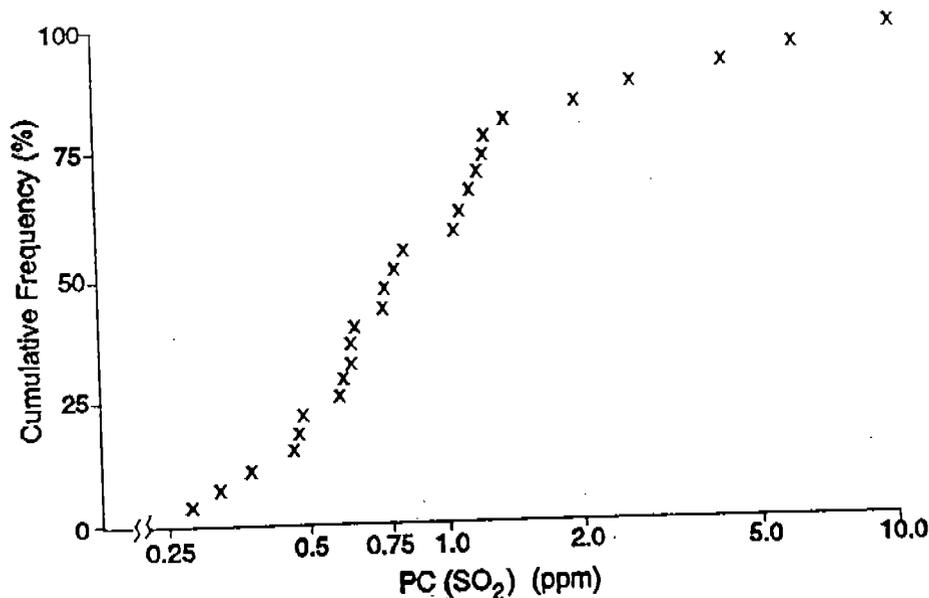


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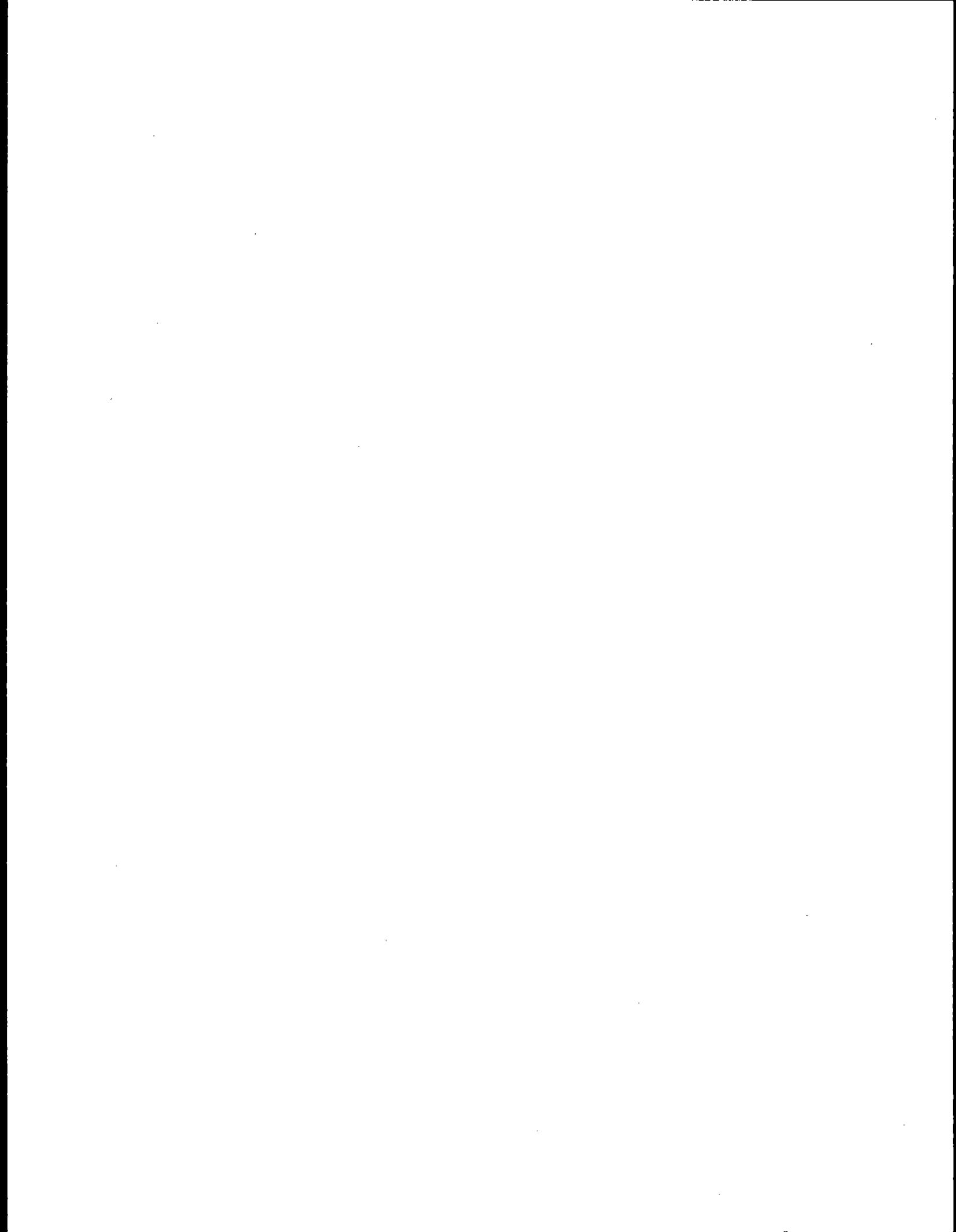
# Review of the National Ambient Air Quality Standards for Sulfur Oxides: Assessment of Scientific and Technical Information

