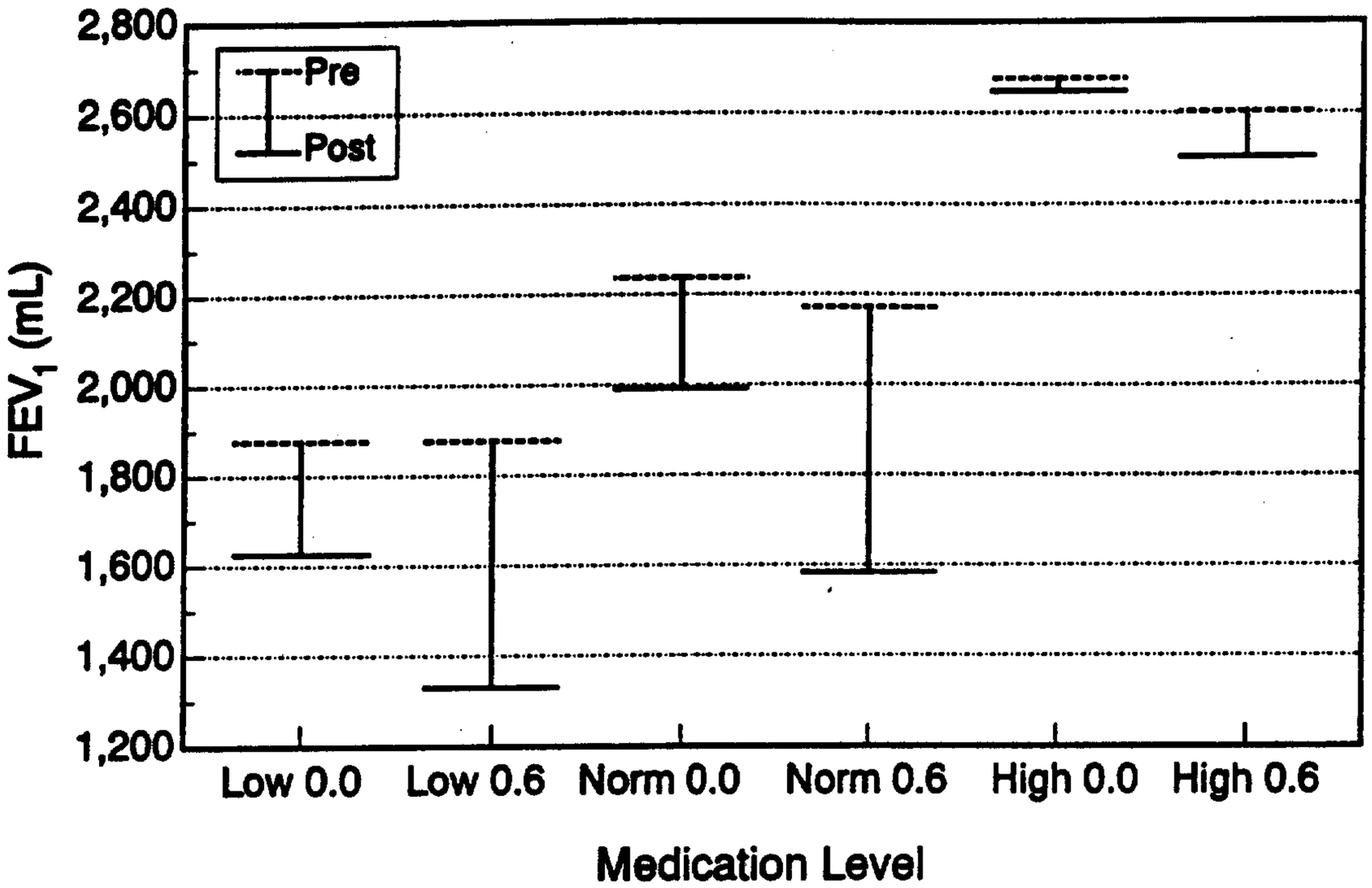

Figure 3. Redrawn from Linn et al. (1990). FEV_1 responses to SO_2 (0.6 ppm) exposure in medication-dependent asthmatic subjects. Horizontal dashed lines represent preexposure FEV_1 and horizontal solid lines are postexposure. The vertical bar indicates change with exercise or exercise plus SO_2 exposure. Three medication states were used: Low = withdrawal of all medication for at least 12 h; normal = typical medication level (mostly theophylline and inhaled beta-agonist but no steroids); high = supplemental metaproterenol before exposure. Exposures lasted 10 min. Standard error of the mean change in FEV_1 due to exposure to SO_2 and exercise was about 100 mL for the SO_2 exposures.

the unmedicated subjects would be cause for additional concern. However, with supplementary metaproterenol, the effect of SO_2 was greatly diminished (about 5% lower postexercise FEV_1 for the 0.6-ppm SO_2 exposure versus air-only exposure under supplementary [high] metaproterenol conditions). In comparison to the normal medication baseline, moderate/severe asthmatic subjects who withheld medication had an overall

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As a percentage of the preexposure resting measurement, these reflect a decrease of 16.1 and 17.8.%, respectively, that can be attributed to SO_2. If expressed as a percentage of the response after exercise in clean air, these percentages would be −18.9 and −20.2, respectively.

reduction of FEV_1 of about 40% from the combined effects of exercise, SO_2 exposure (0.6 ppm), and the absence of their normal medication.

In comparing asthmatic individuals of different degrees of severity, the metric used in this comparison can greatly influence the conclusion that is drawn. It is not clear whether the most appropriate metric is (a) the absolute change in airway resistance or FEV_1 or (b) the relative change. Small absolute increases around a low baseline SR_{aw} (usually in a well controlled or milder asthmatic) result in large relative (i.e., percentage) changes in function, whereas a much larger absolute change in function around a higher baseline may result in a smaller relative change in function. The SR_{aw} data are particularly subject to this sort of potential bias because of the larger range of baseline values, which may vary from 2 to 8 cm $H_2O \cdot L^{-1} \cdot s^{-1} \cdot L$ in healthy people or mild asymptomatic asthmatic subjects.

The manner in which a percentage change is calculated can greatly influence the apparent response. For example, the data of Linn et al. (1990) (see Table 3) for normally medicated subjects gives a percent change in FEV_1 with clean air exposure of −12.2% and for 0.6 ppm SO_2 of −30.0% (calculated as [post-pre] ÷ pre × 100%). If the response after SO_2 exposure is corrected for the effect of exercise in clean air ({2,264 − [1,584 + (2,270 − 1,992)] ÷ 2,264} × 100%), the "SO_2" effect is −17.8% (the same as the difference between −30% and −12.2%). However, it could be argued that the SO_2 effect is that additional change beyond the response in clean air and should be expressed relative to post-clean air response. In this case, the result is ({2,264 − [1,584 + (2,270 − 1,992)] ÷ 1,992} × 100%) or −20.2%. Corresponding calculations made for SR_{aw} responses give pre- to post-increases of +77 and +249% for clean air and SO_2, respectively. Correcting for the clean air response gives an SO_2 response, as above, of +172%. The SR_{aw} response, if expressed relative to the post-clean air exercise response ({27.6 − [7.9 + (14.0 − 7.9)] ÷ 14.0} × 100%) is +97%. Thus expressing the SO_2 response relative to the post-clean air exercise response results in an apparently larger relative FEV_1 response and smaller relative SR_{aw} response. In all cases cited in the main text of this document, the changes in FEV_1 and SR_{aw}, when expressed as percentages, are expressed relative to the baseline value, not the post-exercise value.

Another approach to estimating responses would have been to express them in percent predicted (e.g., FEV_1). The advantage of such an approach would be that the functional

level would be on a more "absolute" scale in terms of functional capacity, and thus would be more relevant to the level of pulmonary disability than is a percent change from baseline. The disadvantage is that the information necessary to determine the predicted level is not always available. When the predicted levels are provided directly, additional variability is introduced because there are a number of acceptable standards for prediction which vary slightly from each other.

Magnussen et al. (1990) also studied the responses of 45 asthmatic individuals (46 subjects are included in the list but data for only 45 are given) to 0.5 ppm SO_2 with 10 min of resting breathing followed by 10 min of eucapnic hyperpnea. Although this mode of exposure has previously been shown to overestimate responses that would occur in natural (oronasal breathing) exposure, it is interesting to note that the group mean response was an increase of SR_{aw} from 6.93 to 18.21 cm $H_2O \cdot L^{-1} \cdot s^{-1} \cdot L$ (also referred to as SR_{aw} "units"). After correcting for the increase in SR_{aw} due to hyperventilation, ($\approx$45%; from 6.27 to 9.10), the increase in SR_{aw} (8.65) as a percentage of the mean baseline (6.60) is 131%. However, only 16 of the 45 subjects experienced at least a doubling of SR_{aw}, indicating that the large mean change is driven by much larger changes in a small group of subjects. Based on the cumulative frequency distribution of $PC_{100}SR_{aw}$ versus SO_2 concentration of Hortsman et al. (1986), approximately 25% of the subjects would be expected to have a doubling of their SR_{aw} at an SO_2 concentration of 0.50 ppm. The somewhat larger fraction (36%) in this group of subjects (see Table 4) may be due to the fact that SO_2 was inhaled via a mouthpiece, which is known to increase SO_2 responses. Also 16 subjects were on inhaled or oral steroid medication (only 6 of the 16 who doubled SR_{aw} used steroids). These subjects would likely be considered to have more severe asthma than those studied by either Linn et al. (1987) or Horstman et al. (1986).

Magnussen et al. (1990) also found only a weak correlation ($r = 0.47$; $R^2 = 0.22$) between histamine response and SO_2 response to changes in SR_{aw}. They concluded that nonspecific bronchial responsiveness (NSBR) to histamine is a poor predictor of response to SO_2. A number of investigators (Roger et al., 1985; Linn et al., 1983b; Witek and Schachter, 1985) have reported a weak correlation between histamine or methacholine responsiveness and functional responses to SO_2. In these studies, it has generally been

concluded that histamine or methacholine response is not a good predictor of responsiveness to SO_2 among asthmatic subjects.

4.3 RANGE OF SEVERITY OF SULFUR DIOXIDE RESPONSES

In order to place the changes in FEV_1 and SR_{aw} that result from SO_2 exposure into broader perspective, responses to exercise and/or cold air breathing were compared under a variety of conditions. The extent of exercise-induced bronchoconstriction is in part dependant upon the intensity of the exercise (Table 5). As seen in this review and the Second Addendum (U.S. Environmental Protection Agency, 1986), mild exercise alone under normal indoor conditions results in small, if any change in FEV_1 or SR_{aw}. For example, after 10 min exercise at 40 L/min ($\approx$35% max), SR_{aw} increased 29% and FEV_1 decreased by only 1.8% in one study (Linn et al., 1987); and, after 5 min exercise at a similar level, SR_{aw} increased 67% in another study (Horstman et al., 1988). These are modest changes, typically not accompanied by symptoms. NIH guidelines (1991) suggest that a decline of 15% in FEV_1 indicates the presence of exercise-induced bronchoconstriction. At higher exercise intensities (60 to 85% of maximum), FEV_1 decreases range from 10 to 30% (Anderson and Schoeffel, 1982; Anderson et al., 1982; Fitch and Morton, 1971; Strauss et al., 1977). With the combination of exercise and inhalation of dry subfreezing air, the decrease in FEV_1 may reach 35 to 40% (Strauss et al., 1977; Smith et al., 1989). Inhalation of warm humid air during exercise markedly reduces or eliminates exercise-induced decreases in FEV_1 (Anderson et al., 1982) or increases in SR_{aw} (Linn et al., 1984, 1985). Balmes et al. (1987) stated that the responses to 5-min exposures to 1 ppm SO_2 were qualitatively similar, in terms of symptoms and function changes, to "maximal acute bronchoconstrictor responses" from other nonimmunologic stimuli (i.e., cold/dry air, hypertonic saline, histamine, or methacholine). This opinion is based on the responses of a small number of subjects who had striking responses to SO_2. This study was not designed to evaluate maximal responses.

The magnitude of functional responses of asthmatics to a variety of physical, chemical, biological, and environmental stimuli varies widely. Mild exercise in mild asthmatics may produce modest changes in pulmonary function (<10% decrease in FEV_1) in the absence of symptoms or breathing difficulty. On the other hand, functional responses of patients

TABLE 5. COMPARATIVE RESPONSES OF ASTHMATIC SUBJECTS TO COLD/DRY AIR AND EXERCISE: FORCED EXPIRATORY VOLUME IN ONE SECOND (FEV_1) AND SPECIFIC AIRWAY RESISTANCE (SR_{aw})

Author	Conditions	Response
<u>Moderate exercise typical of chamber studies</u>		
Linn et al. (1985)	Exercise 5 min at $\dot{V}_E$ = 50 L/min (a) 21 °C, dry (b) 38 °C, humid	(a) SR_{aw} +21% (b) SR_{aw} −4%
Linn et al. (1984b)	Exercise 5 min at $\dot{V}_E$ = 50 L/min (a) −6 °C (b) 7 °C (c) 21 °C, humid	(a) SR_{aw} +94% (b) SR_{aw} +59% (c) SR_{aw} +28%
Bethel et al. (1984)	Eucapnic hyperpnea $\dot{V}_E$ = 30-50 L/min for 3 min (a) ambient humid (b) cold/dry	(a) SR_{aw} +3% (b) SR_{aw} +18%
Linn et al. (1987)	10 min at 40 L/min	(a) SR_{aw} +29% (b) FEV_1 −1.8%
Horstman et al. (1988)	5 min ≈ 40 L/min (mean of two trials) Mild asthmatics	SR_{aw} +67%
<u>Maximum exercise-induced bronchoconstrictor challenge*</u>		
Anderson and Schoeffel (1982)	60-85% $\dot{V}O_2$ peak (predicted) for 6-8 min (exercise)	20-25% decline in FEV_1
Anderson et al. (1982)	70% predicted max. exercise 6-8 min: (a) 23 °C (b) 31 °C, humid	(a) FEV_1 −35% ±13% (b) FEV_1 −10% ±9%
Fitch and Morton (1971)	Exercise 80-85% max.	FEV_1 −28 to −31%
Strauss et al. (1977)	≈75% predicted max exercise 900 kpm 3-5 min $\dot{V}_E$ ≈ 90 L/min (a) ambient (b) sub-freezing air	(a) FEV_1 −20% (b) FEV_1 −40%
Smith et al. (1989)	75% max exercise 5-10 min $\dot{V}_E$ ≈ 42 L/min −5 °C air, dry Children and adolescents (median age 14 years)	FEV_1 −20 to −25%

*NIH guidelines suggest a decrease of ≥15% in FEV_1 as a diagnostic criteria for exercise-induced asthma.

seeking emergency treatment for asthma are striking (Lim et al., 1989; Fanta et al., 1982; Hilman et al., 1986). The average FEV_1 in a group of 16 subjects treated in a hospital emergency room was 41±9% predicted. In another study of subjects with acute severe asthma, the average FEV_1 when first measured was 21±5% predicted. Fanta et al. (1982) reported a mean FEV_1 of 38% predicted for a group of 102 asthmatic patients treated in a hospital emergency room. Although none of these groups constituted a clearly representative population sample, they do illustrate the severity of functional responses (i.e., FEV_1 decrements of −60 to −80% of predicted) observed in asthmatic patients seeking emergency medical treatment.

One diagnostic procedure used in evaluation of asthma is measurement of airway responsiveness. Airway inhalation challenges to histamine or methacholine are typically used to determine the inhaled dose of these drugs which causes a 20% decline in FEV_1 (Cropp et al., 1980; Chatham et al., 1982; Chai et al., 1975). Responses are rapidly induced (within 1 to 2 min), recovery is typically complete within an hour or so, and there are no sequelae. Asthmatics are much more responsive to these nonspecific (i.e., non-allergenic) stimuli; the concentration required to evoke a response is typically 1/10 to 1/100 that required in a healthy non-asthmatic person. The responses to histamine, methacholine, and cold dry air are well correlated in asthmatics (Cockcroft et al., 1977; O'Byrne et al., 1982). Airway responses to these non-specific stimuli can vary widely over time (i.e., many months). Significant circadian or daily variations also occur. Other factors which can alter airway responsiveness include occupational exposures to chemicals such as toluene diisocyanate or plicatic acid, exposure to allergens such as ragweed or dust mites, or viral respiratory tract infections (Clough and Holgate, 1989). In contrast to non-specific stimuli, airway challenge with specific allergens to which the patient is sensitized cause both an acute response, and in many cases, a delayed or "late phase" response. The acute response is somewhat slower to develop (10 to 20 min) and slower to resolve (1 to 2 h) than for the non-specific stimuli. A late phase response, which occurs in 30 to 50% of allergic asthmatics, can be of even greater magnitude than the acute response and resolves with a variable and often prolonged time course (Cockcroft, 1987).

In terms of its behavior as an airway stimulant, SO_2 acts similarly to other non-specific stimuli. It induces a response within a few minutes and the response resolves spontaneously

within an hour or so. There is no reported late phase response to SO_2, and SO_2 exposure does not induce a change in non-specific bronchial responsiveness. Because of the rapid onset and recovery, the responses to non-specific stimuli are thought to be due to constriction of airway smooth muscle. Unlike histamine and methacholine inhalation challenges which are not followed by a refractory period (Beckett et al., 1992), there is a refractory period after SO_2-induced bronchoconstriction. Similarly, exercise or hyperventilation (cold air) challenges are followed by a refractory period (Bar-Yishay et al., 1983; Haas et al., 1986).