## Supplement to the 1986 OAQPS Staff Paper Addendum

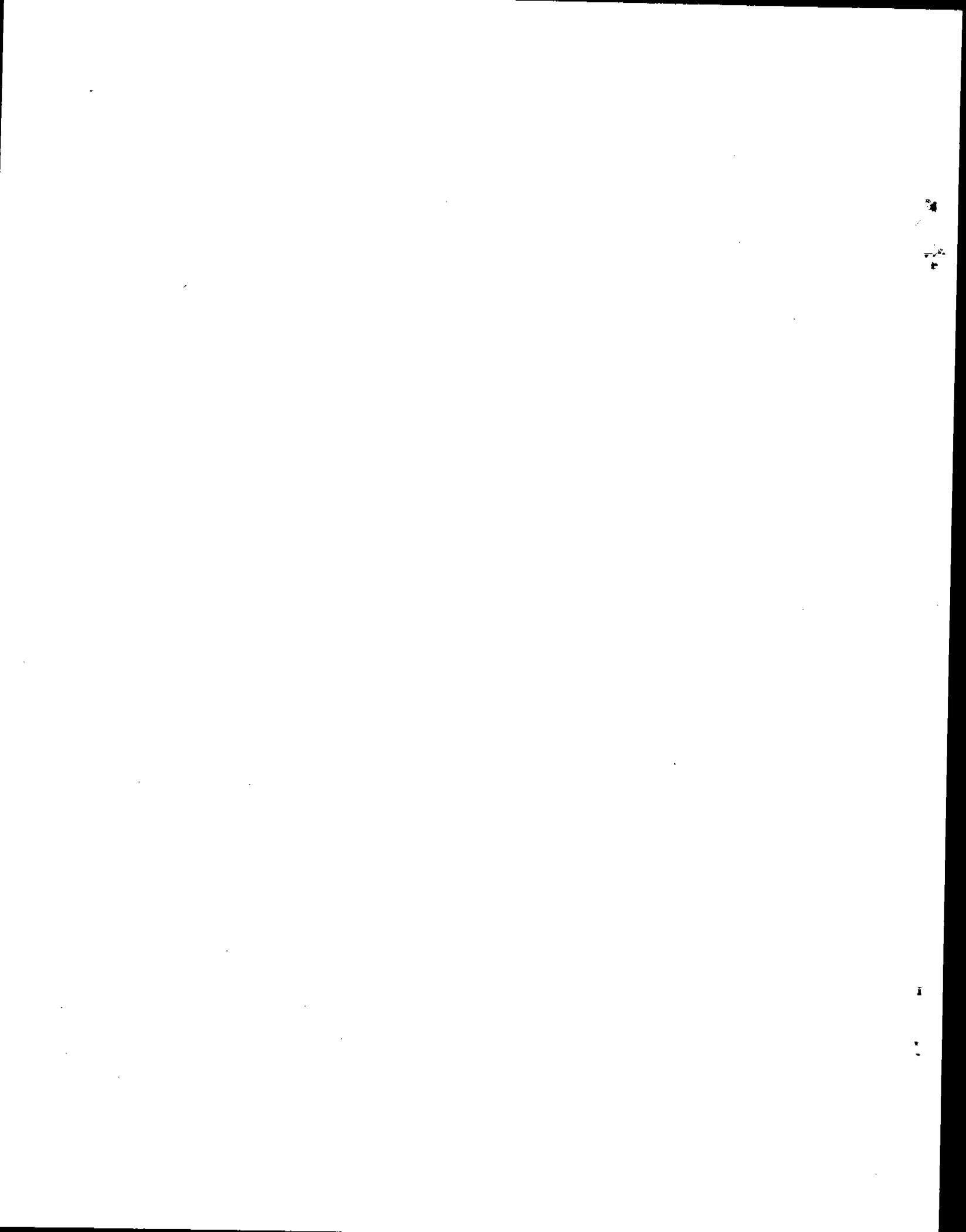


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The cover illustration shows the distribution of airway sensitivity to  $\text{SO}_2$  among mild asthmatics at moderate exercise (Horstman et al., 1986).  $\text{PC}(\text{SO}_2)$  represents the concentration of  $\text{SO}_2$  that, after correction for exercise ( $V_e = 42 \text{ l/min}$ ), resulted in a 100 percent increase in  $\text{S}_{\text{Raw}}$ . Cumulative percentage of subjects is plotted as a function of  $\text{PC}(\text{SO}_2)$  and each data point represents  $\text{PC}(\text{SO}_2)$  for an individual subject. These data show substantial variability in sensitivity to  $\text{SO}_2$  among mild asthmatic volunteers.



## Acknowledgments

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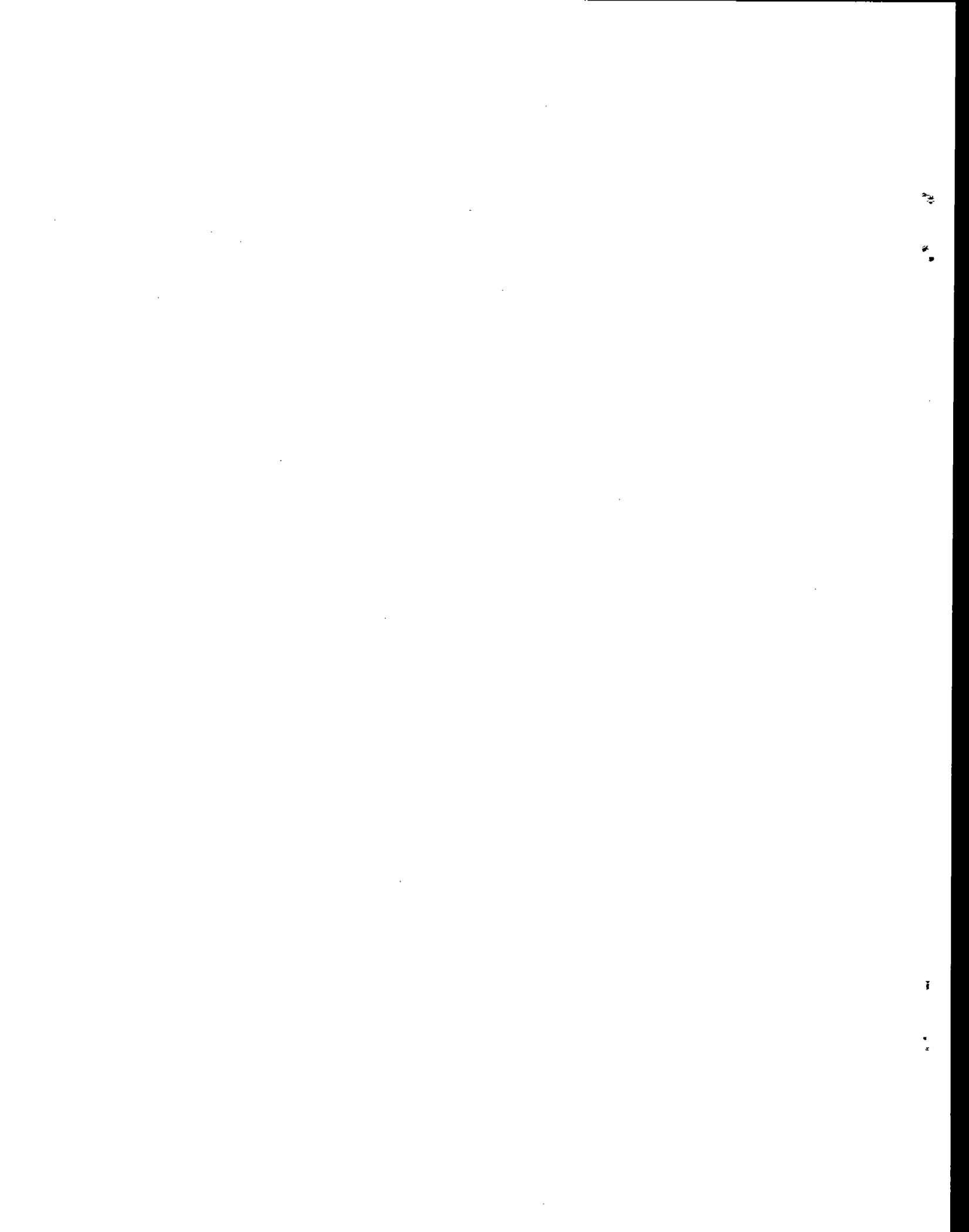
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REVIEW OF THE NATIONAL AMBIENT AIR QUALITY STANDARDS FOR SULFUR  
OXIDES: UPDATED ASSESSMENT OF SCIENTIFIC AND TECHNICAL  
INFORMATION

SUPPLEMENT TO THE 1986 OAQPS STAFF PAPER ADDENDUM

I. INTRODUCTION

A. Purpose

This paper presents a summary of the evaluation and interpretation of key new studies on the health effects associated with short-term sulfur dioxide (SO<sub>2</sub>) exposures examined in the draft Environmental Protection Agency (EPA) document, 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 Asthmatics (EPA, 1994) and represents an update of similar material in the 1986 sulfur oxides (SO<sub>x</sub>) staff paper addendum (EPA, 1986a). Because the recently available health effects information on SO<sub>2</sub> is related to short-term (5- to 10-minute) exposures, this paper also updates available information on the occurrence of short-term (5-minute) peaks of SO<sub>2</sub> in the ambient air and on the likelihood that the at-risk population will be exposed.

This staff paper supplement is intended to help bridge the gap between the scientific review of recent health effects information contained in the 1994 SO<sub>2</sub> criteria document addendum supplement (subsequently referred to as "CD supplement" or "CDS," EPA, 1994) and the judgments required of the Administrator in determining whether new regulatory initiatives are needed to

provide increased protection to asthmatic individuals whose health could be compromised if exposed to high 5- to 10-minute peak SO<sub>2</sub> levels. Factors relevant to this evaluation, as well as staff conclusions and recommendations on alternative regulatory approaches are presented in this paper.

B. Background

1. Legislative Requirements

Two sections of the Act govern the establishment and revision of national ambient air quality standards (NAAQS). Section 108 (42 U.S.C. 7408) directs the Administrator to identify pollutants which "may reasonably be anticipated to endanger public health and welfare" and to issue air quality criteria for them. These air quality criteria are to "accurately reflect the latest scientific knowledge useful in indicating the kind and extent of all identifiable effects on public health or welfare which may be expected from the presence of [a] pollutant in the ambient air . . ."

Section 109 (42 U.S.C. 7409) directs the Administrator to propose and promulgate "primary" and "secondary" NAAQS for pollutants identified under section 108. Section 109(b)(1) defines a primary standard as one "the attainment and maintenance of which, in the judgment of the Administrator, based on the criteria and allowing an adequate margin of safety, [is]

requisite to protect the public health."<sup>1</sup> A secondary standard, as defined in section 109(b)(2), must "specify a level of air quality the attainment and maintenance of which, in the judgment of the Administrator, based on [the] criteria, is requisite to protect the public welfare from any known or anticipated adverse effects associated with the presence of [the] pollutant in the ambient air." Welfare effects as defined in section 302(h) [42 U.S.C. 7602(h)] include, but are not limited to, "effects on soils, water, crops, vegetation, manmade materials, animals, wildlife, weather, visibility and climate, damage to and deterioration of property, and hazards to transportation, as well as effects on economic values and on personal comfort and well-being."

The U.S. Court of Appeals for the District of Columbia Circuit has held that the requirement for an adequate margin of safety for primary standards was intended to address uncertainties associated with inconclusive scientific and technical information available at the time of standard setting. It was also intended to provide a reasonable degree of protection against hazards that research has not yet identified. Lead Industries Association v. EPA, 647 F.2d 1130, 1154 (D.C. Cir.

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<sup>1</sup>The legislative history of section 109 indicates that a primary standard is to be set at "the maximum permissible ambient air level . . . which will protect the health of any [sensitive] group of the population," and that for this purpose "reference should be made to a representative sample of persons comprising the sensitive group rather than to a single person in such a group." S. Rep. No. 91-1196, 91st Cong., 2d Sess. 10 (1970). The legislative history specifically identifies bronchial asthmatics as a sensitive group to be protected. Id.

1980), cert. denied, 101 S. Ct. 621 (1980); American Petroleum Institute v. Costle, 665 F.2d 1176, 1177 (D.C. Cir. 1981), cert. denied, 102 S. Ct. 1737 (1982). Both kinds of uncertainties are components of the risk associated with pollution at levels below those at which human health effects can be said to occur with reasonable scientific certainty. Thus, by selecting primary standards that provide an adequate margin of safety, the Administrator is seeking not only to prevent pollution levels that have been demonstrated to be harmful but also to prevent lower pollutant levels that she finds may pose an unacceptable risk of harm, even if the risk is not precisely identified as to nature or degree.

In selecting a margin of safety, the EPA considers such factors as the nature and severity of the health effects involved, the size of the sensitive population(s) at risk, and the kind and degree of the uncertainties that must be addressed. Given that the "margin of safety" requirement, by definition, only comes into play where no conclusive showing of adverse effects exists, such factors, which involve unknown or only partially quantified risks, have their inherent limits as guides to action. The selection of any numerical value to provide an adequate margin of safety is a policy choice left specifically to the Administrator's judgment. Lead Industries Association v. EPA, supra, 647 F.2d at 1161-62.

Section 109(d)(1) of the Act requires that "not later than December 31, 1980, and at 5-year intervals thereafter, the

Administrator shall complete a thorough review of the criteria published under section 108 and the national ambient air quality standards . . . and shall make such revisions in such criteria and standards . . . as may be appropriate . . . ." Section 109(d)(2)(A) and (B) require that a scientific review committee be appointed and provide that the committee "shall complete a review of the criteria . . . and the national primary and secondary ambient air quality standards . . . and shall recommend to the Administrator any . . . revisions of existing criteria and standards as may be appropriate . . . ."