A 20% reduction in FEV_1 is typically associated with symptomatic complaints of chest tightness and/or wheeze as well as other complaints associated with dyspnea. Killian et al. (1993) showed that there is a wide range of perception of dyspnea after a 20% decrease in FEV_1, rated from 0 to 9 on a 10 point scale. Breathing difficulty at this level of FEV_1 reduction corresponded to that at about 60 to 70% of maximum exercise level. Furthermore, perception of dyspnea is not a good index of functional status. Some patients with near-fatal asthma attacks had a poor perception of their breathing difficulty and were thus unable to perceive an attack of severe bronchospasm (Kikuchi et al., 1994).

4.3.1 Severity of Sulfur Dioxide Respiratory Function Responses

As with all biological responses, there is a range of response to SO_2 in asthmatic individuals irrespective of the other factors that influence response magnitude such as concentration, duration, ventilation, exercise, air temperature, air dryness, etc. Some subjects experienced small or minimal functional responses to SO_2 exposure especially at relatively low SO_2 concentrations. Four studies presented sufficient published individual data to estimate the range of responses in terms of post exposure SR_{aw} in the most responsive quartile of subjects. The most responsive subjects (3 of 12) in Horstman et al. (1988) exposed for 5 min to 1.0 ppm had SR_{aw}'s ranging from 55 to 71 $cmH_2O \cdot s$. In the Linn et al. (1988) study, the most responsive subjects (5 of 20) had SRaw's ranging from +18 to +122 cm $H_2O \cdot s$, when exposed in the untreated condition to 0.6 ppm SO_2 for 10 min. In the Linn et al. (1990) study (10 min at 0.6 ppm), the most responsive subjects (5 of 21) on normal medication had a range of response from 46 to 76 $cmH_2O \cdot s$ representing an increase of 420 to 1,090%. When normal medication was withheld, this range increased to 66 to 95 $cmH_2O \cdot s$. In the Linn et al. (1987) study of mild and moderate asthmatic subjects

(0.6 ppm for 10 min), the range of response for the most responsive quartile (10 of 40) was 21 to 118 $cmH_2O \cdot s$. This represents an increase of SR_{aw} ranging from 390 to 1,600%.

Additional, more detailed information is presented in Appendix B (Table B-1) with regard to the range of severity of respiratory function changes observed among asthmatic subjects exposed to SO_2 in selected recent controlled exposure studies, i.e., those by Roger et al. (1985) and Linn et al. (1987, 1988, 1990). Of most interest are Table B-1 entries concerning: (1) average magnitudes of pulmonary function changes (SR_{aw}; FEV_1) measured at different tested SO_2 exposure concentrations under moderate exercise conditions, and (2) percentages of asthmatic subjects exceeding cutpoints for defining ranges of effects of increasing severity (magnitude) and potential medical concern as a function of SO_2 exposure levels.

The data presented in Table B-1 indicate that the average magnitudes of responses (FEV_1 decreases; SR_{aw} increases) due to SO_2 at 0.4 and 0.5 ppm are not distinguishable, for either mild or moderate asthmatic subjects, from the range of normal variation often experienced by asthmatic persons during a given day, i.e., up to 10 to 20% lower FEV_1 in early morning versus the afternoor and up to 40% higher SR_{aw} (see discussion on page 4). Nor are the average changes due to SO_2 at 0.4 or 0.5 ppm particularly distinguishable from the range of analogous average pulmonary function changes observed among asthmatic persons in response to cold/dry air or moderate exercise levels (see Table 5). Even taking the combined effects of exercise and SO_2 exposure at 0.4 and 0.5 ppm, the average total lung function changes generally do not reach magnitudes identified as being of much medical concern. Similarly, at 0.4 and 0.5 ppm, only relatively small percentages (generally $\leq$10 to 25%) of tested subjects exhibited marked responses to SO_2 (after correction for exercise) that both (a) very markedly exceeded typical daily variations for lung function measures for asthmatic persons or functional changes displayed by them in response to cold/dry air or moderate exercise levels and (b) reached magnitudes falling in a range of likely clinical concern (i.e., SR_{aw} increases $\geq$200% and $FEV_{1.0}$ decreases $\geq$20%). However, as discussed in U.S. EPA (1986), it should be noted that Bethel et al. (1984) reported a significant interaction between oral hyperventilation of cold dry air and 0.5 ppm SO_2 via mouthpiece that resulted in a $>$200% increase in SR_{aw}, whereas breathing SO_2 in warm humid air or breathing cold dry air alone resulted in a $<$40% change in SR_{aw}. This

suggests that airway cooling and drying may exacerbate SO_2-induced airway constriction in hyperventilating asthmatic subjects, but insufficient data exist by which to estimate the magnitude of any combined effects of joint SO_2 and cold, dry air exposure under more natural free-breathing conditions during exercise.

In contrast to the patterns seen at 0.4 and 0.5 ppm, distinctly larger average lung function changes were observed at SO_2 exposures of 0.6 ppm and higher. Of particular importance is that the average total changes due to combined effects of exercise and SO_2 are at the upper end of or exceed (a) the range of typical daily variations in FEV_1, and SR_{aw} and (b) average magnitudes of changes seen in such measures in response to cold/dry air and moderate exercise levels. Also, at 0.6 ppm or higher SO_2 concentrations, substantially higher percentages of tested subjects exhibited lung function changes due to SO_2 that approach or reach levels of medical concern. For example, in response to 0.6 or 1.0 ppm SO_2 exposure under moderate (40 to 50 L/min) exercise conditions, 25 to 55% of both mild and moderate asthmatic subjects exhibited FEV decrements in excess of −20% and SR_{aw} increases that exceeded 200% after correction for exercise. Changes of this magnitude clearly exceed the maximum 20% FEV_1 and 40% SR_{aw} variations often experienced by asthmatic subjects during a given day. Similarly, approximately 15 to 35% of moderate asthmatics exposed at 0.6 or 1.0 ppm SO_2 experienced FEV_1 decrements in excess of −30% and SR_{aw} increases above 300% due to SO_2, after correction for exercise. Respiratory function changes of such magnitude in response to SO_2 clearly fall into a range of medical concern, especially if accompanied by increased respiratory symptoms (e.g., wheezing, chest tightness, shortness of breath, etc.) rated as more severe than due to exercise alone.

4.3.2 Severity of Respiratory Symptom Responses to Sulfur Dioxide

The symptoms associated with responses to SO_2 are typical of those experienced by asthmatic individuals when bronchoconstriction occurs in response to any one of a number of nonimmunologic provocative stimuli. Unfortunately, in most published reports, the quantitative or qualitative description of symptoms is often insufficient for the purpose of comparison between studies. Linn et al. (1987) presented a total score for the sum of 12 symptoms in subjects exposed to 0.2 to 0.6 ppm SO_2. Symptoms were higher in the moderate than in the mild asthmatic subjects, as would be anticipated. In addition, there was

a trend for symptoms to increase with increasing SO_2 concentration. About 25% of asthmatic subjects rated their lower respiratory symptoms (wheeze, dyspnea, etc.) 20 points higher (on a 40 point scale) after exposure to 0.6 ppm SO_2. A 20-point increase represents a change of a previously "mild" symptom to "severe" or the new appearance of "moderate" symptom. Four of 24 moderate/severe asthmatic subjects required a reduced exercise level because of asthma symptoms at 0.6 ppm SO_2. This happened only once at each of the other (lower) concentrations. Analogous findings of distinctly higher and more serious symptomatic response at 0.6 ppm SO_2 than at lower concentrations (0.2 or 0.4 ppm) were reported by Freudenthal et al. (1989), based on comparisons of respiratory symptoms and lung function changes of varying magnitudes derived from detailed evaluation of raw data (N = 23) from an earlier Linn et al. (1983) study. Freudenthal et al. (1989) grouped absent, minimal, and mild symptom levels (as designated by Linn et al.) into an "insignificant" category, and defined two symptomatic response categories as follows: (1) annoying (going from a pre-exposure symptom level of "insignificant" to a post-exposure symptom level of "moderate" or "severe"); and (2) performance-limiting (going from a pre-exposure symptom level of "insignificant" or "moderate" to post-exposure level of "severe"). The subjective symptom responses were labeled according to the symptom score descriptions given by Linn et al. (1983). Distinctly higher numbers of subjects reported annoying symptoms at 0.6 ppm SO_2 during exercise ($\approx$50 L/min) than at 0.2 or 0.4 ppm SO_2 exposure (none at 0.2 ppm) regardless of the associated level (25%, 100%, 200%) of SR_{aw} increase in response to SO_2. Even more indicative of 0.6 ppm SO_2 being a concentration of likely concern was the fact that none of the subjects reported performance-limiting symptoms at 0.2 or 0.4 ppm SO_2 (regardless of associated level of SR_{aw} increase), whereas at least one subject reported performance-limiting symptoms in association with SO_2-induced SR_{aw} increases of 25, 100, and 200%, respectively.

Horstman et al. (1988) presented data for two individual symptom categories, wheezing and shortness of breath-chest discomfort for subjects exposed to 1.0 ppm SO_2 for 2 and 5 min. Wheezing was strongly associated with an increase in SR_{aw} ($r > 0.80$) and the severity of wheezing increased with increased duration of exposure. The four most responsive subjects (n = 12) rated their wheezing at either three or four on a four-point scale (severe or intolerable wheezing was rated as four). Balmes et al. (1987) indicated all

but one of their eight subjects developed wheezing, chest tightness, and dyspnea after 3 min at 1.0 ppm SO_2 that was of sufficient magnitude in two subjects that they were unwilling to undergo a subsequent 5-min exposure.

In addition to the above published information, more detailed analyses by U.S. EPA staff of data from recent studies of SO_2 effects in asthmatic individuals presented in Appendix B (Smith 1994 memo) also show that substantially greater percentages of moderate and mild asthmatics experienced moderate to severe respiratory symptoms at 0.6 or 1.0 ppm SO_2 exposure during moderate (40 to 50 L/min) exercise than occurred in response to comparable exercise alone. Similarly, much greater percentages of asthmatic subjects experienced combinations of large lung function changes and severe symptoms in response to SO_2 exposures than with exercise alone. In addition, up to 15% of mild or moderate asthmatic subjects required reduced workload or termination of exposure at 0.6 ppm or 1.0 ppm SO_2, whereas none exhibited diminished exercise tolerance with comparable exercise alone.

4.4 MODIFICATION OF SULFUR DIOXIDE RESPONSE BY ASTHMA MEDICATIONS

It was shown in the Second Addendum (U.S. EPA, 1986), and has been substantiated more recently, that common asthma medications such as cromolyn sodium and various $beta_2$ adrenergic receptor agonists either reduce or abolish SO_2-induced lung function responses in asthmatic subjects. Since completion of that earlier Addendum, a number of medications have been evaluated in various newly available studies for their efficacy in altering responses to SO_2 exposure, as summarized in Table 6. Some of these medications are routinely used to treat asthma such as inhaled $beta_2$-agonists (metaproterenol and albuterol), oral theophylline, and inhaled steroids such as beclomethasone. Inhaled bronchodilator medications such as metaproterenol and albuterol are the most widely used asthma medications (Kesten et al., 1993). Information on the effects of some other less widely used medications (e.g., ipratropium bromide, antihistamines, cromolyn sodium) are of interest from the point of view that they may provide insight into mechanisms of response to SO_2.

TABLE 6. SUMMARY OF RESULTS FROM CONTROLLED HUMAN EXPOSURE STUDIES OF EFFECTS OF MEDICATIONS ON PULMONARY FUNCTION EFFECTS ASSOCIATED WITH EXPOSURE OF ASTHMATIC SUBJECTS TO SULFUR DIOXIDE

Concentration	Duration	Number of Subjects	Exposure Mode	Exposure Status	Observations	Comments	References
0.0, 0.3, 0.6 ppm	10 min	20 adult mild asthmatic subjects	Chamber 23 °C 85% RH	Exercising $\dot{V}_E \approx 50$ L/min Three pretreatment conditions: drug (metaproterenal); placebo (saline); no pretreatment	With no pretreatment, typical exercise-induced bronchospasm occurred at 0.0 ppm; slightly increased at 0.3 ppm; markedly increased at 0.6 ppm. Similar effects were seen with placebo. Drug pretreatment improved lung function, prevented bronchoconstrictive effect at 0.0 and 0.3 ppm, and greatly mitigated responses at 0.6 ppm SO_2.	Nine of 20 subjects from the no-treatment or placebo group exposed to either 0.3 or 0.6 ppm SO_2 needed medication to treat symptoms following exposure.	Linn et al. (1988)
0.0, 0.3, 0.6 ppm	10 min	21	Chamber 21 °C 50% RH	Exercise $\dot{V}_E \approx 50$ L/min Three medication states: reduced (medication withheld); normal (usual medication schedule); enhanced (usual medication supplemented by inhaled metaproterenal before each exposure)	With normal medication, typical bronchoconstriction occurred with exercise and exacerbated by 0.6 ppm SO_2. With low medication both baseline and postexposure lung function noticeably worse (FEV_1 fell from 2,350 to 1,900 mL; exercise alone decreased FEV_1 by 300 mL and 0.6 ppm SO_2 decreased further) but decrement caused by SO_2 similar to low medication state. With supplementary metaproterenal, SO_2 effect greatly diminished ($\approx$5% decrease in FEV_1). Moderate/severe asthmatic subjects with medication withheld had decrease of 40% from combined effects of exercise, SO_2 (0.6 ppm) and absence of normal medication.	High medication appeared to improve baseline lung function and prevented most bronchoconstrictive effects of SO_2 and exercise.	Linn et al. (1990)
0, 0.5, 1.0 ppm	30 min	9	Oral mouthpiece 22 °C 75% RH	20 min rest followed by 10 min light-moderate exercise $\dot{V}_E \approx 26$ L/min Two medication states: placebo; ipratropium bromide (IB) (60 μg aerosol)	Significant dose-response effect of 1.0 ppm SO_2 on FEV_1, SR_T, $\dot{V}_{max50}$, $\dot{V}_{max75}$. IB resulted in improvements in all baseline measures of pulmonary function, but did not alter the proportionate change in pulmonary function caused by SO_2.	Conclude that IB causes significant bronchodilation but does not completely protect nonallergic asthmatic subjects from the effect of SO_2 inhalation.	McManus et al. (1989)
0.75 ppm	Minutes until SR_{aw} increased 75% above baseline	25	Oral mouthpiece 24 °C 50% RH	Isocapic hyperventilation (started at 15 L/min; then increased in 3 min. steps by 15 L/min). Two medication states: beclomethasone; salbutamol	Regular treatment with salbutamol alone or in combination with beclomethasone did not change responses to hyperventilation with air or SO_2. Medication withheld for at least 6 h prior to challenge.	Absence of salbutamol effect is in contrast to other studies. Peak response to salbutamol occurs in 2-3 h, although some effect may persist for up to 8 h.	Wiebicke et al. (1990)

TABLE 6 (cont'd). SUMMARY OF RESULTS FROM CONTROLLED HUMAN EXPOSURE STUDIES OF EFFECTS OF MEDICATIONS ON PULMONARY FUNCTION EFFECTS ASSOCIATED WITH EXPOSURE OF ASTHMATIC SUBJECTS TO SULFUR DIOXIDE

Concentration	Duration	Number of Subjects	Exposure Mode	Exposure Status	Observations	Comments	References
0.75 ppm	10 min	10	Oral mouthpiece 22 °C 75% RH	Exercise $\dot{V}_E$ = 34 L/min Two medication states: placebo; albuterol (180 μg aerosol). Each subject exposed to four different exposures (albuterol, air; placebo, air; albuterol, SO_2; placebo, SO_2).	After SO_2, FEV_1 decreased 14% and R_T increased 50% with placebo; albuterol eliminated drop in FEV_1 and increase in R_T caused by SO_2.	Suggests involvement of adrenergic nervous system or mast cell degranulation in SO_2-induced bronchoconstriction.	Koenig et al. (1987)
1.0 ppm	10 min	8	Oral mouthpiece 22 °C 75% RH	Treadmill exercise $\dot{V}_E$ = 35 L/min Medicated with cromolyn sodium (CS) 0, 20, 40, or 60 mg by turbinhaler.	20 mg CS had no effect on SO_2 response; 40 mg CS significantly inhibited response; 60 mg completely inhibited response.	Cromolyn sodium reduced bronchorestrictor response to SO_2 in a dose-dependent manner.	Koenig et al. (1988a)
1.0 ppm	10 min	13 Allergic adolescents 12-19 years	Oral mouthpiece 22 °C 75% RH	Treadmill exercise $\dot{V}_E$ = 33.9 L/min Three conditions; placebo, 4 mg or 12 mg chlorpheniramine maleate (CM).	In allergic adolescents (never used inhaler or hospitalized) positive for exercise-induced bronchoconstriction, FEV_1 decreased 11, 12.6, and 12.3% under placebo, 4 mg CM, and 12 mg CM conditions, respectively, from pre- to post SO_2 exposure. No differences between conditions for respiratory symptoms 0-, 6-, or 24-h post SO_2.	No effect of an oral antihistamine on airway response to SO_2 exposure. SO_2 did increase nasal work of breathing that was blocked by antihistamine.	Koenig et al. (1988b)
1.0 ppm	10 min	12 moderate asthmatic subjects 12-39 years	Oral mouthpiece 22 °C 75% RH	Exercise $\dot{V}_E$ = 31.6 L/min (AM) $\dot{V}_E$ = 30.6 L/min (PM) Four conditions AM: Air or SO_2 3-4 h post theophylline. PM: Air or SO_2 8-10 h post theophylline.	No differences in FEV_1 response to SO_2 between morning (AM) or afternoon (PM) exposures. Change in FEV_1 (about −14%) was similar to other studies where placebo evaluated under similar conditions.	Authors concluded no protective effect of chronic theophylline use on response to SO_2.	Koenig et al. (1989)
1.0 ppm	10 min	8	Oral mouthpiece 22 °C 65% RH	Light exercise $\dot{V}_E$ = 13-31 L/min Two medication states: placebo; theophylline (400 mg) daily for 1 week.	After SO_2 FEV_1 dropped 16% with placebo and 7% with theophylline, R_T increased 37% with placebo and 7% with theophylline.	Conclude that sustained release theophylline tablets taken for 1 week mitigate SO_2-induced bronchoconstriction.	Koenig et al. (1992)

Theophylline. Koenig et al. (1992) examined the effect of theophylline, an airway smooth muscle relaxant, on SO_2 induced bronchoconstriction in a group of eight allergic mild asthmatic subjects. There was a trend for the FEV_1 response to be smaller when the subjects took theophylline, but because of the small sample size and the variability of the responses, the trend did not reach statistical significance. However, total respiratory resistance was significantly less in the theophylline than in the placebo group after SO_2 exposure. The mean decrease in FEV_1 in the placebo group (medication withheld for 1 week) was approximately 0.5 L or about 16% and, in the theophylline group, was about 7%. Linn et al. (1990) noted that subjects normally medicated with theophylline had similar responses to SO_2 whether they had high or low blood levels of theophylline. This suggests that, with typical medication levels, theophylline did not afford much protection from the effects of SO_2.