## 2. Existing Sulfur Oxides Standards and Review to Date

The current primary standards for  $\text{SO}_x$ , established in 1971, are 80 micrograms per cubic meter ( $\mu\text{g}/\text{m}^3$ ) [0.03 parts per million (ppm)] annual arithmetic mean, and 365  $\mu\text{g}/\text{m}^3$  (0.14 ppm), maximum 24-hour concentration not to be exceeded more than once per year. The current secondary standard for  $\text{SO}_x$  (to protect public welfare) is 1,300  $\mu\text{g}/\text{m}^3$  (0.5 ppm), maximum 3-hour concentration, not to be exceeded more than once per year. For both primary and secondary standards,  $\text{SO}_x$  are measured as  $\text{SO}_2$ . Thus,  $\text{SO}_2$  is the current indicator for the  $\text{SO}_x$  standards.

Review of the original  $\text{SO}_2$  criteria and standards was initiated in 1978. The Clean Air Scientific Advisory Committee (CASAC) closed on the revised criteria document (which also addressed particulate matter) in January 1982. An addendum to the CD, which summarized recent controlled human studies on the health effects of  $\text{SO}_2$ , was issued the same year. A staff paper,

which identified critical issues and summarized the staff's interpretation of key studies, received verbal closure at a CASAC meeting in August 1982 and formal written closure in August 1983.

In 1986, in response to the publication in the scientific literature of a number of new studies on health effects of particulate matter and  $\text{SO}_2$ , a second addendum to the criteria document and a corresponding addendum to the  $\text{SO}_x$  staff paper were prepared. The CASAC sent the Administrator closure letters on the criteria document addendum, dated December 15, 1986, and on the staff paper addendum, dated February 19, 1987. In the closure letter on the staff paper addendum, the majority of the CASAC recommended consideration of a 1-hour standard in the range of 0.2 to 0.5 ppm  $\text{SO}_2$  to protect against 5-minute peaks of 0.4 to 1.0 ppm  $\text{SO}_2$ . The closure letter on the staff paper addendum is reprinted in Appendix A.

On April 26, 1988 (53 FR 14926), the EPA announced its proposed decision not to revise the existing primary and secondary  $\text{SO}_x$  standards (measured as  $\text{SO}_2$ ). In reaching the provisional conclusion that the current standards provide adequate protection against the health and welfare effects associated with  $\text{SO}_2$ , the EPA was particularly mindful of uncertainties in the available evidence concerning the possible need for a new 1-hour standard to protect against health effects associated with 5- to 10-minute  $\text{SO}_2$  exposures. Therefore, the EPA specifically requested broad public comment on the alternative of adding a new 1-hour primary standard of 0.4 ppm

and making related changes to the existing standards. The EPA's consideration of short-term health effects of SO<sub>2</sub> as well as its rationale for other proposed changes are set forth in the April 26, 1988 notice.

The EPA took final action on the secondary standard portion of the 1988 proposal on April 15, 1993. The rationale for the decision is presented in detail in the April 21, 1993 Federal Register notice that announced the decision (58 FR 21351).

With respect to the primary standards portion of the 1988 proposal, the EPA has entered into a consent decree that requires by November 1, 1994, either: 1) final action on the 1988 proposed decision not to revise the primary standards; or 2) reproposal. The EPA is to take final action on a reproposal 1 year after completion of the public comment period.

The principal question to be resolved with respect to the primary standards is whether a new short-term standard is needed to protect asthmatics at elevated ventilation levels from 5- to 10-minute peak SO<sub>2</sub> levels. During the comment period on the 1988 proposal, a number of issues were raised concerning the possible need for such a standard. These included: 1) the health significance of the responses reported in controlled human studies to 5- to 10-minute SO<sub>2</sub> exposures, particularly at levels below 0.75 ppm; 2) the possibility that moderate to severe asthmatics may experience greater responses than the primarily mild asthmatics studied to date; 3) whether asthmatics already medicated to protect against other environmental stimuli would

also be protected against SO<sub>2</sub> exposures; 4) whether a 1-hour standard based on a typical peak-to-mean ratio of 2 to 1 will provide appropriate protection from the full range of sources that have the potential to emit high peak SO<sub>2</sub> levels<sup>2</sup>; and 5) the adequacy of the exposure analysis, which focused only on asthmatics living near power plants.

In order to be better able to address these and other issues, the EPA concluded that the 1986 addendum to the criteria document and the associated SO<sub>2</sub> staff paper addendum should be updated to take into account more recent information.

### C. Approach

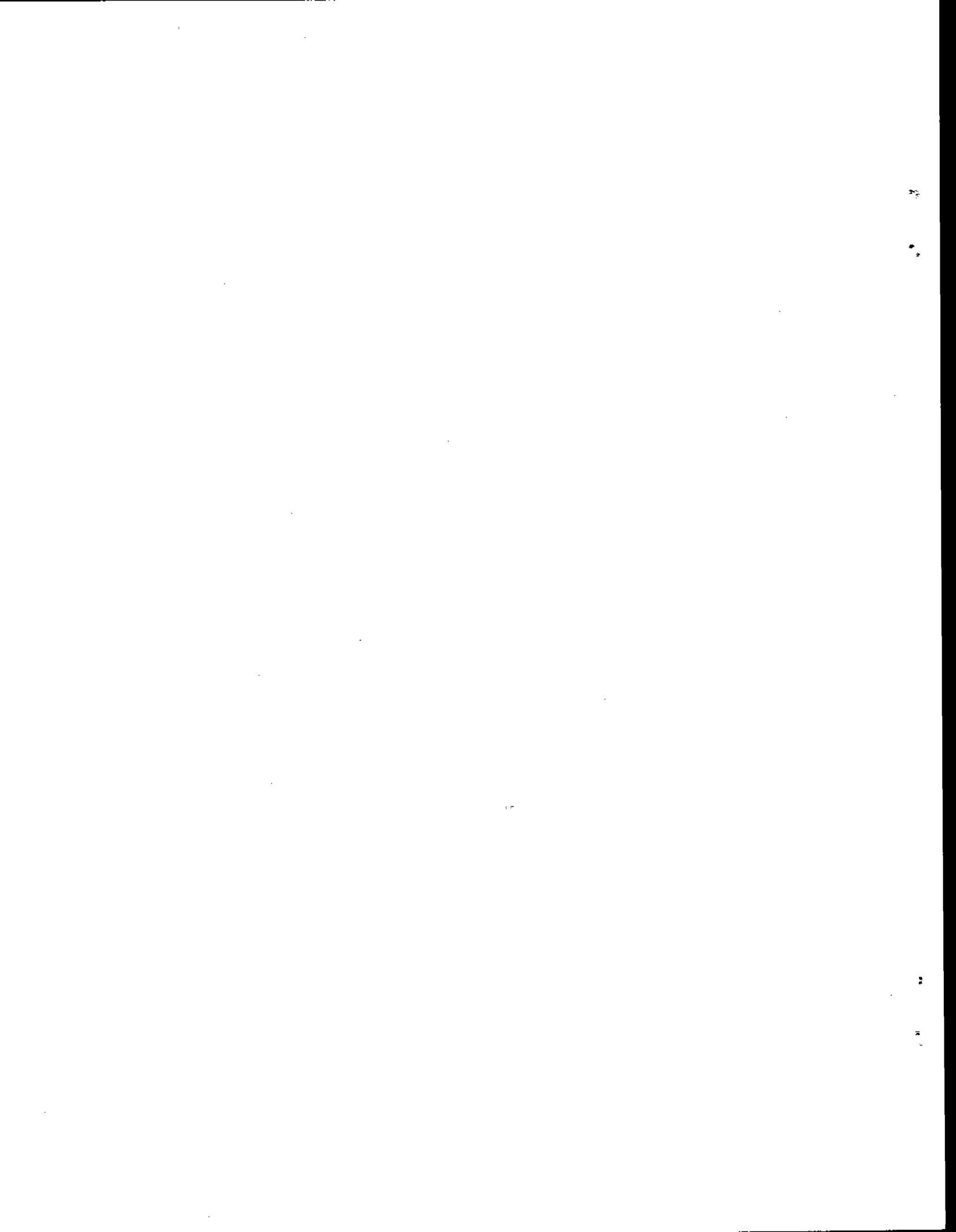
The approach in this paper is to draw from the criteria document supplement's (EPA, 1994) evaluation and interpretation of the newly available health effects information on short-term SO<sub>2</sub> exposures and to integrate that information with the available information on the occurrence of 5- to 10-minute peak SO<sub>2</sub> levels in the ambient air and associated estimates of potential exposures. Particular attention is drawn to judgments related to determining an appropriate regulatory response given the nature of the reported effects and the likelihood of exposure to short-term peak SO<sub>2</sub> levels. Previous staff conclusions

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<sup>2</sup>For present purposes, the peak-to-mean ratio of interest is the ratio of the maximum 5-minute concentration for an hour divided by the hourly average (thus a peak-to-mean ratio of 2 to 1 indicates for that hour the maximum 5-minute average was twice the concentration of the hourly average).

related to the existing primary standards or the secondary standard will not be addressed here.

Section II provides a concise summary of key findings presented in the criteria document supplement on health significance of the effects of brief, concentrated exposures to SO<sub>2</sub> on asthmatics at elevated ventilation. Emphasis is placed on those factors that should be considered in assessing the public health significance of the reported effects. Section III focuses on the available air quality and exposure information to support discussions on the possible need for new regulatory initiatives to address short-term peak levels of SO<sub>2</sub>. Drawing from the discussion in Sections II and III, Section IV identifies alternative regulatory options and those factors EPA staff believe should be considered in selecting among the alternatives.



## II. ASSESSMENT OF HEALTH EFFECTS

### A. Sensitive Population Groups

Based on the assessment in the criteria document supplement, the staff concludes that mild and moderate asthmatic children, adolescents, and adults that are physically active outdoors represent the population segments at most risk for acute SO<sub>2</sub> induced respiratory affects. Individuals with more severe asthmatic conditions have poor exercise tolerance and, therefore, are less likely to engage in sufficiently intense outdoor activity to achieve the requisite breathing rates for notable SO<sub>2</sub>-induced respiratory effects to occur (EPA, 1994, p. 48).

Healthy nonasthmatic individuals are essentially unaffected by acute exposures to SO<sub>2</sub> at concentrations below 2 ppm. It has been suggested that nonasthmatic atopic<sup>3</sup> individuals may be at increased risk (EPA, 1986a, pg. 59; 53 FR 14932, April 26, 1988). However, questions have been raised concerning whether the subjects referred to as atopics in one set of studies (e.g., Koenig et al., 1987; Koenig et al., 1988a,b) might be more appropriately considered very mild asthmatics. Another recent study (Linn et al., 1987), that compared the response of atopics and mild asthmatics, found that the atopic group was not

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<sup>3</sup> "Atopic" is a term used to indicate individuals, not diagnosed as asthmatics, with disorders manifested as hypersensitivity to environmental antigens. Examples include hay fever and other allergies. Approximately 8 percent of the U.S. population is estimated to be atopic. Some additional percentage of the population not diagnosed as atopic or asthmatic may also display hyperreactive airway responses to SO<sub>2</sub>.

particularly responsive to SO<sub>2</sub>. The difference in the incidence of bronchoconstriction in atopics between the different studies is most likely due to criteria used for diagnostic classification, rather than real population differences. As noted in the CDS (EPA, 1994, p. 52), there may be a significant number of undiagnosed asthmatics and a number of subjects without asthma who have exercise-induced bronchospasm. In the process of estimating the number of individuals who are likely to be affected by environmental SO<sub>2</sub> exposure, this uncertainty regarding the incidence of SO<sub>2</sub> sensitivity in the population should be considered.

#### B. Asthma

In assessing the significance of the SO<sub>2</sub>-induced respiratory effects in asthmatic individuals, it is important to have an understanding of asthma as a disease in order to place the findings from the controlled human exposure studies in perspective. 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.

As indicated in Table 2-1, there is a broad range of severity of asthma ranging from mild to severe.

Drawing from the discussion in the criteria document supplement, the key information about the disease is presented below:

- 1) About 10 million people or 4 percent of the population of the United States are estimated to have asthma (NIH, 1991). The true prevalence may be somewhat higher. Some researchers have estimated that 7 to 10 percent of the United States population may be asthmatic (Evans et al., 1987), because some individuals with mild asthma may be unaware that they have the disease and thus go unreported. The prevalence is higher among African-Americans, older (8- to 11- year-old) children, and urban residents (Schwartz et al., 1990).
- 2) Common symptoms include cough, wheezing, shortness of breath, chest tightness, and sputum production.
- 3) 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).
- 4) Daily variability in lung function measurements is a typical feature of asthma, with the poorest function (i.e., lowest forced expiratory volume in 1 second (FEV<sub>1</sub>) and highest specific airway resistance (SRaw) being experienced in the early morning hours and the

TABLE 2-1. CLASSIFICATION OF ASTHMA BY SEVERITY OF DISEASE<sup>a</sup>

Characteristics	Mild	Moderate	Severe
<b>A. Pretreatment</b>			
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 <sup>b</sup> <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 <sub>20</sub> >20 mg/mL. <sup>c</sup>	Methacholine PC <sub>20</sub> between 2 and 20 mg/mL.	Methacholine PC <sub>20</sub> <2 mg/mL.
<b>B. After optimal treatment is established</b>			
Response to and duration of therapy	Exacerbations respond to broncodilators without the use of systemic corticosteroids in 12-24 h. <b>Regular drug therapy not usually required</b> 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.