Koenig et al. (1989) examined the effects of 1 ppm SO_2 on a group of 12 moderate asthmatic individuals who were on chronic theophylline therapy. Subjects were exercised in the morning 3 to 4 h after drug administration and on a different day in the afternoon, 8 to 10 h after drug, with no inhaler use within 4 h of exposure. Mean theophylline levels were similar in the morning and the afternoon. There were no differences in FEV_1 response to SO_2 between morning and afternoon exposures. The change in FEV_1, about -14%, was similar to other studies where a placebo was evaluated under the same conditions. There was no correlation between theophylline levels in the blood and FEV_1 decrements in response to SO_2 exposure. The authors concluded that there was no protective effect of chronic theophylline use on response to SO_2.

Ipratropium Bromide. McManus et al. (1989) examined the effects of ipratropium bromide (IB) (a muscarinic receptor [cholinergic] blocking agent) on a group of nonallergic ("intrinsic") asthmatic subjects (age > 55 years). Although IB improved baseline lung function, the fall in FEV_1 after exposure to 0.5 and 1.0 ppm SO_2 was similar to the response with placebo. These subjects experienced an approximate 15% reduction in FEV_1 after 20 min of rest and 10 min of mild exercise ($\dot{V}_E$ = 26 L/min) at 1 ppm SO_2. They experienced about an 8.5% drop in FEV_1 from the resting exposure alone. Typically, resting exposure has not produced appreciable responses, even with mouthpiece exposure

systems, suggesting that these subjects could be more responsive to SO_2 than younger allergic asthmatic subjects studied under similar conditions (Koenig et al., 1983).

Inhaled Steroids. Wiebicke et al. (1990) recently examined the effects of regular treatment over a 5-week period with an inhaled steroid (beclomethasone) and a beta-agonist (salbutamol/albuterol) on nonspecific bronchial responsiveness to histamine, methacholine, hyperventilation, and SO_2. All medications were withheld for at least 6 h prior to any challenge. Salbutamol treatment alone had no effect on responsiveness to standard challenges with histamine or methacholine. The eucapnic hyperpnea challenge involved a progressive increase (steps of 15 L/min) in target ventilation (maintained for 3 min) until the SR_{aw} increased by 75% above baseline. Breathing was performed via a mouthpiece with or without SO_2 added to the airstream. Salbutamol treatment did not change the responses to hyperventilation with air or with 0.75 ppm SO_2. Combined treatment with salbutamol and beclomethasone caused a reduction in baseline SR_{aw} and also reduced airway responsiveness to methacholine, histamine, and hyperpnea with air. However, treatment with salbutamol plus beclomethasone did not cause a significantly decreased response to SO_2, although the SO_2 response did tend to be less. The absence of an effect of salbutamol in this study is in contrast to the significant reduction in SO_2 response with metaproterenol (Linn et al., 1988) and albuterol (i.e., same drug as salbutamol) (Koenig et al., 1987) seen in other studies. The suspension of drug treatment at least 6 h prior to any challenge exceeds the duration ($\approx$2 to 3 h) of the peak therapeutic effect for salbutamol (Gilman et al., 1990). Any persistent effect of salbutamol was apparently insufficient to alter SO_2 responses.

Beta Agonists. Linn et al. (1988) examined effects of metaproterenol on responses of asthmatic subjects to 0.3 and 0.6 ppm SO_2. Pretreatment with metaproterenol (dose administered 5 min prior to pretesting) caused an improvement in baseline lung function (increased FEV_1 and decreased SR_{aw}) and a reduced response to SO_2 exposure in an environmental chamber. The estimated average SR_{aw} SO_2 response, adjusted for exercise-induced bronchospasm (EIB), of no treatment and placebo treatment was a 66 or 166% increase in SR_{aw} at 0.3 and 0.6 ppm, respectively. These percentages were derived by taking the average ΔSR_{aw} reported by Linn et al. (1988) for untreated and placebo groups at 0.0 ([8.8 + 6.1] /2 = 7.45), 0.3 ([12.8 + 9.9] /2 = 11.95), and 0.6 ppm ([17.5 + 17.1] /2 = 17.3) as a percentage of the average baseline (5.94) and then subtracting the 0.0 ppm

from the 0.3 and 0.6 ppm responses (125, 191, and 291%, respectively). Metaproterenol given prior to exposure blocked the responses to SO_2. Symptoms were markedly reduced but not eliminated. Following the 0.6-ppm SO_2 exposure with either the no-treatment or placebo treatment condition, 9 out of 20 subjects needed medication to treat symptoms caused by at least one of the exposures.

Koenig et al. (1987) studied a group of allergic adolescents with exercise-induced bronchospasm but who were not classified as asthmatic (never wheezed except with exercise, never used beta-agonist). These subjects exhibited a 14% decrease, from post-placebo baseline, in FEV_1 after 10 min of moderate exercise (34 L/min) at 0.75 ppm SO_2. Albuterol markedly attenuated the drop in FEV_1 caused by SO_2, although it caused a modest (7%) but significant improvement in baseline FEV_1. These observations in a group of subjects not previously identified as asthmatic suggest that the population at risk may be slightly larger than suggested earlier. However, by the objective criteria presented in this paper, many would classify these subjects as asthmatic.

Cromolyn Sodium. Koenig et al. (1988a) examined the effects of four different dose levels of cromolyn sodium (a nonspecific mast cell degranulation inhibitor) on subjects exposed to 1.0 ppm SO_2 for 10 min with exercise ($\dot{V}_E \approx 35$ L/min). Subjects received either 0, 20, 40, or 60 mg cromolyn 20 min prior to exposure to SO_2. The SO_2 response with the 20-mg dose was not significantly different than the response with the placebo. However, the 40-mg dose caused a partial blockade, and 60 mg almost completely obliterated the response to SO_2. These observations support the previous observations of Myers et al. (1986a) that cromolyn sodium reduced responses to SO_2 in asthmatic individuals in a dose-dependant manner. However, the Koenig et al. (1988) data are more relevant to clinically acceptable doses of cromolyn.

Chlorpheniramine Maleate. Koenig et al. (1988b) evaluated the effect of an oral antihistamine, chlorpheniramine maleate, on SO_2 responses in a group of allergic adolescents with exercise-induced bronchoconstriction (but who had never been treated for or diagnosed with asthma). Subjects were exposed to 1.0 ppm SO_2 via mouthpiece while exercising with a ventilation of about 34 L/min. Medication was taken 12 h prior to exposure and included placebo or 4 or 12 mg chlorpheniramine. The FEV_1 responses were similar under the three conditions, with decrements of -11, -12.6, and -12.3%, respectively. The authors

concluded that this oral antihistamine did not provide any protective effect from SO_2-induced bronchoconstriction in these allergic adolescent subjects. However, changes in nasal function induced by SO_2 were blocked by antihistamine.

In the Second Addendum (U.S. EPA, 1986), medication usage after SO_2 exposure was cited as an adverse outcome that could be quantified, as summarized in Table 7 based on information reported in pertinent published studies. In the more recent studies, medication use following exposure has been carefully noted. After 2- to 5-min exposures to 1.0 ppm SO_2, 7 of 8 subjects in one study (Balmes et al., 1987) and 4 of 12 in another (Horstman et al., 1988) required bronchodilator medication after exposure. Two of the subjects in Balmes et al. (1987) were unable to complete the 5-min exposure in addition to requiring medication. Linn et al. (1988) found that 7 of 20 mild asthmatic subjects exposed to 0.6 ppm SO_2 needed medication to treat their symptoms following exposure, whereas only 2 of 20 did so after 0.3 ppm SO_2 exposure or after exposure to clean air at comparable exercise rates.

TABLE 7. MEDICATION USE AFTER SULFUR DIOXIDE EXPOSURE[a]

Reference	Type of Exposure	Medication After Exercise in Clean Air	Proportion of Subjects Tested Using Medication After SO_2 Exposure (in ppm)
Bethel et al. (1984)	Mouthpiece	-0-	2/7 @ 0.5 ppm + cold
Koenig et al. (1985)	Facemask	-0-	2/10 @ 0.5 ppm
Linn et al. (1984a)	Chamber	-0-	1/24 @ 0.6 ppm
Linn et al. (1984b)	Chamber	-0-	3/24 @ 0.6 ppm
Linn et al. (1988)	Chamber	2/20	2/20 @ 0.3 ppm 7/20 @ 0.6 ppm
Linn et al. (1990)	Chamber	13/21 (low) 3/21 (norm)	6/21 @ 0.3 ppm (low med) 5/21 @ 0.3 ppm (norm med) 12/21 @ 0.6 ppm (low med)[c] 10/21 @ 0.6 ppm (norm med)[c]
Balmes et al. (1987)	Mouthpiece	—	7/8 @ 1.0 ppm
Horstman et al. (1988)[b]	Chamber	—	4/12 @ 1.0 ppm

[a]Medication use indicates that the subject either took their own medication or else requested medication from the investigators conducting the study.
[b]Subjects prescreened as earlier having at least 100% increase in SRaw in response to SO_2 at 1.0 ppm.
[c]Medication use data obtained from Hackney et al. (1988) may not agree with independently provided individual data.

Many asthmatic subjects take medication to relieve the symptoms and functional responses associated with exacerbations of the disease. The most commonly used of these medications (beta agonists) also inhibit responses to SO_2. Thus, there have been suggestions that asthmatic persons may be protected from responses to SO_2 because of medication that they would have used in any case. However, several lines of evidence suggest that this is not likely the case.

Mild asthmatic persons who constitute the majority of asthmatic individuals, use beta agonists on an as needed basis. Even once a week use exceeds the norm for such individuals, as discussed in Section 2.2. Only about 20% of moderate asthmatic persons regularly use inhaled bronchodilators, the most effective medication in minimizing SO_2 responses. Even among moderate asthmatic persons on regular bronchodilator therapy (oral and inhaled), compliance with medication use ranges from 50% to 70%. Thus one third to one half of regularly medicated asthmatics do not take all prescribed medication. National Heart Lung and Blood Institute guidelines indicate that daily bronchodilator use suggests the need for additional therapy. Indeed there is some suggestion that excessive use of beta-agonists leads to a worsening of asthma status (Sears et al., 1990b; van Schuyk et al., 1991). The frequency of use of medication prior to outdoor exercise is unknown. Furthermore there are a substantial number of individuals with EIB who are not aware of the need for or benefits of treatment (Voy, 1984).

4.5 MODIFICATION OF SULFUR DIOXIDE RESPONSIVENESS BY OTHER AIR POLLUTANTS

The effect of prior ozone exposure on response to SO_2 was examined by Koenig et al. (1990) in 13 allergic adolescent asthmatic individuals. A 45-min exposure to 0.12 ppm ozone caused a modest and transient exacerbation (from a 3% decrease to an 8% decrease) of FEV_1 response to 0.1 ppm SO_2. Ozone does produce an increase in nonspecific bronchial responsiveness (NSBR); these observations may reflect a change in NSBR due to ozone or an additive effect of ozone, SO_2, and exercise. The importance of these observations, from a risk assessment point of view, depends upon the prevalence in the ambient environment of the sequential occurrence of elevated levels of ozone followed by SO_2 peaks. However, the possibility that stimuli such as ozone that may cause changes in NSBR and may also alter

responses to SO_2 is important because other non-specific stimuli (e.g., cold air, exercise, etc.) may occur in temporal and spatial proximity to increased levels of SO_2.

The effects of prior NO_2 exposure on SO_2-induced bronchoconstriction has been examined in two other studies (Jörres and Magnussen, 1990; Rubinstein et al., 1990). Jörres and Magnussen (1990) exposed 14 mild to moderate asthmatic subjects to 0.25 ppm NO_2 for 30 min while breathing through a mouthpiece at rest. There were no changes in SR_{aw} as a result of the exposure. After the exposure, airways responsiveness to SO_2 was assessed by eucapnic hyperpnea of 0.75 ppm SO_2 using stepwise increases in ventilation; the initial level was 15 L/min with subsequent increases to 30, 45 L/min, and so forth. After each 3-min period of hyperpnea, SR_{aw} was determined. The ventilation of SO_2 required to produce a 100% increase in SR_{aw} ($PV_{100}SR_{aw}[SO_2]$) was estimated using interpolation of ventilation versus SR_{aw} (dose-response) curves. The $PV_{100}SR_{aw}(SO_2)$ was significantly reduced after NO_2 exposure compared to after filtered air exposure, suggesting that the airways were more responsive to SO_2 as a result of the prior NO_2 exposure. However, this response is not specific to SO_2 as other studies have suggested increased *nonspecific* bronchial responsiveness in subjects exposed to NO_2 (Folinsbee, 1992).

Rubinstein et al. (1990) exposed nine asthmatic subjects to 0.30 ppm NO_2 for 30 min (including 20 min light exercise). There were no significant effects of NO_2 exposure on lung function (single breath nitrogen washout, SR_{aw}, FVC, FEV_1) or respiratory symptoms, although a slight increase in SR_{aw} was observed as a result of exercise. After exercise, an SO_2-bronchoprovocation test was administered, but using a different technique than Jörres and Magnussen (1990). Increasing amounts of SO_2 were administered by successive doubling of the SO_2 concentration (0.25, 0.5, 1.0, 2.0, 4.0 ppm) at a constant, eucapnic hyperpnea of 20 L/min, maintained for 4 min. Specific airway resistance was measured after each step increase in SO_2 concentration. The concentration of SO_2 required to increase SR_{aw} by 8 units ($PD_{8u}SO_2$) was interpolated from a dose-response curve of SO_2 concentration versus SR_{aw}. The $PD_{8u}SO_2$ was 1.25 $\pm$ 0.70 ppm after air exposure and 1.31 $\pm$ 0.75 after NO_2 exposure, indicating no mean change in responsiveness to SO_2. Only one subject showed a tendency toward increased responsiveness to SO_2 after NO_2 exposure.

The contrasting findings in these two studies are somewhat puzzling because the subjects of Rubinstein et al. (1990) were exposed to a higher NO_2 concentration and

exercised during exposure. However, Jörres and Magnussen's subjects appeared to have had slightly more severe asthma and were somewhat older. The modest increase in SR_{aw} induced by exercise in the Rubinstein et al. study may have interfered with the response to SO_2 (i.e., the subjects may have been in a refractory state). Finally, the different method of administering the SO_2 bronchoprovocation test (i.e., increased $\dot{V}_E$ at constant SO_2 versus increasing SO_2 at constant $\dot{V}_E$) may produce a different response, because hyperpnea alone could contribute to the increase in SR_{aw} (Deal et al., 1979; Eschenbacher and Sheppard, 1985). Thus, although similar, the two SO_2 challenges are not necessarily comparable.

5.0 SUMMARY AND CONCLUSIONS

In general, the conclusions reached in the 1986 Second Addendum have been supported by subsequent research. Those conclusions were restated at the beginning of the present supplement, and there is little point in repeating them here. However, the newer studies reviewed in this supplement provide further information useful in drawing conclusions of relevance to developing criteria for a possible short-term ($\leq$1 h) SO_2 NAAQS.

5.1 EXPOSURE DURATION/HISTORY AS SULFUR DIOXIDE RESPONSE DETERMINANTS

Two new studies (Balmes et al., 1987; Horstman et al., 1988) have shown that airways resistance changes resulting from SO_2 exposure can occur with as little as 2 min exposure at SO_2 levels ranging from 0.5 to 1.0 ppm. Significant changes were seen with 2 min exposure at 1.0 ppm and with 3 min exposure at 0.5 ppm. These observations clearly indicate that brief exposures to high concentrations, which may be masked by ambient SO_2 monitoring procedures using averaging times of 1 h or greater, can have detectable health consequences.

Other studies (e.g., Linn et al., 1987; Roger et al., 1985) evaluated the effects of prior exposure to SO_2 on the magnitude of bronchoconstriction responses to subsequent SO_2 exposures. Prior exposure history to SO_2 over the course of several weeks (as opposed to several hours) was found to be largely irrelevant in determining responsiveness to later SO_2 exposures. However, the response to a second exercise period was diminished in comparison to initial bronchoconstriction observed in response to a first exercise period within a 1-h SO_2

exposure, thus further confirming a likely refractory period to SO_2 exposures accompanied by exercise or hyperpnea repeated within a span of a few hours.

5.2 SULFUR DIOXIDE RESPONSES AND ASTHMA SEVERITY

Several new studies have evaluated responses to SO_2 among asthmatic individuals with moderate or severe disease. One new study (McManus et al., 1989) of older (>55 years) "intrinsic" asthmatic individuals suggests that they may experience bronchoconstriction with mouthpiece SO_2 exposure while resting. Another study (Linn et al., 1987), while indicating similar relative responses to SO_2 among mild and moderate asthmatic subjects, demonstrated larger absolute increases in airway resistance among the moderate to severe asthmatic subjects. While current studies are suggestive of greater SO_2 responsiveness among those asthmatic patients with more severe disease, this issue cannot be unequivocally resolved. However, because of the lower baseline function in moderate and severe asthmatic persons, especially those lacking optimal medication, any effect of SO_2 would further reduce their lung function toward levels that may become cause for medical concern.

5.3 RANGE OF SEVERITY OF SULFUR DIOXIDE RESPONSES

Efforts have been made to help characterize the range of severity of respiratory effects exhibited by asthmatic subjects in response to SO_2 exposure, and some of these were discussed in earlier sections of this Supplement. Many of the newly available studies provide substantial additional information that is helpful in delineating the range of severity of SO_2-induced respiratory responses. For example, two additional studies support the concept advanced by Horstman et al. (1986) of the estimation of a median response to SO_2 among asthmatic individuals. Results from the studies by Linn et al. (1987) and Jörres and Magnussen (1990), using relatively large groups of subjects, are consistent with the estimation of Horstman et al. (1986). These data suggest that the average asthmatic individual will experience increased airway resistance (i.e., at least a doubling of baseline resistance) with exposure to 0.75 ppm SO_2 for 10 min while performing moderate exercise. Numerous factors can modify these responses, as noted previously in the Second Addendum (U.S. EPA, 1986), and there is a broad range of response among asthmatic individuals.

In the earlier Second Addendum (U.S. EPA, 1986), a table was presented which defines a continuum of responses of increasing severity and concern in asthmatic subjects. A modification of this table is presented below as Table 8. In Section 4.2 of this supplement, the range of responses among asthmatic subjects exposed to SO_2 was discussed. Although most asthmatic subjects tested in studies reviewed here had only relatively mild responses at low SO_2 concentrations (0.2 to 0.5 ppm), some of the more responsive asthmatic subjects had responses to SO_2 exposures at 0.6 ppm or higher that included SR_{aw} increases exceeding 50 units, FEV_1 decreases (corrected for exercise response) exceeding 20%, the presence of marked wheezing and breathing discomfort, and the need for medication to resolve these symptoms. Such responses, in the most sensitive subjects, which would be considered to be severe or incapacitating according to definitions of increasing severity in Table 8, likely constitute adverse health effects. Also, tables contained in Appendix B materials provide further detailed, quantitative analyses of combinations of respiratory function effects, severity of symptoms and post-SO_2 exposure medication use, by which to estimate percentages of mild or moderate asthmatic subjects that experience SO_2-induced responses that meet Table 8 criteria for moderate, severe or incapacitating respiratory effects. Based on the Appendix B analyses, it is clear that (a) substantial percentages of mild and moderate asthmatic subjects experience combinations of lung function changes and respiratory symptoms at 0.6 or 1.0 ppm SO_2 that meet the criteria in Table 8 for severe or incapacitating effects and (b) the magnitude of the observed SO_2 responses for such individuals clearly exceed the range of daily average variations in lung function or responses to other stimuli (i.e., cold air, exercise) often experienced by them. It is also notable that up to 15% of mild or moderate asthmatics experienced sufficiently severe lung function changes and/or respiratory symptoms at 0.6 or 1.0 ppm SO_2 so as not to be able to continue to maintain moderate exercise workload levels under the SO_2 exposure conditions or to have to terminate SO_2 exposure entirely—in contrast to none requiring reduced workloads in response to comparable exercise alone.

TABLE 8. COMPARATIVE INDICES OF SEVERITY OF RESPIRATORY EFFECTS SYMPTOMS, SPIROMETRY, AND RESISTANCE

	Gradation of Response Severity				
Type of Response	None	Mild	Moderate	Severe	Incapacitating
Change in SR_{aw}	No change	Increase <100%	Increase up to 200% or up to 15 units	Increases more than 200%, or more than 15 units[a]	Increases much greater than 300% or total SR_{aw} exceeds 50 units[a]
Change in spirometry ($FEV_{1.0}$, FVC)	No change	<10%	Decrease of 10 to 20%	Decrease >20%	Decrease much greater than 20% or <50% predicted.
Duration of effect/ treatment needs	NA	Spontaneous recovery <30 min	Spontaneous recovery <1 h	Bronchodilator required to resolve symptoms	Possible emergency treatment required if persistent
Symptoms	No respiratory symptoms	Mild respiratory symptoms, no wheeze or chest tightness	Some wheeze or chest tightness	Obvious wheeze, marked chest tightness, breathing distress	Severe breathing distress

[a]SR_{aw} units are cm $H_2O \cdot L^{-1} \cdot S^{-1} \cdot L$

Source: Modified from Figure 7 on page 4-7 of U.S. EPA (1986).

5.4 MODIFICATION OF SULFUR DIOXIDE RESPONSE BY ASTHMA MEDICATIONS

Asthma medications can reduce or eliminate the airway resistance increase in response to SO_2 exposure. The most effective medications appear to be $beta_2$ sympathomimetic medications, such as albuterol or metaproterenol. Cromolyn sodium, a nonspecific mast cell degranulation inhibitor, given in therapeutic doses will partially or completely prevent bronchoconstriction in response to SO_2 exposure. Other standard asthma medications such as inhaled steroids or methylxanthine medications appear to be less effective. Withdrawal of normal asthma medication causes degradation of baseline lung function but does not necessarily increase the response to SO_2, although this has not been studied extensively. In the two investigations where patients on "normal medication" (mainly theophylline) were exposed to SO_2, there did not appear to be any protective effect (Koenig et al., 1989; Linn et al., 1990). Specifically, the SO_2 responses were similar whether the patients were using medication or not, although baseline function was depressed by the absence of regular medication.

Only anecdotal information on medication use after SO_2 exposures was mainly available from studies earlier reviewed in the Second Addendum (U.S. EPA, 1986). That information indicated that a few of the most sensitive asthmatic individuals exposed at 0.5 or 0.6 ppm SO_2 during moderate exercise required medication after such SO_2 exposure, but not after comparable exercise levels in clean air (see Table 7). Newer studies reviewed in this supplement have more systematically evaluated medication use as a response endpoint of clinical significance. Two of the newer studies Linn et al. (1988, 1990) found no greater proportions of subjects to require medication use after 0.3 ppm SO_2 exposure than after clean air exposure at comparable exercise levels. On the other hand, additional new information presented from recent studies conducted by three different laboratories (Balmes et al., 1987; Horstman et al., 1988; Linn et al., 1988, 1990) indicates that many asthmatic individuals (who either withheld medication prior to SO_2 exposure or did not normally require medication) did need medication due to severity of responses after exposure to SO_2 at 0.6 or 1.0 ppm. However, in some cases, a substantial number of asthmatic subjects also needed medication following clean air exercise exposure as well (Linn et al., 1990); in the study reported by Hackney et al. (1988) and Linn et al. (1990), for example, approximately half of the asthmatic subjects used medication after 0.6-ppm SO_2 exposure, but among those on a reduced (low) medication regime, approximately the same number used medication following the exercise-alone exposure. Overall, the available published findings point toward more substantial percentages of individuals likely requiring medication use after SO_2 exposure $\geq$0.6 ppm than at exposure concentrations of 0.5 ppm or below (as is also indicated by the more detailed Appendix B Smith memo analyses of raw data from the 1988 and 1990 Linn et al. studies).

5.5 MODIFICATION OF SULFUR DIOXIDE RESPONSIVENESS BY OTHER AIR POLLUTANTS

One new study by Koenig et al. (1990) reported that prior exposure to ozone at the current NAAQS level (0.12 ppm, 1 h) causes a transient moderate exacerbation of lung function decrements due to a later exposure to 0.1 ppm SO_2. However, the particular results make it difficult to separate out clearly the degree of nonspecific bronchial responsiveness due to O_3 alone or to combined effects of O_3, SO_2, and exercise.

Other pollutants may also modify the response to SO_2 exposure, although currently available evidence is still inconclusive. More specifically, NO_2 may also possibly increase responses to SO_2 in asthmatic individuals. One study by Jörres et al. (1990) appears to provide indications of increased responsiveness to SO_2 after prior NO_2 exposure, whereas a second study by Rubenstein et al. (1990) failed to find analogous NO_2 exacerbation of SO_2 effects. This may have been due to somewhat older and slightly more severe asthmatic subjects being exposed in the first study. It appears that a pollutant that increases nonspecific bronchial responsiveness may also increase airway responses to SO_2.

5.6 HEALTH RISK IMPLICATIONS

Based both on earlier criteria evaluations (U.S. EPA, 1982a,b,c,d, 1986) and the present supplemental assessment of more recent findings on SO_2 respiratory effects, several salient points can be made with regard to implications of the reviewed findings for assessing health risks associated with ambient SO_2 exposures. First, it is now clear that, whereas healthy nonasthmatic individuals are essentially unaffected by acute ($\leq$1 h) exposures to SO_2 at concentrations of 0 to 2 ppm, even very brief (2 to 10 min) exposures of asthmatic subjects to SO_2 concentrations at or below 1.0 ppm can cause detectable respiratory function changes and/or symptoms—*if* such exposures occur while the subjects are sufficiently active to achieve breathing rates typical of at least moderate exercise (i.e., 30 to 50 L/min). Given this fact, mild to moderate asthmatic persons are much more likely to be at risk for experiencing respiratory effects in response to ambient SO_2 exposures than are those with chronically severe asthma. The individuals with severe asthma, by definition (NIH, 1991; see Table 1), have very poor exercise tolerance with marked limitation of activity and, therefore, are less likely to engage in sufficiently vigorous activity (exercise) so as to achieve requisite breathing rates for notable SO_2 respiratory effects to occur.

Of key importance, then, for criteria development purposes is the characterization of exposure-response relationships for the induction by SO_2 of respiratory function changes and symptoms in mild to moderate asthmatic subjects and to provide a framework which will assist in determining which SO_2 responses may be of sufficient magnitude and severity so as to be of significant health concern. The health significance of SO_2 respiratory effects can be evaluated in terms of several criteria, such as: (1) the point at which substantial percentages

of SO_2 exposed asthmatic subjects experience respiratory function changes or symptoms that exceed usual daily variations or responses to other commonly encountered stimuli (e.g., exercise, cold/dry air, etc.) that trigger bronchoconstriction and other asthma symptoms; (2) whether the responses evoked by SO_2 are sufficient to require reductions in exercise workloads, termination of the SO_2 exposure entirely, use of asthma medication after the SO_2 exposure, and/or seeking of medical attention; and (3) the persistence of the observed acute SO_2 exposure effects and/or their relationship to any other more serious chronic health impacts.

Collectively, the foregoing analyses of exposure-response relationships and severity of acute ($\leq$10 min) SO_2 exposure effects in asthmatic subjects suggest the following:

(1) Overall, the responses to SO_2 demonstrated by controlled laboratory studies of exercising asthmatic subjects are similar in many ways to effects evoked by other commonly encountered non-specific stimuli (such as exercise, cold/dry air, psychological stress, etc.). That is, bronchoconstriction and/or respiratory symptoms occur with rapid onset after exposure (within 5 to 10 min.), but typically the acute-phase bronchoconstriction and any accompanying symptoms reverse on their own within 1 to 2 h and are not followed by additional late-phase responses (often much more severe and dangerous) that typify asthmatic reactions to more specific stimuli (e.g., pollen, dust mites, or other biocontaminants). Moreover, the acute-phase responses to SO_2 are followed by a short-lived refractory period and can be prevented or ameliorated by inhalation of beta-agonist aerosol medications. On the other hand, it has been well documented in numerous studies that SO_2 may interact with weather factors (e.g., cold/dry air) and/or exercise to cause exaggerated bronchonstriction and accompanying symptoms when asthmatic individuals are exposed to sufficiently high SO_2 concentrations while engaged in exercise of sufficient intensity to require oronasal breathing. Of particular concern are a subset of asthmatic individuals that appear to be hyperresponsive to SO_2 in displaying dramatically greater-than-average bronchoconstriction and more marked symptomatic responses at given SO_2 concentrations than do most other potentially affected asthmatic persons. Quantitative estimation of SO_2 concentrations at which notable numbers (percentages) of such SO_2-sensitive asthmatic subjects display bronchocontriction responses and symptoms of sufficient magnitude or severity to be of health concern is discussed below.

(2) At most, only about 10 to 20% of mild or moderate asthmatic individuals are likely to exhibit lung function decrements in response to SO_2 exposures of 0.2 to 0.5 ppm during moderate exercise that would be of distinctly larger magnitude than typical daily variations in their lung function or average changes in lung function experienced by them in response to other often encountered stimuli, e.g., comparable exercise levels alone and/or cold/dry air. Furthermore, it appears that only the most sensitive responders might experience sufficiently large lung

function changes and/or respiratory symptoms of such severity as to be of potential health concern, leading to disruption of ongoing activities (e.g., reduction or termination of physical exertion), the need for bronchodilator medication, or seeking of medical attention. If so affected, however, it is also likely that use of bronchodilator medication would be effective in rapidly ameliorating the affected individual's distress or that the SO_2-induced effects would be short-lived (i.e., less than a few hours; usually less than 1 h). Further, although the persons' symptoms, however brief, may be perceived by some as an "asthma attack", it is unlikely that many would seek emergency medical treatment (i.e., physician or hospital visit), given the rarity with which such individuals normally respond in such a fashion to other "asthma" events (as discussed in Section 2.1). Also, given the refractory period found to exist after SO_2 exposures, it would be less likely for the individual to experience notable responses upon reexposure to SO_2 within the next several hours after the initial exposure, should they choose to resume physical exertion after amelioration or cessation of any initial SO_2-induced distress.

(3) In contrast to the above projected likely consequences of ambient exposures to 0.2 to 0.5 ppm SO_2 of mild or moderate asthmatic persons, considerably larger lung function changes and respiratory symptoms of notably greater severity would be expected to occur due to exposure of such individuals to SO_2 concentrations of 0.6 to 1.0 ppm while physically active. That is, substantial percentages ($\geq$20 to 25%) of mild or moderate asthmatic individuals exposed to 0.6 to 1.0 ppm SO_2 during moderate exercise would be expected to have respiratory function changes and severity of respiratory symptoms that distinctly exceed those experienced as typical daily variation in lung function or in response to other stimuli, e.g., moderate exercise or cold/dry air. The severity of the effects for many of the responders, furthermore, are likely to be sufficient to be of concern, i.e., to cause disruption of ongoing activities, use of bronchodilator medication, and/or possible seeking of medical attention. Again, however, for those thusly affected, bronchodilator treatment would likely lead to rapid amelioration of the distress or it would be relatively transient (not more than a few hours) and unlikely to reoccur if reexposure to SO_2 occurred within the next several hours after initial exposure. Also, the intensity of distress is much more likely to be perceived as an "asthma attack" than would be the case for most 0.2 to 0.5 ppm SO_2 effects, although it still would appear to be relatively unlikely that the short-lived symptoms would be sufficient to cause many to seek emergency medical attention for reasons noted above.

(4) The relative health significance of the above types of responses is difficult to judge. However, the degree of concern for effects of the magnitude and severity expected at 0.6 to 1.0 ppm SO_2 exceeds that for those responses likely to be seen with 0.2 to 0.5 ppm exposures of physically active asthmatic individuals. For most mild to moderate asthmatic persons, effects induced by acute, brief (2 to 10 min) exposures to SO_2 at such concentrations ($\leq$0.5 ppm) would generally be barely perceptible (if perceived at all) and not of any medical concern. For a few others among the most sensitive responders, responses may be of such magnitude

and severity to be viewed as more than a mild annoyance—although the resulting distress would probably be short-lived even if not treated with medication and has not been demonstrated to be a harbinger of any more serious, chronic health sequelae. At 0.6 to 1.0 ppm SO_2, on the other hand, the effects *per se* are more likely to be of sufficient magnitude and severity for ≥20 to 25% of mild or moderate asthmatic individuals to be both perceptible and thought of as being of some immediate health concern. If such effects were to be experienced often in response to ambient SO_2 exposures, then the degree of concern would increase. Therefore, the likely frequency of occurrence of such SO_2-induced effects is one of the factors that should be considered in determining the public health significance of ambient SO_2 exposures.

(5) The possibility exists that bronchodilator medication use before engaging in physical exercise might prophylactically protect against the above types of effects due to SO_2 exposure during physical exertion. This may be true for some asthmatic individuals, but given relatively low medication usage compliance rates for many mild or moderate asthma patients (see Section 4.4 and Appendix B Smith memo), pre-exercise bronchodilator use may not occur (and, therefore, offer protection) for many potentially affected sensitive individuals. For a large number of mild asthmatics with normal baseline lung function or well controlled moderate asthmatics on a regular regimen of medication, SO_2 probably represents a limited public health concern, in that exposure is unlikely to reduce their lung function below a critical level that would be of immediate medical concern. However, many moderate asthmatics who come from families with lower socioeconomic status may not have adequate access to the health care system, may have poor compliance for medication use (possibly based on limited availability of medication) and may thus be prone to frequent deterioration of their lung function. Such individuals would be at increased risk from SO_2 exposure because of their potentially poorer baseline level of lung function in addition to the likelihood of exposure to additional airway irritants (e.g., NO_2, cockroach antigen, and dust mite antigen). Exposure of unmedicated moderate asthmatics to SO_2 could cause additional deterioration of lung function that could be cause for medical concern. In evaluating the possible frequency with which mild to moderate asthmatic persons may be sufficiently affected by SO_2 exposures so as to disrupt their normal daily activities, attention should be focussed on estimation of the frequency of occurence of SO_2 exposures (at 0.6 to 1.0 ppm or higher) in combination with increased physical activity (moderate or greater exercise levels). Greater concern would exist for SO_2 effects in that fraction of adolescent or adult mild or moderate asthmatic population segments who regularly exercise outdoors (e.g., jogging, tennis, etc.), are involved with outdoor athletics (e.g., high school sports), or are employed in occupations requiring frequent increased physical exertion. Similarly, children with mild to moderate asthma may also be of concern, given the tendency for children to generally be much more physically active than adults.