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

<sup>b</sup>Variability means the difference either between a morning and evening measure or among morning peak flow measurements each day for a week.

<sup>c</sup>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).

best function (i.e., highest FEV<sub>1</sub> and lowest SRaw) occurring in the mid-afternoon.

- 5) The degree of exercise tolerance varies with the severity of disease. Mild asthmatic individuals have good exercise tolerance but may not tolerate vigorous exercise such as prolonged running. Moderate asthmatic individuals have diminished exercise tolerance and individuals with severe disease have very poor exercise tolerance that markedly limits physical activity.
- 6) Exercise-induced bronchoconstriction is followed by a refractory period of several hours during which an asthmatic individual is less susceptible to bronchoconstriction (Edmunds et al., 1978). This refractory period may alter an asthmatic individual's responsiveness to SO<sub>2</sub> or other inhaled substances.
- 7) Asthma attacks can result in hospitalization or emergency room treatment. It is estimated that incidence of hospitalization for all asthmatic individuals in the United States is about 45 per 1,000 asthmatics per year (NIH, 1991). Attendance at emergency rooms for asthma in Vancouver, Canada was estimated to account for 1.2 percent of all emergency room visits.
- 8) Data on asthma attack rates in the United Kingdom suggest an incidence of asthma attacks requiring medical attention, of <1 asthmatic patient-year (Ayres,

1986; Nevill et al., 1993). A similar attack incidence was estimated for the United States patients (Lebowitz et al, 1985; Van Essen-Zandoliet et al., 1992).

- 9) In assessing the rate of incidence, it should be noted that based on the Los Angeles asthma panel data (EPRI, 1988), only 15 percent of mild asthmatic individuals see a physician annually for their asthma compared to about 67 percent of the moderate asthmatics.
- 10) Death due to asthma is a rare event; about one per 10,000 asthmatic individuals. Mortality rates are higher among males and about 100 percent higher among non-whites. It has been reported that in two large urban centers (New York and Chicago) mortality rates from asthma among non-whites 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). There may be several possible explanations for this, but the cause of these higher mortality rates has not been explained.

In assessing the results from the controlled human exposure studies discussed below, it should be noted that the individuals who participate in such studies may not be representative of the entire population of individuals with asthma. The subjects of controlled 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. In addition, African-American and Hispanic adolescents and young adults have not been studied systematically. Subjects who participate in controlled exposure studies are also generally self-selected and this may introduce some bias. Thus, the extent to which the participants in the studies reflect the characteristics of the asthmatic population at large is not known. Nevertheless, the high degree of consistency among studies suggests either 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.

### C. Medication Use

Many asthmatic individuals take medication to relieve symptoms and functional responses associated with exacerbation of this disease. One of the most commonly used asthma medications (beta-agonists) also inhibits responses to SO<sub>2</sub>. This has led to suggestions that asthmatic individuals may be protected from responses to SO<sub>2</sub> because they medicate prior to exercise.

However, as discussed in the CD supplement (EPA, 1994), the available data suggest that probably a substantial proportion of asthmatic individuals would not be "protected" by medication use. Most mild asthmatic individuals use medication only when symptoms arise. Roth Associates (1988) reported that out of a panel of 52 asthmatic subjects, whose exercise patterns showed a wide range

of variability, one third of the mild asthmatic subjects studied had not used any asthma medication within the past year, and that fewer than half used an inhaled bronchodilator at least once during the past year. Only 20 percent of the moderate asthmatics subjects studied use an inhaled bronchodilator on a regular basis. Marks et al., (1992) also reported that beta-agonist use was infrequent.

Even medication compliance for those on regular medication varies considerably among asthmatic individuals (from none to full compliance). Average compliance figures range from 50 to 70 percent (Smith et al., Weinstein and Cuskey, 1985; Smith et al., 1986; Partridge, 1992). Given the relatively low medication use and compliance rates for many mild and moderate asthmatics individuals, pre-exercise bronchodilator use would not be likely to occur for many potentially  $SO_2$ -sensitive individuals.

For a large number of mild asthmatic individuals 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 thus may be prone to frequent deterioration of their lung function. Such individuals would be

at increased risk from SO<sub>2</sub> exposure because of their potentially poorer baseline level of lung function. Exposure of unmedicated moderate asthmatics to SO<sub>2</sub> could cause additional deterioration of lung function that could be cause for medical concern (EPA, 1994, p. 51).

D. Nature and Time Course of Response

The most striking acute response to SO<sub>2</sub> for asthmatics and others with hyperactive airways is bronchoconstriction (airway narrowing), usually evidenced as increased airway resistance, decreased FEV<sub>1</sub>, or decreased peak flow, and the occurrence of symptoms such as wheezing, chest tightness, and shortness of breath (EPA, 1982a; EPA 1986a). This bronchoconstriction response occurs quickly (within 5- to 10-minutes of exposure), with two recent studies showing that the response can begin in as little as 2-3 minutes, although the response does not reach maximal levels until the exposure lasts five or more minutes (Balmes et al., 1987; Horstman et al., 1988). The response is also generally brief in duration; numerous studies have shown that lung function typically returns to normal for most subjects within an hour of exposure. This duration is similar to that experienced in response to exercise and somewhat less than experienced in response to allergens (EPA, 1994). Even if exposure continues beyond the initial 5-10 minutes, lung function may still return to normal as long as the subject ceases to exercise and their ventilation rate decreases to resting levels (Hackney, et al., 1984; Schatcher et al., 1984).

A mild "refractory period" seems to exist in which diminished responsiveness is seen when an individual is re-exposed to SO<sub>2</sub> while at exercise. Lung function responses of approximately 75 percent of those observed after an initial exposure to SO<sub>2</sub> are observed after a second exposure ten to fifteen minutes later (Roger et al., 1985; Kehrl et al., 1987). The response diminishes further with subsequent exposures. However, a few individuals may experience a worsening of response upon re-exposure (Roger et al., 1985). The duration of this refractory period is uncertain, although it does not appear to last longer than 5 hours on average (Linn et al., 1984). Furthermore, longer periods of exposure while at exercise (i.e., 30 minutes) do not lead to a statistically significant worsening of the initial response (Kehrl et al., 1987, p. 352).