5.7 POPULATION GROUPS AT RISK

As highlighted above, mild or moderate asthmatic children and physically active adolescents or adults with mild or moderate asthma clearly represent population segments likely to be at special risk for potential SO_2 exposure effects.

In addition, certain minority group (e.g., Black, Hispanic) individuals might be hypothesized as being at increased potential risk for SO_2 respiratory effects, given distinctly higher asthma mortality rates reported among non-white individuals in large urban centers such as Chicago and New York, as discussed in Section 2.1. However, no specific evidence has been brought forward to date that specifically implicates SO_2 as contributing to the increased asthma mortality rates observed among non-white population groups. Nor have epidemiologic evaluations of possible SO_2 effects on asthma rates in New York City's "asthma alley" areas (Brooklyn, Harlem) found evidence of significant associations between either 24 h average SO_2 concentrations or briefer 1 h SO_2 excursions above 0.1 ppm and increased visits to hospital emergency rooms for asthma (Goldstein and Block, 1974; Goldstein and Arthur, 1978; Goldstein and Weinstein, 1986). Lastly, Heath et al. (1984) found no significant differences between respiratory function changes of 10 African American and 12 Caucasian methacholine positive asthmatic male subjects in response to controlled exposure to 1.0 ppm SO_2 while exercising, although both groups showed significant ($p < 0.04$) increases in total respiratory resistance following the SO_2 exposure.

Another population group that could be hypothesized as being at increased risk for SO_2 effects are atopic allergic individuals, based on reports (e.g., by Koenig et al., 1987, 1988) of allergic adolescent subjects showing similar responses to SO_2 as mild asthmatic subjects. However, the allergic adolescent subjects with exercise-induced bronchospasm (EIB) shown by Koenig et al. to have a similar response to SO_2 as mild asthmatics would be considered by many experts to fall into the diagnostic category of mild allergic exercise-induced asthmatics (see Clean Air Scientific Advisory Committee, 1993, transcript). In the clinic population from which Koenig et al. (1987, 1988) drew these subjects, the incidence of EIB among allergic adolescents is reported to be approximately 40% (Kawabori et al., 1976). However, Custovic et al. (1994) found no EIB among children with allergic rhinitis and atopic dermatitis. The difference in incidence of EIB in these two groups of allergic subjects is most likely due to criteria used for diagnostic classification rather than a real population

difference in incidence of EIB. As noted in Section 2.1, there may be a number of undiagnosed asthmatics and a number of subjects without asthma who have exercise-induced bronchospasm. In the process of estimating the number of persons potentially at risk to be affected by ambient SO_2 exposure, this uncertainty regarding the incidence of SO_2 sensitivity in the population should be considered.

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APPENDIX A

SUMMARY OF STUDIES (1982 TO 1986) AS EARLIER REVIEWED IN SECOND ADDENDUM (U.S. EPA, 1986) WITH REGARD TO ACUTE EXPOSURE EFFECTS OF SULFUR DIOXIDE ON LUNG FUNCTION IN ASTHMATICS

TABLE A-1. SUMMARY OF KEY CONTROLLED HUMAN EXPOSURE STUDIES (PRIOR TO 1987) OF PULMONARY FUNCTION EFFECTS DUE TO EXPOSURE OF ASTHMATICS TO SO_2 (AS EVALUATED IN U.S. EPA, 1986)

Concentration	Duration	Number of Subjects*	Exposure Mode	Exposure Status	Observations	Comments	References
0.1 ppm	3 min	8	Oral-mouthpiece 22 °C 0% RH AH < 1	Hyperventilation to V_E = 51 l/min	Ventilation rate needed to increase SR_{aw} by 80% over resting baseline shifted by 3.8 l/min (7%) less than that needed for comparable HIB in dry air.	Symptom data not reported. Suggests marginal increase in hyperventilation needed to produce HIB in dry air. Health significance unclear.	Sheppard et al. (1984)
0.2 ppm	5 min	23	Chamber- 23 °C 85% RH AH = 17.5	Exercising V_E = 48 l/min	No significant change in SR_{aw}, FEV_1, FVC, PEFR, $V_{max25-75}$ over exercise control. Possibly statistically significant increase in overall symptom score but not for any one symptom.	No measurable physiologic changes with possible increase in symptom scores of uncertain significance.	Linn et al. (1983b)
0.2 ppm	5 min	8	Chamber- 5 °C (1) 50% RH AH = 3.4 (2) 85% RH AH = 5.8	Exercising V_E = 50 l/min	No significant changes in SR_{aw}, FEV_1, FVC, SG_{aw} over exercise control for either RH level. Suggestion of small increase in symptoms but no statistics given.	No measurable enhancement of SO_2 response for 5 °C, 50% RH. Symptom score results of uncertain significance.	Linn et al. (1984a)
0.25 ppm	10 to 40 min	10	Chamber- 23 °C 70% RH AH = 14.4	Exercising V_E = 35 l/min	No significant changes in R_{aw}, FEV_1, MEF_{40}, with small (4%) change in V_{max50}. No clear increase in symptoms, suggestion of increased response in 2 of 10 subjects.	Indicates no effect. Changes even in sensitive subjects of uncertain health significance.	Schachter et al. (1984)
0.25 ppm	5 min	(1) 19 (2) 9	Chamber 23 °C D.P. = 7.6 °C (36% RH) AH = 7.4	Exercising (1) V_E = 60 l/min estimated (750 kpm-min) (2) V_E = 80-90 l/min estimated (1,000 kpm-min)	With 750 kpm/min exercise, increase in SR_{aw} in SO_2 (mean = 134%) signif. greater than clean air (mean = 77%). At 1,000 kpm/min, no sig. diff. between SO_2 and clean air.	Effects at this level small or non-existent in comparison to heavy exercise alone. No symptoms reported. Response highly variable. Suggests 0.25 close to threshold for bronchoconstriction.	Bethel et al. (1985)
0.25 ppm	10 min to 75 min	28	Chamber 26 °C 70% RH AH = 17.1	Intermittent exercise (3 10 min periods) V_E = 42 l/min	No significant changes in SR_{aw}, TGV, resistance impedence for any of measurement periods. No significant changes in symptoms.	No measurable physiological or symptoms changes seen with .25 ppm SO_2 at this exercise level.	Roger et al. (1985)

TABLE A-1 (cont'd). SUMMARY OF KEY CONTROLLED HUMAN EXPOSURE STUDIES (PRIOR TO 1987) OF PULMONARY FUNCTION EFFECTS DUE TO EXPOSURE OF ASTHMATICS TO SO_2 (AS EVALUATED IN U.S. EPA, 1986)

Concentration	Duration	Number of Subjects*	Exposure Mode	Exposure Status	Observations	Comments	References
0.25 ppm	3 min	8	Oral-mouthpiece 22 °C 0% RH AH = <1	Hyperventilation to V_E = 51 l/min	Ventilation needed to increase SR_{aw} by 80% over resting base-line shifted to 5.6 l/min (10%) less than that needed for comparable HIB in dry air.	Symptom data not reported. Suggests small decrease in exercise needed to produce HIB in dry air. Health significance unclear.	Sheppard et al. (1984)
0.3 ppm	5 min	24	Chamber 80% RH (1)-6 °C (2) 7 °C (3) 21 °C (1) AH = 2.5 (2) AH = 6.2 (3) AH = 14.7	Exercising V_E = 50 l/min	At −6 °C, SR_{aw} increased 94% in air and 105% in SO_2. At 7 °C SR_{aw} increased 59% in air and 87% in SO_2. At 21 °C SR_{aw} increased 28% in air and 59% in SO_2. Increase in symptom scores at all temperatures slightly greater in SO_2 than in air.	Significant main effects at 0.3 ppm not reported. Symptom score changes generally mild and of uncertain significance to health. Under test conditions, results indicate that SO_2 and moist cold air effects are additive or less than additive.	Linn et al. (1984b)
0.4 ppm	5 min	23	Chamber 23 °C 85% RH AH = 17.5	Exercising V_E = 48 l/min	Increased SR_{aw} in SO_2 (69%) sig. diff. than increase in clean air (35%). Significant decrements in V_{max} (25-75) (mean = 10%), but no significant changes in FEV_1. Significant increase in overall symptom score, but only one of 12 symptom categories signif. increased. One subject required medication to relieve distress.	Indicates moderate broncocontriction. Overall symptom changes mild, but responses suggestive of clinical significance in at least one subject.	Linn et al. (1983b)
0.4 ppm	5 min	8	Chamber 5 °C (1) 50% RH (2) 81% RH (1) AH = 3.4 (2) AH = 5.8	Exercising V_E = 50 l/min	Apparent increase in SR_{aw} (based on graphical depiction) and symptom score over exercise alone. Symptom score increase clearly larger for 50% RH than for 81% RH.	No statistics reported for SR_{aw} changes. Significance of SG_{aw} and FEV_1 at 0.4 ppm not reported; indicates subjective response enhanced for dryer cool air even when measure of functional changes comparable to moist air.	Linn et al. (1984a)
0.5 ppm	10 to 40 min	10	Chamber 23 °C 70% RH AH = 14.4	Exercising V_E = 35 l/min	No signif. changes in Raw, FEV_1, MEF_{40} with small (mean = 6%) decrement in V_{max50}. No clear increase in symptoms. Some suggestions of increased FEV_1 response in 2 or 3 subjects.	Indicates minimal constriction for group at this exercise rate.	Schachter et al. (1984)
0.5 ppm	5 min	10	Chamber 23 °C 41% RH AH 8.4	Exercising V_E = 60 l/min estimated (750 kpm-min)	Increase in SR_{aw} in SO_2 (mean = 238%) sig. diff. than increase in clean air (mean = 39%). Substantial variability in subjects; one showed eight-fold increase	Indicates substantial SO_2-induced bronchoconstriction at high exercise rate and mod. RH. No symptom data reported but extent of SR_{aw} changes suggestive of clinical significance.	Bethel et al. (1983a)

TABLE A-1 (cont'd). SUMMARY OF KEY CONTROLLED HUMAN EXPOSURE STUDIES (PRIOR TO 1987) OF PULMONARY FUNCTION EFFECTS DUE TO EXPOSURE OF ASTHMATICS TO SO_2 (AS EVALUATED IN U.S. EPA, 1986)

Concentration	Duration	Number of Subjects*	Exposure Mode	Exposure Status	Observations	Comments	References
0.5 ppm	5 min	9	80% RH, 23 °C (1) Face mask (2) Mouthpiece AH = 16.5	Exercising (1) V_E = 27 l/min (2) V_E = 41 l/min (3) V_E = 61 l/min	Facemask exposure: No stat. sig. mean change in SR_{aw} with air or SO_2 at low or mod. exercise rate. For high exercise, increase in SR_{aw} in SO_2 (219%) sig. larger than increase in clean air (25%) compared to mean baseline SR_{aw}. Percent ventilation breathed orally for the three exercise rates were: (1) 50%, (2) 52%, (3) 61%. Mouthpiece exposure: No sig. mean change in SR_{aw} for low exercise rate with moderate exercise, increased SR_{aw} in SO_2 (231%) sig. larger than clean air (5%). With high exercise, increased SR_{aw} in SO_2 (306%) sig. larger than clean air (25%).	Indicates SO_2 induced constriction enhanced by increased work rate, with protection afforded by oronasal (vs. oral) breathing greater at mod. than at high exercise rates. Asthmatics with rhinitis or other nasal blockages breathe more through mouth and appear at greater risk to SO_2 effects.	Bethel et al. (1983b)
0.5 ppm	30 min rest 10 min exercise	9	22 °C 75+% RH AH = 14.6+	Mouthpiece 5-6 × rest V_E	Mouthpiece exposure: FEV_{10} decreased, −15% (−4% in air); R_T increased 47%; V_{max50}, V_{max75} decreased −30, −35%.	Indicates that mouthpiece breathing exacerbates the effect of SO_2 in asthmatics.	Koenig et al. (1983)
		7		Facemask 5-6 × rest V_E	Facemask: No significant changes.		
0.5 ppm	30 min rest 20 min exercise	10 (14-18 yr)	22 °C 75% RH AH = 14.6	Mouthpiece 43 l/min exercise	Increase in nasal resistance of 32%, but not significant. FEV_1 decrease −24%, V_{max50} −46%; V_{max75} −56%. R_T increased 60%.	Indicates SO_2 may cause increased nasal resistance in asthmatics, which may result in more oral breathing and consequently more bronchoconstriction.	Koenig et al. (1985)
				Facemask	Significant increase in nasal resistance of 30%. FEV_1 decreased −16% V_{max5}, V_{max75} −26%		

TABLE A-1 (cont'd). SUMMARY OF KEY CONTROLLED HUMAN EXPOSURE STUDIES (PRIOR TO 1987) OF PULMONARY FUNCTION EFFECTS DUE TO EXPOSURE OF ASTHMATICS TO SO_2 (AS EVALUATED IN U.S. EPA, 1986)

Concentration	Duration	Number of Subjects*	Exposure Mode	Exposure Status	Observations	Comments	References
0.5 ppm	10 min to 75 min	28	Chamber 26 °C 70% RH AH = 17.1	Intermittent exercise (three 10 min periods) V_E = 42 l/min	Increased SR_{aw} in SO_2 (93%) sig. larger than in clean air (47%). SR_{aw} increase after second and third exercise periods sig. less than after first exercise period. No significant changes in FVC, FEV_1, FEF. Group mean symptoms for 20 subjects not sig. increased. Substantial variability in subjects, with one showing 11-fold increase in SR_{aw} and requiring medication to relieve pronounced symptoms.	Extent of effects are decreased after short-term repeated exercise. Broad degree of sensitivity to SO_2 with about 25% of subjects showing a 100% increase in SR_{aw}. Symptoms in at least one subject of clear clinical significance.	Roger et al. (1985)
0.5 ppm	3 min, repeated 3 times in succession at 30 min intervals, again after 24 h and 1 week later	8	Oral-mouthpiece 23 °C 82% RH AH = 16.9	Hyperventilation (varied for each subject)	Sig. increase in SR_{aw} ($\bar{x}$ = 104%) after first 3 min exposure. After 30 min rest, second response sig. but smaller ($\bar{x}$ = 35%); response after third exposure still smaller ($\bar{x}$ = 30%). SR_{aw} increase at 24 h ($\bar{x}$ = 83%) and 1 week ($\bar{x}$ = 129%) not sig. diff. from increase after first 3 min exposure.	Indicates repeated esposures to SO_2 can induce tolerance to bronchoconstrictive effects of SO_2 over short periods (>30 min) but not for longer periods.	Sheppard et al. (1983)
0.5 ppm	3 min	7	Oral-mouthpiece (1) 23 °C 77% RH (2) -11 °C, "Dry" (1) AH = 15.8 (2) AH < 1	Hyperventilation to "Threshold" V_E for each subject (30-50 l/min)	By design, increases in SR_{aw} or symptoms not sig. for SO_2 in warm, humidified air or cold dry air alone. Sig. increase in SR_{aw} ($\bar{x}$ = 222%) for combination of SO_2 and cold dry air. Six of seven subjects report wheezing and/or shortness of breath; two asked for medication. Symptoms not good indicator of of measured SR_{aw}.	Indicates that airway cooling or drying can increase SO_2 associated bronchoconstriction in hyperventilating asthmatics. Suggests possible synergism for these combinations.	Bethel et al. (1984)

TABLE A-1 (cont'd). SUMMARY OF KEY CONTROLLED HUMAN EXPOSURE STUDIES (PRIOR TO 1987) OF PULMONARY FUNCTION EFFECTS DUE TO EXPOSURE OF ASTHMATICS TO SO_2 (AS EVALUATED IN U.S. EPA, 1986)

Concentration	Duration	Number of Subjects*	Exposure Mode	Exposure Status	Observations	Comments	References
0.6 ppm	5 min	24	Chamber 80% RH (1) -6 °C (2) 7 °C (3) 21 °C (1) AH = 2.5 (2) AH = 6.2 (3) AH = 14.7	Exercising V_E = 50 l/min	Increased SR_{aw} in SO_2 sig. greater than in clean air for all three temperatures. At −6 °C, SR_{aw} increased 94% in air and 187% in SO_2. At 7 °C, SR_{aw} increased 58% in air and 207% in SO_2. At 21 °C, SR_{aw} increased 28% in air and 150% in SO_2. Symptom scores sig. greater in SO_2 than in air at all three temperatures.	Suggests that the bronchconstrictive effects of cold air and SO_2 combine in an additive or less-than-additive fashion. Also some suggestion of cold air-SO_2 interaction in total asthma score. SR_{aw} changes are suggestive of clinical significance at all temperatures.	Linn et al. (1984b)
0.6 ppm	5 min	22	Chamber 21 °C, 38 °C 20% RH, 80% RH AH = 3.7, 14.7 at 21 °C AH = 9.3, 37.0 at 38 °C	Exercise V_E = 50 l/min	SR_{aw} changes in clean air ranged from -4% to +12%. With SO_2, at 21 °C SR_{aw} increased 206% with dry and 157% with humid air, while at 38 °C SR_{aw} increased 89% in dry air and 39% in humid air.	Indicates the importance of airway drying as an exacerbating factor in the induction of SO_2-bronchoconstriction.	Linn et al. (1985)
0.6 ppm	Total 6 h on 2 successive days (2 × 5 min exerc. each day, separated by 5 h)	14 (18-33)	Chamber 22 °C 85% RH AH = 16.5	Exercise V_E = 50 l/min	After correction for clean air EIB, SR_{aw} increased 136, 120, 147, 100% on the early-day 1, late-day 1, early-day 2, late-day 2. No difference between times or days.	Indicates that refractory period for SO_2-induced bronchoconstriction is less than 5 h.	Linn et al. (1984c)
0.6 ppm	5 min	24	Chamber- 85% RH (1) 5 °C (2) 22 °C (1) AH = 3.4 (2) AH = 16.5	Exercising V_E = 50 l/min	At 5 °C, increased SR_{aw} with SO_2 (182%) sig. greater than clean air (38%). At 22 °C, increased SR_{aw} with SO_2 (132%) sig. greater than clean air (27%). Lower respiratory and total symptom scores much greater in SO_2 than in clean air.	Suggests bronchoconstrictive effects of cold, moist air may increase SO_2 effects, but under these conditions, enhancement is inconsistent and not significant). Both symptoms, SR_{aw} changes suggestive of clinical significance at both temperatures.	Linn et al. (1984a)

TABLE A-1 (cont'd). SUMMARY OF KEY CONTROLLED HUMAN EXPOSURE STUDIES (PRIOR TO 1987) OF PULMONARY FUNCTION EFFECTS DUE TO EXPOSURE OF ASTHMATICS TO SO_2 (AS EVALUATED IN U.S. EPA, 1986)

Concentration	Duration	Number of Subjects*	Exposure Mode	Exposure Status	Observations	Comments	References
0.6 ppm	5 min	8	Chamber- 5 °C (1) 50% RH (2) 81% RH (1) AH = 3.4 (2) AH = 5.8	Exercising V_E = 50 l/min Pilot study	Significant increase in SR_{aw} and symptom scores over exercise alone for both humidities (graphical depiction). No sig. diff. between humidities at this temperature.	Suggests that under these conditions, SO_2 response apparently not enhanced by lower humidity or cool air which has a low water content already.	Linn et al. (1984a)
0.6 ppm	5 min	23	Chamber- 23 °C 85% RH AH = 17.5	Exercising V_E = 48 l/min	Increased SR_{aw} in SO_2 (120%) sig. greater than in air (36%). Significant decline in FVC (mean = 3%), FEV_1 (mean = −13%), PEFR (mean = -26%) $Vmax_{25-75}$ ($\bar{x}$ = −26%). Sig. increase in: total symptom score; number of subjects with increased symptom score (21 of 23), and positive reading on discomfort meter (12 of 23), and in 4 individual symptom categories (cough, substantial irritation, wheezing and chest tightness). Three subjects required medication to relieve symptoms. No apparent effects next day or week.	Bronchoconstriction function changes, high symptom scores, and medication requests indicate SO_2 effects of likely medical significance. However, effects short-lived, do not persist into next day.	Linn et al. (1983b)
0.75 ppm	3 h 10 min exercise at beginning	17	Chamber 22 °C, 85% RH AH = 16.5	Exercising 45 l/min	No clean air control. With SO_2, SR_{aw} increased 263%, FEV1 decreased 20% after exercise (SR_{aw} increased 322% in second series with no spirometry). Symptom scores increased after exercise. SR_{aw} and symptom scores were not significantly elevated after 1 h of recovery in SO_2.	Indicates that recovery is complete for most subjects within 1 h of SO_2 + exercise-induced bronchoconstriction.	Hackney et al. (1984)
0.75 ppm	10 min	23	Chamber 23 °C, 90% RH (1) oralnasal (2) mouthpiece AH = 18.5	Exercising V_E = 40 l/min	In clean air, SRaw increased 54% by either oronasal or mouthpiece breathing. In SO_2, SR_{aw} increased 186% by oronasal breathing and 321% by mouthpiece. Decline in FVC, FEV_1, PEFR, and $V_{max25-50}$ for both exposure routes. Sig. increase in symptom score, both routes. SR_{aw} increase sig. greater for oral exposures; symptoms/other functional measure changes greater for oral, but not sig. so.	Indicates oronasal breathing ameliorates bronchoconstrictive effects of SO_2, but less effective against symptoms. Functional changes and symptoms indicate clinical significance.	Linn et al. (1983a)

TABLE A-1 (cont'd). SUMMARY OF KEY CONTROLLED HUMAN EXPOSURE STUDIES (PRIOR TO 1987) OF PULMONARY FUNCTION EFFECTS DUE TO EXPOSURE OF ASTHMATICS TO SO_2 (AS EVALUATED IN U.S. EPA, 1986)

Concentration	Duration	Number of Subjects*	Exposure Mode	Exposure Status	Observations	Comments	References
0.75 ppm	10 to 40 min	10	Chamber- 23 °C 70% RH AH = 14.4	Exercising V_E = 35 l/min	Significant changes in FEV_1 (mean = -8%), MEF_{40} (mean = −22%), $Vmax_{50}$ (mean = 11%), and RAW (mean = 40%). No sig. discomfort persisted 10 min after exposure. Apparent large increase in lower airway symptom complaints. Wide variable responses among subjects.	Indicates bronchoconstriction Symptoms, functional changes and additive effects of clinical significance began between 0.5 and 0.75 ppm for this study group and conditions on average.	Schachter et al. (1984)
0.75 ppm	10 min	10	22 °C 75% RH AH = 14.6	Mouthpiece Exercising V_E = 34 l/min	Premedication with albuterol blocked the 15% decrease in FEV_1 which occurred with SO_2. Albuterol also caused a 6-8% increase in baseline $FEV_{1.0}$.	No symptoms. Albuterol prevented SO_2-induced bronchoconstriction.	Koenig et al. (1987)
1.0 ppm	30 min rest 10 min exercise	9	22 °C 75% RH AH = 14.6	Mouthpiece 5-6 × rest V_E (30-50 l/min)	FEV_{10} (−23%), V_{max50} (−51%), V_{max75} (−61%), R_T (+71%). Recovery was slower than after 0.5 ppm exposures.	Suggests that more severe SO_2-induced bronchoconstriction requires longer recovery than less pronounced changes at lower concentration.	Koenig et al. (1983b)
1.0 ppm	10 to 40 min	10	Chamber- 23 °C 70% RH AH = 14.4	Exercising V_E = 35 l/min	Significant changes in FEV_1 (mean = −14%), MEF_{40} (mean = 27%), V_{max50} (mean = −22%), and RAW (mean = −54%). No sig. decrements persist 10 min after exposure. Apparent large concentration-related increase in lower airway symptom complaints. Three subjects apparently nonresponsive (based on FEV_1) even at this concentration, with at least one very sensitive subject showing > 50% FEV_1 decline.	Indicates bronchoconstriction. Symptoms and functional changes suggestive of clinical significance.	Schachter et al. (1984)

TABLE A-1 (cont'd). SUMMARY OF KEY CONTROLLED HUMAN EXPOSURE STUDIES (PRIOR TO 1987) OF PULMONARY FUNCTION EFFECTS DUE TO EXPOSURE OF ASTHMATICS TO SO_2 (AS EVALUATED IN U.S. EPA, 1986)

Concentration	Duration	Number of Subjects*	Exposure Mode	Exposure Status	Observations	Comments	References
1.0 ppm	10 to 75 min	27	Chamber- 26°C 70% RH AH = 17.1		Sig. decrease in SR_{aw} after all 3 exercise periods but response decreases with time. First Exercise: Increased SR_{aw} in SO_2 (190%) sig. greater than air (47%). Second Exercise: Increased SR_{aw} in SO_2 (147%) sig. greater than air (34%). Third Exercise: Increased SR_{aw} in SO_2 (116%) sig. greater than in air (30%). Group mean symptom analysis for 20 subjects showed sig. increase in shortness of breath and chest discomfort. Substant. variability in subject response; one unable to go beyond 35 min point.	Respiratory impedence suggests SO_2 induced bronchoconstriction mostly in peripheral airways. Decreased response with time suggests short-term tolerance, but effects of clincal significance occur even after third exercise period.	Roger et al. (1985)
1.0 ppm	(1) 10 mins., reported 3 times in succession with 15 min intervals (2) 30 min continuous exercise	10	Chamber 26°C 70% RH AH = 17.1	Intermittent Exercise V_E = 41 l/min	First Exercise: Significant increase in total SR_{aw} (mean = 172%). Second Exercise: Significant increase in total SR_{aw} (mean = 137%). Third Exercise: Sig. increase in total SR_{aw} (mean = 106%). Attenuation with time occurred in 4 of 10 subjects. Continuous Exercise: Sig. increase in total SR_{aw} (mean = 233%) after 30 min.	Indicates mechanism responsible for apparent tolerance to repeated short-term exposures to SO_2 does not reduce responses to continuous exercise for comparable time periods.	Kehrl et al. (1987)
0.25 to 2 ppm	10 min, different days	27	Chamber 26°C 70% RH AH = 17.1	Exercise V_E = 42 l/min	Concentration response relationships for four exposures interpolated for each subject to determine $PC(SO_2)$, the SO_2 concentration producing a 100% increase in SR_{aw} over exercise in clean air. Cumulative plot shows 25% of subjects with $PC(SO_2) < 0.5$ ppm, median $PC(SO_2)$ was 0.75 ppm, and about 20% of subjects have a $PC(SO_2) > 1.95$ ppm.	Reflects additional analyses of data from first exposure period in experiment reported in Roger et al. (1985). Quantifies the variability in response among asthmatics for functional changes of potential clinical significance. Suggests effects of concern in some subjects may extend down to near 0.25 ppm.	Horstman et al. (1986)

TABLE A-1 (cont'd). SUMMARY OF KEY CONTROLLED HUMAN EXPOSURE STUDIES (PRIOR TO 1987) OF PULMONARY FUNCTION EFFECTS DUE TO EXPOSURE OF ASTHMATICS TO SO_2 (AS EVALUATED IN U.S. EPA, 1986)

Concentration	Duration	Number of Subjects*	Exposure Mode	Exposure Status	Observations	Comments	References
0.125 to 2 ppm	3 min, doubling successive exposures with no breaks	8	Oral-mouthpiece (1) -20°C 0% RH (2) 22°C 0% RH (3) 22°C 70% RH (1) AH <1 (2) AH <1 (3) AH = 13.6	Hyperventilation (to V_E = 30 to 40 l/min)	By design, SR_{aw} increase for clean air alone not sig. Concentration response relationships for 4 to 5 exposures interpolated for each subject to determine PC_{100} (SO_2 level producing a 100% increase over resting baseline). Mean PC_{100} for differing conditions were: Dry Cold Air - 0.51 ppm; Dry Warm Air - 0.60 ppm; Humid Warm Air = 0.87 ppm; PC_{100} for humid warm air sig. greater than for dry cold or dry warm air (which were not sig. different from each other).	Nature of doubling concentrations may have affected PC_{100} estimates. Results quantify wide variability among subjects. Indicates very dry air potentiates SO_2 bronchoconstriction regardless of temperature.	Sheppard et al. (1984)
0.25 to 8 ppm	3 min at each concentration	10	23°C (Dewpoint 15°C) AH = 12.5 RH = 61%	Mouthpiece Isocapnic Hyperpnea V_E = 40 l/min	Premedication with placebo, 20 mg., or 200 mg cromolyn. SO_2 dose-response to 3 min exposures starting at 0.25. SO_2 dose which increased SR_{aw} by 8 units was 0.35, 0.94, and 1.98 ppm respectively.	Cromolyn decreased airway reactivity to SO_2. High dose of cromolyn caused increased response to methacholine.	Myers et al. (1986a)
0.25 to 8 ppm	3 min at each concentration	10	23°C (Dewpoint 15°C) AH = 12.5 RH = 61%	Mouthpiece Isocapnic Hyperpnea V_E = 40 l/min	Premedication (200 mg cromolyn plus 2 mg atropine) more effective than either drug alone in inhibiting SO_2-induced bronchoconstriction. SO_2 dose which increased SR_{aw} by 8 units was 1.16 ppm (atropine), 1.20 ppm (cromolyn), or 3.66 ppm (both).	Similar effect on dry air hyperpnea-induced bronchoconstriction. The reproducibility of SO_2 dose response was poor.	Myers et al. (1986b)

AH = absolute humidity = g H_2O vapour/m^3 of air.
g/m^3 = mg/ℓ.
HIB = Hyperventilation Induced Bronchoconstriction

APPENDIX B

U.S. EPA STAFF ANALYSES OF SEVERITY OF SULFUR DIOXIDE-INDUCED RESPIRATORY FUNCTION CHANGES AND SYMPTOMS IN ASTHMATIC SUBJECTS BASED ON DATA FROM RECENT CONTROLLED HUMAN EXPOSURE STUDIES

TABLE B-1. AVERAGE MAGNITUDES OF LUNG FUNCTION CHANGES AT TESTED SO_2 EXPOSURE LEVELS AND PERCENTAGES OF SUBJECTS EXHIBITING CHANGES OF INCREASING SEVERITY AT MODERATE TO HIGH EXERCISE LEVELS (VENTILATION RATE 40 TO 50 L/MIN), BASED ON U.S. EPA EVALUATION OF DATA FROM SELECTED RECENT CONTROLLED HUMAN STUDIES

			LUNG FUNCTION DATA[1,2]				CUMULATIVE NO. OF RESPONDERS[3]				
SO_2 Conc. (ppm)	Status[4]	No. of Subj	Lung Fxn Measure	% Total Change	% Change from Exercise	% Change from SO_2	≥100% ≤−15%	≥200% ≤−20%	≥300% ≤−30%	≥500% ≤−40%	References
0.4	Mild R1	16	SR_{aw}	84	36	48	25%(4)	6%(1)	0	0	Linn et al. (1987)
0.4	Mod R1	24	SR_{aw}	107	83	24	21%(5)	8%(2)	4%(1)	4%(1)	Linn et al. (1987)
0.4	Mild R1	16	FEV	−13.4	−1.6	−11.8	38%(6)	25%(4)	6%(1)	0	Linn et al. (1987)
0.4	Mod R1	24	FEV	−16.3	−8.3	−7.9	25%(6)	21%(5)	17%(4)	8%(2)	Linn et al. (1987)
0.5	Mild	28	SR_{aw}	108	48	60	18%(5)[5]	4%(1)	4%(1)	4%(1)	Roger et al. (1985)
0.6	Mild R1	16	SR_{aw}	206	36	170	38%(6)	25%(4)	13%(2)	6%(1)	Linn et al. (1987)
0.6	Mod R1	24	SR_{aw}	221	83	138	33%(8)	29%(7)	21%(5)	13%(3)	Linn et al. (1987)
0.6	Mild	20	SR_{aw}	247	58	190	60%(12)	35%(7)	10%(2)	5%(1)	Linn et al. (1988)
0.6	Mod	21	SR_{aw}	208	39	168	48%(10)	33%(7)	14%(3)	5%(1)	Linn et al. (1990)
0.6	Mild R1	16	FEV	−18.5	−1.6	−17.0	63%(10)	50%(8)	0	0	Linn et al. (1987)
0.6	Mod R1	24	FEV	−25.3	−8.3	−17.0	42%(10)	42%(10)	33%(8)	17%(4)	Linn et al. (1987)
0.6	Mild	20	FEV	−19.4	−3.1	−16.3	55%(11)	55%(11)	5%(1)	0	Linn et al. (1988)
0.6	Mod	21	FEV	−28.3	−13.8	−14.5	45%(9)	35%(7)	19%(4)	19%(4)	Linn et al. (1990)
1.0	Mild	28[6]	SR_{aw}	196	48	148	50%(14)[7]	25%(7)	14%(4)	4%(1)	Roger et al. (1985)

[1]Lung function (LF) changes given as: the percent total change observed after SO_2 exposure, relative to baseline; the percent attributable to exercise, as determined from a control exposure with no SO_2; and the percent change attributable to SO_2, which is the difference between the total change and the change due to exercise. The calculations performed were: % Total Change: ((SO_2 Post-Exposure LF—Baseline LF Prior to SO_2 Exposure)/Baseline LF Prior to SO_2 Exposure) • 100; % Change due to Exercise: ((Exercise [Clean Air] Post-Exposure LF—Baseline LF prior to exercise exposure)/Baseline LF prior to exercise exposure) • 100. Thus, in abbreviated form: % Change due to SO_2 : ((SO_2 Post LF—SO_2 Base LF)/SO_2 Base LF)—((Exc Post LF—Exc Base LF)/Exc Base LF)) • 100; Change due to SO_2 and % Change due to Exercise may not total exactly to % Total Change due to rounding.

[2]Changes in LF calculated by averaging each subject's own individual percent change in LF, rather than from group mean LF measurements.

[3]Numbers in these columns indicate both percentage and number of subjects (in parenthesis) having a LF change, after correction for exercise, greater than or equal to designated LF cutpoints. The numbers are cumulative; thus the ≥100% SR_{aw} category includes individuals with SR_{aw} changes of 200%, 300% etc. For instance, 5 moderate asthmatic subjects from Linn et al. (1987) study experienced at least a 100% change in SR_{aw} at 0.4 ppm; of these 5, 2 had at least a 200% change and, of these 2, 1 had at least a 500% change. For FEV_1 as the LF measure, the lower numbers in the column heading apply. Also, FEV_1 cutpoints refer to number of subjects with a 15% or greater *decrease* in FEV_1, (i.e., FEV_1 changes 15% or more in a negative direction, indicated as ≤ −15% decrease).

[4]Status of asthmatics as mild ("Mild") or moderate ("Mod"). "R1" indicates data from first round of Linn et al. (1987) study was used here.

[5]Another subject had a LF change of 99+%; if considered essentially a 100% SRaw change, then 21%(6) had doubling of SRaw.