An important distinction between the response of asthmatic individuals to SO<sub>2</sub> as compared to their response to allergens is that no evidence indicates that the SO<sub>2</sub> response is accompanied by any "late response," such as that often seen 4 to 8 hours after allergen exposure.

The effects of SO<sub>2</sub> increase with both increased overall ventilation rates and an increased proportion of oral ventilation in relation to total ventilation (EPA, 1986a, p. 10). Oral ventilation is thought to accentuate the response because the scrubbing of SO<sub>2</sub> by the nasal passageways is bypassed. For this reason, in most clinical studies which have observed effects from SO<sub>2</sub>, the subjects have been exercising at ventilation rates of 35

to 50 L/min, which equal or exceed the "switching point" (35.3 L/min) from exclusively nasal breathing to oronasal breathing found on average for the general population by Niinimaa et al. (1980).

Ventilation rates in the range of 35-40 L/min are comparable to ventilation rates induced by climbing 3 flights of stairs, light cycling, shoveling snow, light jogging, or playing tennis (Cohen, 1983), and can be induced in the laboratory by walking at 3.5 mph up a 4 percent grade (Kehrl et al., 1987; Folinsbee, personal communication). Ventilation rates in the range of 45-50 L/min are equivalent to moderate cycling, chopping wood, or light uphill running, and can be induced by walking at 3.5 mph up an 8 percent grade (Folinsbee, personal communication). Even though such exercise is not strenuous per se (in that it does not approach an individual's maximum oxygen consumption or the ventilation rates of moderate jogging, heavy cycling, playing basketball, or running), activity and ventilation data indicate that individuals engage in outdoor activities at these ventilation rates only a small percentage of the time (see Section III.D.1).

Since oronasal scrubbing of SO<sub>2</sub> is important in mitigating the effects of SO<sub>2</sub> (EPA, 1986b, p. 4-26), asthmatic individuals who are obligate mouthbreathers, or who are breathing through the mouth due to some temporary condition, may be at greater risk of experiencing responses to SO<sub>2</sub> (since their nasal scrubbing may be bypassed at lower ventilation rates and to a greater extent than

for those individuals capable of typical nasal breathing). Several studies have estimated mouthbreathers to constitute approximately 15 percent of the general population (Saibene et al., 1978; Niinima et al., 1980; EPA, 1986b, p. 4-26).

Bronchoconstriction effects may also be exacerbated by cold, dry air and diminished under warm, humid conditions (EPA, 1986b, pp. 4-35 to 4-37). As discussed in the criteria document addendum (EPA, 1986b), Bethel et al. (1984) reported a significant interaction between oral hyperventilation of cold dry air and 0.5 ppm SO<sub>2</sub> via mouthpiece that resulted in a >200 percent increase in SRaw, whereas breathing SO<sub>2</sub> in warm humid air or breathing cold dry air alone resulted in a <40 percent change in SRaw. It has been well documented in numerous studies that SO<sub>2</sub> may interact with weather factors (e.g., cold/dry air) and/or exercise to cause exaggerated bronchoconstriction. This suggests that airway cooling and drying may exacerbate SO<sub>2</sub>-induced airway constriction in hyperventilating asthmatic subjects, but insufficient data exist by which to estimate the magnitude of any combined effects of joint SO<sub>2</sub> and cold, dry air exposure under more natural free-breathing conditions during exercise (EPA, 1994, p. 31).

Many features of the SO<sub>2</sub>-induced bronchoconstriction response resemble those of exercise-induced bronchoconstriction, including the duration of the effect and the absence of a substantial late response. However, it should be noted that above a sufficient concentration, the response to SO<sub>2</sub> clearly

exceeds the response attributable to exercise, and that a number of subjects can experience an effect from SO<sub>2</sub> when at exercise while experiencing little or no effect from exercise in clean air (Linn et al., 1987).

E. Concentration-Response Information

The CD Supplement extensively reviewed several recent, large-scale chamber studies with the aim of further investigating the concentration where clinically significant responses began. Because of the well-documented range in sensitivity to SO<sub>2</sub> among asthmatic persons (e.g., Figure 2-1), variability in an asthmatic individual's day-to-day responsiveness, and the nature of the response itself, it was judged that neither simple group mean statistics nor the responses of particularly sensitive individuals were an appropriate focus. Rather, attention should be focused on the concentrations where a significant proportion of asthmatic individuals tested began to experience effects of concern. Assessing effects of concern involved comparing the responses experienced to SO<sub>2</sub> with those typically experienced in response to typical daily variation in lung function, and to other frequently experienced stimuli, such as exercise or cold/dry air, and noting the frequency with which subjects felt compelled to take medication or diminish workload. The CD Supplement (EPA, 1994) summarized its evaluation of the recent data as follows:

- a) At most, only about 10 to 20 percent of mild and moderate asthmatic individuals exposed to 0.2 to 0.5 ppm SO<sub>2</sub>