[6]Only 27 subjects exposed to 1.0 ppm in Roger et al. (1985) study. The other subject was unable to complete the protocol at 0.5 ppm after experiencing greater than 500% increase in SRaw, and he was not exposed to 1.0 ppm. However, all numbers in this row include this subjects' lung function changes at 0.5 ppm, under the assumption that, on average, he would experience at least as great changes in lung function at 1.0 ppm.

[7]Another subject had a SRaw change of 99+%; if considered to be a 100% change in SRaw, then 54%(15) of the subjects doubled SR_{aw}.

June 30, 1994

MEMORANDUM

SUBJECT: Assessment of data from recent chamber studies pertaining to the severity of effects experienced at 0.6 to 1.0 ppm SO_2 by asthmatic subjects

FROM: Eric Smith
Ambient Standards Branch, OAQPS

TO: Dr. Lester D. Grant, Director
Environmental Criteria and Assessment Office, RTP (MD-52)

This memorandum evaluates responses seen among asthmatic subjects to the highest SO_2 concentrations administered (0.6 and 1.0 ppm SO_2) in four recent clinical chamber studies. Extensive data on individual subjects made available to U.S. EPA by the responsible investigators has allowed detailed assessment of the range and combination of responses seen in individual asthmatic subjects in response to SO_2 exposure. As per requests by the Clean Air Scientific Advisory Committee (CASAC) to portray the responses of asthmatics to SO_2 in the context of other responses an asthmatic individual may frequently experience (CASAC Meeting, August 19, 1993), information is also presented for many of the subjects concerning their typical circadian variation in lung function, frequency of symptoms and perceived asthma attacks, and frequency of medication usage. The detailed evaluations provided here are intended to assist judgements concerning the adversity of effects that result from 0.6 to 1.0 ppm SO_2 exposures and, as such, augment the analyses of published findings contained in the main body of the present Supplement (CDA Supplement) to the Second Addendum (1986) to the U.S. EPA document Air Quality Criteria for Particulate Matter and Sulfur Oxides (1982).

The Studies

Data from four recent large-scale clinical studies are summarized and discussed below. These studies examine the effects of SO_2 on mild asthmatic subjects (Linn et al., 1987, 1988; Roger et al., 1985) and moderate asthmatic subjects (Linn et al., 1987, 1990) at exercise. Details on classification are provided in Smith (1994). The Roger et al. (1985) subjects (referred to in general as the "1985 mild asthmatic subjects") were exposed to 1.0 ppm SO_2 while at exercise, while all the Linn et al. subjects (from the 1987, 1988 and 1990 studies,

generally referred to as "the 1987 mild asthmatic subjects," "the 1987 moderate asthmatic subjects," "the 1988 mild asthmatic subjects," and "the 1990 moderate asthmatic subjects") were exposed to 0.6 ppm SO_2. The 1987 and 1990 moderate asthmatic groups are fairly similar, but the 1987 and 1988 mild groups are distinguished by the fact that a number of the 1988 subjects used medication at least once a week (Hackney et al., 1988a), while no 1987 mild asthmatic subjects used medication that frequently (Hackney et al., 1987).

For the 1985 and 1987 studies, which involved an 1-h exposure to SO_2 with three 10-min exercise periods interspersed with rest, only data gathered immediately following the first exercise period is used (and for the 1987 study, only the first round of the two identical rounds of exposure was used). This more accurately reflects the likely ambient conditions (brief peaks resulting in high concentrations of SO_2) and allows the results to be more easily compared with those from the single 10-min exposures used in the 1988 and 1990 studies. The 1988 and 1990 studies were designed in part to assess the effect of supplementary use of an inhaled bronchodilator just prior to SO_2 exposure. For this analysis, the "untreated" case was used for the 1988 mild asthmatic subjects and the "normal medication" case was used for the 1990 moderate asthmatic subjects. No supplementary bronchodilator was administered in either case.

Assessment of Responses

For the assessment of the four studies shown in Table 1, data on each individual subject was obtained and responses were scored according to Table 8 of the Criteria Document Addendum Supplement (CDA Supplement). Each study was assessed in terms of the lung function and symptomatic responses observed, and, when available (the 1988 and 1990 studies), duration of response and medication use post-exposure as well. Four indices of severity of response were examined, with the data presented as the percentage of subjects experiencing: (1) a severe effect in at least one category of response (lung function, symptoms, and for the 1988 and 1990 studies, medication use); (2) a moderate response in both or all three of these categories; (3) a severe lung function response accompanied by a moderate symptom response; and (4) a severe response in both or all three categories. These varying indices permit those making judgments on the adversity of effects to select a point where they believe the effects become adverse and determine the number of subjects

Table 1. COMPARISON OF VARIOUS INDICES OF SEVERITY OF RESPONSE* AT 0.6 TO 1.0 PPM SO_2

0.6 ppm SO_2 Single Exposure Studies	1990 Mod Asth ~50 L/min Normal Meds		1988 Mild Asth ~50 L/min Untreated	
Exposure	SO_2	EXC	SO_2	EXC
SEV for any 1 category (FEV_1 Chg, SYM, MEDUSE)	81%	33%	55%	10%
MOD for all 3 categories	52%	10%	35%	0
SEV FEV_1 + MOD SYM	43%	5%	35%	0
SEV for all 3 cat.	10%	0	30%	0

0.6 ppm SO_2 First Exercise Period	1987 Mod Asth 44 L/min Round 1		1987 Mild Asth 44 L/min Round 1	
Exposure	SO_2	EXC	SO_2	EXC
SEV for FEV_1 Chg or SYM	58%	8%	50%	0
MOD for FEV_1 + SYM	33%	0	13%	0
SEV FEV_1 + MOD SYM	33%	0	6%	0
SEV for both cat.	8%	0	0	0

1.0 ppm SO_2 First Exercise Period	1985 Mild Asth 42 L/min	
Exposure	SO_2	EXC
SEV for SR_{aw} Chg or SYM	43%	0
MOD for SR_{aw} + SYM	18%	0
SEV SR_{aw}, MOD SYM	18%	0
SEV for SR_{aw} and SYM	4%	0

*Responses rated as per Table 8 in Section 5.3 of CDA Supplement (1994), using Total Lung Function change, the maximum symptom for chest tightness, shortness of breath, and wheeze, and, for the 1988 and 1990 studies, medication usage. (Duration of response > 1/2 h [a "moderate" response] was able to be considered for only one subject in the 1990 study. All the rest of the subjects with at least moderate lung function change and symptoms took medication [a "severe" response]).

experiencing that level of response. Further details on how responses were scored are provided with Table 1. Supplementary information on the data and the judgments entering into this analysis is also provided in Smith (1994) for all sections of this memorandum.

One choice made in scoring responses should be highlighted: change in total lung function was used rather than change in lung function attributable to SO_2. The change from SO_2 alone has often been emphasized in the past, and with good reason: since asthmatic individuals can have considerable bronchoconstriction from exercise alone, subtracting out the exercise effect from the total response to determine the lung function change due to SO_2 allows for a clearer picture of the specific effects of the pollutant. However, for this analysis, the symptom and medication use categories of response intrinsically reflect the combined effect of SO_2 and exercise. For consistency with these indicators, coupled with the fact that the subject actually experiences the total change in lung function, not just the SO_2-specific change (thus total lung function change correlates better with severity of symptoms and medication use post-exposure), the total change in lung function was used. A sense of the magnitude of the exercise effects can be obtained from the prevalence of responses given for exercise alone. To compare the present results with results using only the lung function change attributable to SO_2, see Smith (1994). More information about each category of response can be obtained in Sections 3, 4, and 5 of this memorandum and from the spreadsheets in Smith (1994).

One point distinctly stands out from Table 1: 10-min exposure of moderately exercising asthmatic subjects (42 to 50 L/min) to 0.6 ppm to 1.0 ppm SO_2 clearly causes substantially more subjects to experience responses of greater than mild severity than does exercise alone. Such an observation is not wholly unexpected, given that the responses to the SO_2 exposure represent the sum of exercise and SO_2 effects, but the differences can be dramatic; that is, in each study a sizeable number of subjects after exercise in 0.6 to 1.0 ppm SO_2 experienced responses that none of the subjects experienced from exercise alone at the same ventilation rate.

The results are fairly consistent when compared across studies. The most recent single exposure studies of moderate (1990) and mild (1988) asthmatic subjects at the highest ventilation rate ($\sim$50 L/min, compared to the 42 to 44 L/min for the 1985 and 1987 studies) have the highest prevalence of responses exceeding mild severity. This is likely due in part

to the higher rates of ventilation, as indicated by the greater prevalence of responses from exercise alone, plus the fact subjects in these studies were given complete discretion over medication use post-exposure, thus being more likely to medicate post-exposure, a response automatically scored as a "severe effect." The largest differences are between the 1988 and 1987 studies of mild asthmatic subjects, making it important to consider the possible effects of including 9 out of 20 subjects using medication fairly regularly (at least once a week) in the 1988 group. Five of the 1988 subjects taking medication comprised the most sensitive subjects in the group in terms of lung function responses to SO_2. These subjects also accounted for the bulk of severe symptoms reported (although one non-medication-using subject had severe symptoms as well, and several had pronounced lung function changes, especially when changes due to SO_2 alone were considered).

The 1985 study of mild asthmatic subjects exposed to 1.0 ppm shows a prevalence of responses that fall between the 1988 mild group and 1987 mild group. One might expect a study at 1.0 ppm to show greater responses than studies at 0.6 ppm because of the increased oral dose rate (approximately 30% greater [EPA, 1986b, p. A-2]). Symptom prevalence for this study may be somewhat reduced by the fact that recording of symptoms was not given much emphasis for the 1985 study, with symptoms being recorded only after all lung function testing was complete (Dr. Don Horstman, personal communication). This may explain why no subject in the Roger et al., 1985 study reported any wheeze symptoms, while subjects in the Linn et al. studies often reported wheeze symptoms. A more recent study from the same laboratory (Horstman et al., 1988) found more prevalent and pronounced symptom responses, including wheeze symptoms, among a second group of mild asthmatics, even after correction for the fact that this study involved only subjects who experienced at least a 100% increase in SRaw due to SO_2 at 1 ppm (Smith, 1994). However, SRaw responses are also lower for the 1985 subjects compared to the 1987 and 1988 mild asthmatic subjects at 0.6 ppm SO_2 (Table B-1). Possible explanations for this difference include simple variation between studies, potential differences in the sensitivity of asthmatic individuals from the two geographic areas in which the studies were conducted (Raleigh-Durham and Los Angeles), and special caution in choosing asthmatic subjects for the 1985 study (see Smith, 1994).

Within the expected variation between studies, the four most recent studies are relatively consistent in the effects observed. However, the earliest study (Roger et al., 1985) does not show greater responses even though it was conducted at a higher concentration (1.0 ppm versus 0.6 ppm), possibly due to one of the reasons discussed above.

The next three sections provide further information on the separate distributions of lung function, symptoms, and medication use responses that, when combined, form the basis of the assessment of responses in Table 1. In addition, information is included that provides a context that allows the severity of these responses to be judged in relation to the responses typically experienced for these asthmatic subjects.

Distribution of Lung Function Changes

Table 2 shows the distribution of lung function changes, as indicated by the 50th and 75th percentile responses, observed at 0.6 and 1.0 ppm. The 50th percentile response designates the minimum change in lung function seen by the most sensitive 50% of the subject group, while the 75th percentile response designates the minimum change in lung function experienced by the most sensitive 25% of the group. Results for 0.6 ppm are given as changes in FEV_1 for the Linn et al. studies (the top two rows). For the Roger et al., 1985 study at 1.0 ppm (bottom row), only SRaw values are available and are given in Table 1. The changes for mild asthmatic subjects at 0.6 ppm are the average of the results from the 1987 and 1988 mild asthmatic groups, while the changes for moderate asthmatic subjects are an average of results from the 1987 and 1990 moderate asthmatic groups. Results for each study individually are given in Smith (1994).

The values for typical daily change (in FEV_1) for mild and moderate asthmatic individuals were obtained from a field study of Los Angeles asthmatic individuals (Linn, 1991). The study included a substantial number of the subjects in the 1987, 1988, and 1990 clinical studies, but was not restricted to these subjects.

Table 2 shows that sensitivity to SO_2 varies considerably across mild and moderate asthmatic subjects, as indicated by the noticeably larger responses for the most sensitive 25% of subjects versus the most sensitive 50%. SO_2 at these concentrations (0.6 and 1.0 ppm) produces some rather marked changes in lung function, at least for the most sensitive 25% of the subjects. Furthermore, since the 50th and 75th percentile results represent the minimum

Table 2. LUNG FUNCTION CHANGES IN RESPONSE TO 0.6 AND 1 PPM SO2 COMPARED TO TYPICAL CIRCADIAN CHANGE AND RESPONSES TO EXERCISE

Asthmatic Severity	Daily Change	Percentile of Test Subjects	Moderate Exercise	SO_2 Change (corrected for exc.)	Total Change
MILD (87+88 Avg) FEV_1 n=16;20	-8%	50th	-2%	-21%	-21%
		75th	-7%	-26%	-30%
MODERATE (87+90 Avg) FEV_1 n=24;21	-13%	50th	-8%	-10%	-25%
		75th	-14%	-31%	-39%
MILD (1985) SR_{aw} n=28	?	50th	+46%	+118%	+164%
		75th	+59%	+230%	+249%

Changes due to SO_2, exercise, and total change figures for the Mild (87+88) and Moderate (87+90) groups are averages of the 50th and 75th percentile values for the two studies at 0.6 ppm involving that classification of asthmatic subject. The 1985 Mild group was exposed to 1.0 ppm SO_2. Changes are determined by subtracting the changes seen due to exercise alone from the total change in lung function seen after SO_2 exposure at exercise for each subject: SO_2 Chg = Total - Exercise. However, the 50th and 75th percentile Exercise and SO_2 changes do not sum to the 50th and 75th percentile of total change, because percentiles are determined by separate ranking of exercise changes, SO_2-attributable changes (Total-Exercise), and Total changes. Thus, different subjects are accounting for the 75th percentile change in exercise versus the 75th percentile change due to SO_2. All lung function figures are changes in FEV_1, except for the 1985 mild asthmatic subjects, for whom the changes are in SR_{aw}.

lung function change for that fraction of subjects, every individual in that fraction experienced a response equaling or exceeding that minimum change. Comparing across a given percentile, the effect of exercise is much less than the total change or change attributable to SO_2[1] seen in response to 0.6 ppm for both groups, except for the 50th percentile SO_2 change for moderate asthmatic subjects, which is only slightly larger than the 50th percentile exercise response.

The average circadian change is also substantially smaller than the total and SO_2 changes except for the 50th percentile SO_2 change for the moderate asthmatic subjects, which

[1]In this memo, the term "change attributable to SO_2" or "due to SO_2" is used to indicate the amount of change determined by correcting total changes in lung function in response to SO_2 for the effects of exercise (Total—Exercise). The difference is the "change attributable to SO_2." "Total Change," "Total FEV_1," or "Total SR_{aw}" are used when the total change in lung function, representing both the change due to exercise and the change due to SO_2, is given.

is slightly smaller than the average circadian change. For the 1985 study, no direct information on circadian changes in SRaw is available, but given the magnitude of changes seen in the Linn et al. mild subjects and the information presented in the CDA Supplement (EPA, 1994, p. 4), it seems the 50th and 75th percentile changes are well in excess of the typical daily change for these subjects.

It is possible that those who respond the most to SO_2 also have the largest circadian changes, thus the circadian changes of the 50th or 75th percentile responders may not be captured by the average circadian changes used for the group. To provide some insight into this question, the circadian changes for those subjects common to both the field study and the chamber studies were compared to the changes post-SO_2 exposure. Fifty-nine percent of the subjects had FEV_1 changes attributable to SO_2 in excess of their individual circadian change, while 74% had total changes after SO_2 exposure in excess of their circadian change. The proportions increase substantially (to 74% and 89%, respectively) when only those subjects showing at least a moderate FEV_1 response attributable to SO_2 were examined. (Of course, one would expect the proportion to increase. A focus on those subjects responding to SO_2 can be considered appropriate because it is arguably more relevant than determining whether small changes in response to SO_2 exceed or do not exceed circadian change).

These findings are limited by the fact that the subset of subjects for whom circadian information is available is not a representative sample of all of the Linn et al. subjects (Smith, 1994). Nevertheless, the findings do provide support for the findings of Table 2 that a large proportion of subjects, especially those responsive to SO_2, have changes that exceed their circadian change.

A related approach to examining the magnitude of lung function changes is to examine the change in percent predicted lung function (FEV_1). An analysis of the 1987 subjects revealed that, after exposure to 0.6 ppm SO_2 at exercise, the lung function of 54% of the moderate asthmatic subjects and one quarter of the mild asthmatic subjects was less than 50% of their predicted FEV_1. (After exercise alone, 17% of the moderate asthmatic subjects and 0% of the mild asthmatic subjects experienced predicted FEV_1 of less than 50%). Some of the moderate asthmatic subjects had even more pronounced changes, with the lung function of 29% of the subjects being less than 40% of their predicted FEV_1 after SO_2 exposure (versus 8% after exercise alone), and 8% had less than 30% of predicted FEV_1 (versus 0%

at exercise alone). For the moderate asthmatics especially, it should be noted that a number of subjects began the exposure with a somewhat reduced predicted FEV_1 (half the moderate subjects had less than 70% of their predicted lung function prior to exposure, with one subject having a starting predicted lung function of slightly below 50%).