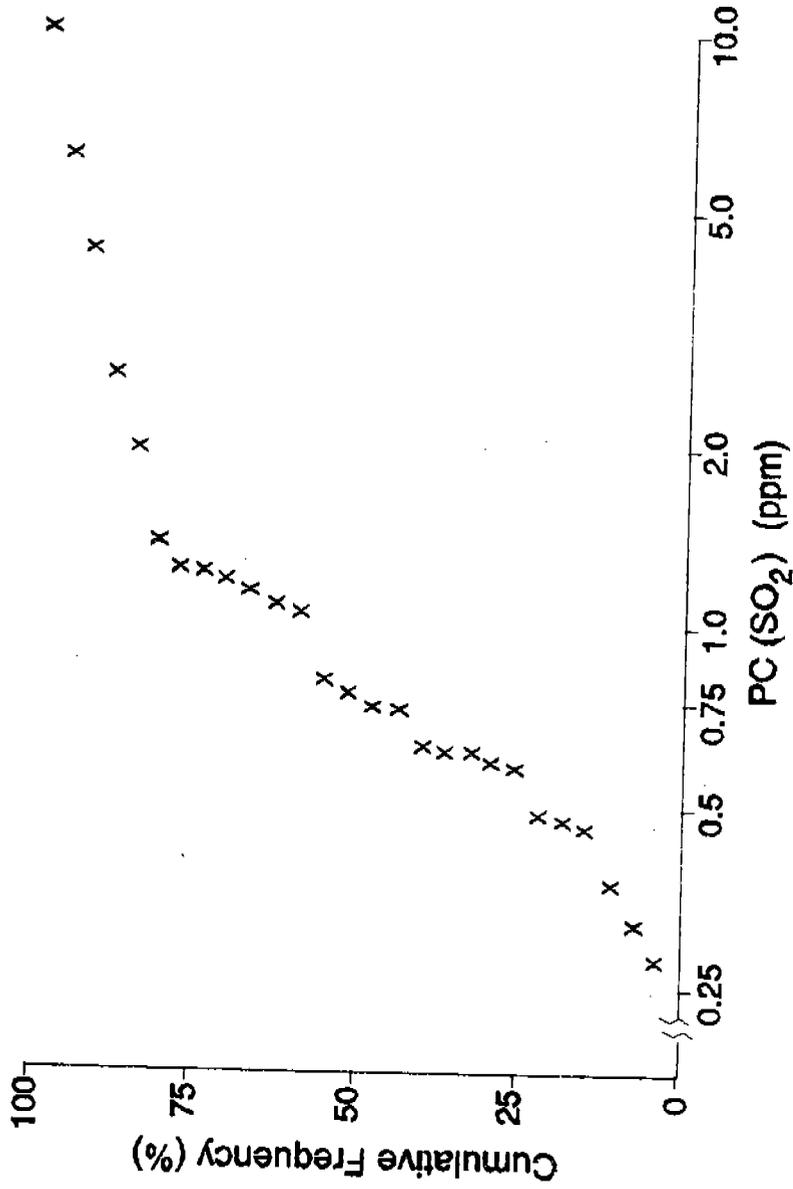


Figure 2-1. Distribution of individual airway sensitivity to SO<sub>2</sub> (Horstman et al., 1986). PC (SO<sub>2</sub>) represents concentration of SO<sub>2</sub> that, after correction for exercise ( $V_e = 42$  l/min), resulted in a 100 percent increase in SRaw. Cumulative percentage of subjects is plotted as a function of PC (SO<sub>2</sub>) and each data point represents PC (SO<sub>2</sub>) for an individual subject. These data show substantial variability in sensitivity among mild asthmatic volunteers.

Source: Horstman et al. (1986)

during moderate exercise are likely to experience lung function changes distinctly larger than those they typically experience. Furthermore, only exceptionally sensitive responders might experience sufficiently large lung function changes and/or respiratory symptoms of such severity to be a potential health concern, leading to the disruption of ongoing activities, the need for bronchodilator medication, or seeking of medical attention.

b) In contrast to the above projected likely consequences of ambient exposures to 0.2 to 0.5 ppm SO<sub>2</sub> of mild and 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<sub>2</sub> concentrations of 0.6 to 1.0 ppm SO<sub>2</sub>. That is, substantial percentages (≥20 to 25 percent) of mild or moderate asthmatic individuals exposed to 0.6 to 1.0 ppm SO<sub>2</sub> while physically active 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 these responders, furthermore, is 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. 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<sub>2</sub> effects, although it would still appear relatively unlikely that the short-lived symptoms would be sufficient to cause many to seek emergency medical attention.

The CD supplement (EPA, 1994) concludes that while the relative health significance of the responses seen to SO<sub>2</sub> are difficult to judge (see further discussion below), more concern should be focused on the response to  $\geq 0.6$  ppm SO<sub>2</sub> than to concentrations of SO<sub>2</sub>  $\leq 0.5$  ppm (EPA, 1994, p. 46).

#### F. Other Considerations

In addition to information on the nature and severity of effect as indicated by clinical parameters, there are several other factors that the Administrator may wish to consider:

##### 1. SO<sub>2</sub> Responsiveness and Asthma Severity

One concern voiced in the last review was whether more severe asthmatic individuals than those studied to date might be more responsive or experience more severe effects from SO<sub>2</sub>. At that time, the evidence was judged insufficient to answer that question (Appendix A).

Several of the more recent studies reviewed in the CD supplement (Linn et al., 1987, 1990; McManus et al., 1989) provide information on this question by reporting the responses of asthmatic individuals with moderate to severe disease, medication-dependent disease, or older individuals with "intrinsic" asthma. When airway resistance was examined, the moderate asthmatic subjects were observed to have similar relative changes but larger absolute changes to those observed

for mild asthmatic individuals (Linn et al., 1987). As the CD supplement suggests (EPA, 1994, pp. 21-24), similar function declines may have a greater impact on individuals with lower baseline lung function, a situation more typical of moderate or severe asthmatics.

In addition, a recent study suggests that older "intrinsic" asthmatic subjects (McManus et al., 1989) may experience bronchoconstriction, albeit from a mouthpiece exposure, even while resting. The CD supplement concludes that while the data is suggestive of greater responsiveness among those with more severe disease, the question remains to 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 (EPA, 1994, p. 44).

The CD supplement also notes that severe asthmatics are less likely to be sufficiently physically active, because of low exercise tolerance, to be frequently at risk from peak concentrations of  $SO_2$ . In addition, this segment of the asthmatic population would be most likely to premedicate prior to engaging in substantial outdoor activity.

## 2. Effects of Asthma Medications on the $SO_2$ Response

Interest has been expressed concerning the ability of typical asthma medications to protect against the effects of  $SO_2$ . An argument can be made that if medications routinely used by an

asthmatic, for reasons separate from the pollutant itself, also confer protection against the effects of the pollutant, then this consideration should be factored into the evaluation of risk. It now appears that most regularly administered medications, such as inhaled steroids and methylxanthine medications (such as theophylline) appear relatively ineffective in protecting against the SO<sub>2</sub> response (EPA, 1994, p. 34-41). In contrast, inhaled beta-agonist bronchodilators are highly effective in reducing or eliminating the lung function responses to SO<sub>2</sub> (EPA, 1994, p. 38). Since bronchodilators are most effective in preventing effects if taken relatively shortly before exposure, the frequency with which asthmatic individuals premedicate prior to exercise is of interest.

As pointed out in Section C above, many asthmatics do not use bronchodilators at all or do not use them with a frequency to suggest that they consistently premedicate prior to exercise. In fact, as pointed out above (Section E), many of the mild asthmatic individuals, including those responsive to SO<sub>2</sub>, have little or no exercise-induced bronchoconstriction at the exercise levels examined here, and thus would probably not feel a compelling need to premedicate prior to exercise. Data on the medication use of some of subjects in the clinical studies bear out the conclusions that in general, mild asthmatics use bronchodilators infrequently, as do some moderate asthmatics; although a substantial portion of moderate asthmatic may use bronchodilators frequently (EPA, 1994, Appendix B memo).