Symptoms

Table 3 compares the proportion of each subject group at 0.6 ppm reporting symptoms of moderate severity or worse in response to the chamber exposures to 0.6 ppm SO_2 or exercise alone versus the frequency (the proportion of the weeks[2]) that subject group reported symptoms of moderate or greater severity at all other times during the study period (8-9 weeks). The information on frequency of weeks with symptoms was obtained from information available on symptoms for the day and week post-exposure for each subject in the 1987, 1988, and 1990 studies. This information was made available in the form of maximum symptoms experienced during the day and week post-exposure. Although it would be even more desirable to specifically determine the number of days with symptoms of a given severity, the information provided only reports whether the maximum symptom in the week achieved a certain level. Thus it is impossible to determine the number of days within the week those symptoms were experienced. Although these subjects are being exposed to varying concentrations of SO_2 at regular times during the 8-9 week experimental period, such exposure is viewed as being unlikely to confound these reports of typical symptoms, since Linn et al. (1987) reported that, using some of this data, there was little or no noticeable effect of SO_2 on symptoms in the week post-exposure.

The frequency of symptoms in response to 0.6 ppm SO_2 shown in Table 3 indicates that the lung function changes presented in Table 2 do not go unperceived by the subjects. As pointed out in the CDA Supplement (p. 27), perceived symptoms resulting from a given lung function change can vary markedly from subject to subject, thus it is possible to have symptoms without a large change in lung function. However, by comparing the figures from

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[2]To be precise, the "percentage of weeks with symptoms" (of a given severity) referred to in this section actually designates the percentage of subject-weeks, i.e., when 32% of the weeks are designated as having maximum symptoms of moderate or worse, this means that when all the weeks with available data are pooled, 32% of these subject-weeks have maximum symptoms of moderate or worse. Some subjects have higher individual rates of weeks with maximum symptoms and some have lower.

Table 3. COMPARISON OF SYMPTOMS POST-EXPOSURE WITH SYMPTOMS DURING STUDY PERIOD

	% of weeks MAX SYMP = MOD or worse	% of Subjects SO_2 SYMP = MOD or worse	% of Subjects EXC SYMP = MOD or worse
1990 Moderate Asthmatic Subjects Normal Medication	32%	62%	19%
1987 Moderate Asthmatic Subjects	40%	33%	4%
1988 Mild Asthmatic Subjects	17%	40%	10%
1987 Mild Asthmatic Subjects	12%	13%	6%

Table 3 on the incidence of moderate symptoms post-SO_2 exposure with the proportion of subjects in Table 1 experiencing severe lung function changes coupled with moderate symptoms post-SO_2, one can determine that most (but not all) of the subjects are experiencing the moderate or worse symptoms after SO_2 exposure in conjunction with greater than a 20% decrease in FEV_1.

Table 3 shows that the subjects of the 1988 and 1990 studies experienced the highest prevalence of symptoms after SO_2 exposure, with roughly half of the subjects (40 to 62%) reporting at least moderate symptoms. A proportion of these asthmatic subjects (10 to 19%) also experienced such symptoms simply from exercise alone. However, these asthmatic groups did not experience symptoms of this severity with great frequency during the study period. For 68% of the weeks the moderate asthmatic subjects of the 1990 study reported no worse than mild symptoms (i.e., approximately 43 or more of the 63 days of the study). The 1988 mild asthmatic subjects reported no worse than mild symptoms for approximately 83% of the weeks, or approximately 52 or more of the 63 days in this study. Furthermore, the actual prevalence in terms of days with these symptoms may be substantially lower, since the number of days with symptoms within any week that these symptoms were reported is unknown (they may be reported only 1 out of 7 days, for instance).

In addition, although not shown in Table 3, 19% of the 1990 moderate asthmatic subjects and 30% of the 1988 mild asthmatic subjects experienced severe symptoms in response to 0.6 ppm SO_2, a response even less likely to be equaled during the study period (severe symptoms being reported for only 9% of the weeks for the 1990 moderate asthmatic subjects and only 5% of the weeks for the 1988 mild asthmatic subjects).

In the 1987 studies at slightly lower ventilation (44 L/min), somewhat fewer subjects (approximately 13 to 33%) reported moderate or worse symptoms. The moderate asthmatic subjects reported a greater frequency of moderate or worse symptoms (40%) than in the more recent studies (although this frequency was still considerably less than half the weeks). The 1987 mild asthmatic subjects had a very low frequency of moderate or worse symptoms (12% of weeks), although a relatively small percentage of subjects experienced moderate or worse symptoms in response to SO_2 (13%). Very few 1987 subjects (4 to 6%) reported moderate or worse symptoms after exercise at this ventilation.

It should be pointed out that the data presented above on frequency of symptoms is unavoidably less precise than the data taken in the clinical setting. Although the Linn et al. studies did feature daily logging of symptoms (later collated into weekly statistics), a recall problem still exists. Subjects may rate symptoms higher when queried immediately after exposure, as they were after SO_2 or exercise exposures, than when recalling symptoms over a full day.

The use of medication may also complicate comparisons of symptoms experienced during the study period to symptoms during exposure. Some of the moderate asthmatic or 1988 mild asthmatic subjects who used medication may have medicated themselves to ameliorate symptoms, and thus the symptom rating may tend to be lower than if they had not used a bronchodilator in addition to their usual medication.

However, a related approach that may provide a separate, rough estimate of the general prevalence of symptomatic responses also indicates that pronounced symptom responses for these asthmatic individuals may be infrequent. The Linn et al. subjects kept records of the occurrence of what they perceived to be asthma attacks. The frequency of these perceived asthma attacks during the 9-week 1988 and 1990 studies is given in Table 4 below.

As can be seen, a majority of both moderate and mild asthmatic subjects experienced episodes that they perceived as asthma attacks during the study period, but most of these

Table 4. FREQUENCY OF ASTHMA ATTACKS DURING STUDY PERIOD (9 WEEKS)

	1990 Moderate Asthmatics	1988 Mild Asthmatics
HAD ATTACKS	81%	65%
HAD MORE THAN 1 ATTACK PER WEEK	38%	15%
HAD MORE THAN 5 ATTACKS PER WEEK	14%	0

subjects did not experience attacks as frequently as even once a week. Some moderate asthmatic subjects did experience 5 or more attacks a week. This comparison could also be confounded by the use of medication by medication-using asthmatic subjects allowing them to avert altogether an episode they might otherwise perceive as an asthma attack.

Perception of what constitutes an "asthma attack" would be likely to vary considerably from subject to subject. Whether these asthmatics would rate their response to SO_2 as an asthma attack is also unclear, although at least some subjects recorded events of very brief duration as asthma attacks.

Because of these caveats, caution must be exercised, but the available information on perceived asthma attacks is consistent with the data on symptom frequency. This data indicates that the symptoms experienced by those subjects experiencing substantial symptoms after 0.6 ppm SO_2 are generally worse than the symptoms they otherwise typically experience. For most of these adult asthmatic subjects, including many of the more moderate subjects, asthmatic episodes may be an infrequent experience.

Medication Usage

Table 5 presents the prevalence of medication (bronchodilator) use post-exposure in the 1988 and 1990 studies. For all subjects, medication use included an inhaled bronchodilator except for one 1990 subject who took the bronchodilator Alupent in tablet rather than inhaled form. The 1987 moderate and mild groups also had a very few subjects who took medication while in the chamber. Medication use by the 1987 subjects was not considered for the assessment of responses in Table 1, but is indicated on spreadsheets in Smith (1994).

Table 5. USE OF BRONCHODILATORS POST-EXPOSURE

Study	SO_2	EXC
1990 Moderate Asthmatics	71%	29%
1988 Mild Asthmatics	40%	10%

Medication use has previously been considered as a fairly severe response to an exposure to an environmental pollutant. The 1988 and 1990 Linn et al. studies, in which subjects were given complete discretion over the decision whether or not they needed medications, show much higher prevalence of medication use than did previous studies (e.g., see Table 8 in EPA, 1986a). Given the discretionary nature of medication use for these two Linn et al. studies, it would be interesting to determine how frequently these subjects use bronchodilators in response to other stimuli.

Unfortunately, direct information on medication use is only available for the 1987 study, not the 1988 or 1990 studies. This information indicates that less than one-third of the 1987 mild asthmatic subjects used inhaled bronchodilators at all during the 8 weeks of the study, and none of them used inhaled bronchodilators as often as once a week. Assessing the medication use of the moderate asthmatic subjects was more difficult. Occasionally multiple types of inhaled bronchodilators were used by these subjects in a week, creating ambiguity over whether these medications were taken together or separately, and in some instances it was ambiguous whether inhalation was the means by which a drug was being administered (e.g., Alupent spray versus Alupent tablets). However, it appears that approximately 85% of the moderate asthmatic subjects in the 1987 study took inhaled bronchodilators at least once a week, and slightly less than half of the moderate asthmatic subjects used inhaled bronchodilators at least five times a week, on average. About one-quarter of the moderate asthmatic subjects may use inhaled bronchodilators very frequently (apparently greater than 15 times a week).

The large dichotomy in medication use between the mild and moderate asthmatic subjects is likely a result of the fact that, for this study, classification as being a mild or moderate asthmatic subject was determined to a large extent on the basis of medication use

(Hackney et al., 1987), with those subjects not using medications being classified as mild and those using medication being classified as moderate asthmatic individuals.

Of particular interest would be the medication use patterns of the 1988 mild subjects who used medication regularly, because the 1988 subjects in general, and a subset of these medication-using subjects in particular, showed a considerably pronounced response to SO_2. While direct information is not available, 6 of the 9 subjects using medication regularly were subjects in the 1987 study and had logged their medication use then. Although medication use may vary over time and season, the available data from the previous year indicated that 4 of these 6 subjects used inhaled bronchodilators approximately once per week on average. Included in this group of infrequent medication users is one of the five most responsive subjects of the study. However, two of the five most responsive subjects in the 1988 study used inhaled bronchodilators approximately 4 and 10 times a week on average during the 1987 study period. The other two responsive medication-using subjects were not part of the 1987 study, so no inferences about their medication use can be drawn. For the 1990 study, less information is available, but the three subjects in this study who participated in the 1987 study all used bronchodilators with great frequency (approximately 15 or more times per week).

Medication use by subjects in these studies is of interest for several reasons. Consistent with the symptoms data, medication use post-exposure clearly shows that subjects are perceiving the effects of SO_2 to which they are being exposed. Such information on bronchodilator use also allows the probability of medication use prior to exercise to be roughly estimated. The available data on medication use suggests that few mild asthmatic individuals in these studies would have been expected to use a bronchodilator routinely before exercise. The 1987 asthmatic subjects reported infrequent use of bronchodilators, and the 1988 mild asthmatic subjects who used medications reported using them to relieve symptoms or in anticipation of respiratory stress (allergens or irritants), with few citing exercise specifically as a respiratory stress (Hackney et al., 1988a). Thus, it seems unlikely that a significant portion of these mild asthmatic individuals would routinely use bronchodilators prior to exercise in daily life.

Among the moderate asthmatic subjects, some of the 1987 moderate subjects (approximately 15%) used inhaled bronchodilators only infrequently during the study period

(<2 times per week on average). A few of these subjects responded markedly to SO_2. However, the large majority of moderate subjects used inhaled bronchodilators more frequently and about half used bronchodilators 5 or more times per week on average. The frequency with which these subjects would be expected to premedicate before exercise is uncertain, but seems likely that a sizeable percentage of these subjects frequently using bronchodilators would generally use medication prior to any planned, lengthy exercise.

Third, in contrast to the symptoms frequency and asthma attacks results, in which baseline responses similar to those seen with SO_2 are relatively infrequent, a substantial portion of medication-using asthmatic subjects used inhaled bronchodilators fairly frequently. This complicates assessment of the severity of medication use post-exposure. While for any individual subject, taking medication is clearly a more serious response than not taking medication (e.g., even though the 1990 moderate asthmatic subjects were prone to take medication post-exercise, more than twice as many took medication after SO_2 than after exercise alone), comparison across subjects is more difficult. Taking an inhaled bronchodilator may be a fairly atypical action for some subjects, and a fairly routine step for others. (This is one reason why an index of simply "Severe lung function + Moderate symptoms" was included in Table 1: comparisons across all the studies can be made without having to interpret the significance of the medication use data).

In addition, if the subjects that are administering bronchodilators frequently are doing so in response to environmental stimuli, then the bronchodilator use data suggests that this subset of asthmatic individuals are experiencing a number of responses that are at least sufficiently bothersome to motivate them to administer medication. However, the symptoms and asthma attack data for these subjects in general suggest that significant episodes may be infrequent. The resolution between these different indicators of typical asthmatic health for the subjects in these studies remains uncertain.

Diminished Workload

Another indicator traditionally used to judge the effects of a pollutant is the degree to which subjects in clinical trials have felt compelled to diminish their workload or terminate exposure to a pollutant. Such changes in activity are not expressly considered in the criteria

used to judge the effects of SO_2, but have been used to evaluate the effects of other pollutants such as ozone (Table VII-5 in EPA, 1989).

Despite the fact that clinical exposures to SO_2 in these studies are fairly brief (one or several 10-min periods at exercise), a small number (2-3) of subjects in every subject group except the 1987 mild asthmatic subjects felt compelled to alter their activity or terminate exposure. The fraction of subjects diminishing workload or terminating exposure is given below in Table 6.

Table 6. FRACTION OF SUBJECTS REQUIRING DIMINISHED WORKLOAD OR TERMINATING EXPOSURE IN RESPONSE TO 0.6 OR 1.0 PPM SO_2 EXPOSURE*

	SO_2	EXC
1990 Mod Asthmatics (Norm Meds)	9.5%	0
1988 Mild Asthmatics	15%	0
1987 Mod Asthmatics	12.5%	0
1987 Mild Asthmatics	0%	0
1985 Mild Asthmatics	7% term. exp. by 1.0 ppm	0

*All results given for 0.6 ppm except the 1985 asthmatic subjects at 1.0 ppm.

In the multiple exposure studies (1987 moderate and 1985 mild asthmatic subjects) at slightly lower ventilation rates, however, all subjects except 1 (4%) moderate asthmatic individual were able to complete the first 10-min exposure without reducing workload or terminating exposure. The percentages given for those two groups indicate the number of subjects who had to alter activity or terminate exposure during the first, second, or third exercise period. In general, protocols for these studies were not designed to elicit changes in workload or termination of exposure, and such changes were probably actively discouraged by the investigators conducting the studies, since changes in activity and ventilation rate complicate the assessment of the effects of SO_2 at a given ventilation rate.

Conclusions

Several conclusions can be reached:

1. When responses of asthmatic subjects are assessed relative to the cutpoints given in Table 8 of the CDA Supplement, a much higher percentage of subjects exposed to 0.6 to 1.0 ppm SO_2 while at moderate exercise experience responses of moderate or greater severity than while exercising in clean air alone.

2. After correction for the effect of exercise, the changes in lung function due to SO_2 in a sizeable subset of asthmatic individuals (at least 25% for moderate asthmatic subjects and 50% for mild asthmatic subjects) at 0.6 ppm are considerably larger than the effects of exercise alone. These changes in response to SO_2 are also well in excess of average circadian change for mild or moderate asthmatic persons as a group. In addition, a subject-by-subject comparison indicates that for most subjects showing at least a moderate FEV_1 response (attributable to SO_2 alone), this response exceeds their average circadian change.

3. The total FEV_1 decrease after SO_2 exposure for the most responsive 25% of mild and moderate asthmatic subjects equals or exceeds 30%.

4. Calculations of percent predicted FEV_1 indicate that slightly more than half of the 1987 moderate asthmatic subjects and one quarter of the 1987 mild asthmatic subjects have an FEV_1 that is less than 50% of predicted after 0.6 ppm SO_2 exposure. None of the mild asthmatic subjects and a smaller percentage (17%) of the moderate asthmatic subjects had such a response after exercise alone, although it should be noted that, among moderate asthmatics, FEV_1 may be significantly less than predicted even prior to exposure.

5. Moderate symptoms are much more prevalent after 0.6 ppm SO_2 exposure at exercise than after exercise alone. The prevalence of these symptoms shows that subjects are perceiving the change in lung function caused by SO_2.

6. During the majority of the weeks for each of the Linn et al. studies, subjects on average did not experience even one day of moderate symptoms. One reservation is that medication-using subjects may be medicating in a manner to diminish their symptomatic response. The relatively low incidence of reported asthma attacks also suggests that asthmatic episodes are relatively infrequent for these subjects. However, data on bronchodilator use suggest that, for at least some moderate asthmatic subjects, asthmatic episodes may be a routine occurrence. This possible contradiction is currently unresolved.

7. Medication use is more prevalent after 0.6 ppm SO_2 exposure than exercise alone, for both mild and moderate asthmatic subjects. Such medication use also indicates subjects are perceiving their change in lung function caused by SO_2.

8. For most or all of the mild asthmatic subjects in the Linn et al. studies, bronchodilator use prior to exercise appears to be rare. For the moderate asthmatic subjects, approximately three-quarters took inhaled bronchodilators at least once a week, and one-half took bronchodilators at least 5 times a week, with some subjects taking bronchodilators considerably more frequently. Thus many of the moderate asthmatic individuals might be likely to medicate prior to engaging in planned exercise.

9. Some subjects are unable to maintain their assigned workload, even during a 10-min exposure to 0.6 ppm SO_2.

In summary, it appears that SO_2 concentrations of 0.6 ppm or greater cause lung function changes in a substantial proportion of subjects which exceed their typical circadian variation or response to moderate exercise. A greater proportion of subjects also reported symptoms (moderate or worse) in response to 0.6 ppm SO_2 than from exercise alone, and, for many of these subjects, these SO_2-induced symptoms may exceed the symptoms that they routinely experience. More subjects also took bronchodilators after SO_2 exposure than after exercise alone; however, some moderate asthmatic subjects may routinely administer bronchodilators. Finally, in several of the studies, some subjects diminished workload or terminated exposure in response to exercise plus SO_2 but not in response to exercise alone.

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