review of WHO regional office for europe proposed short-term SO_2 air quality guideline

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ABSTRACT

The World Health Organization (WHO) regional office for Europe recommends an SO_2 guideline of 500 $\mu g/m^3$ (0.175 ppm) for a 10 minute sampling time, an uncertainty factor of 2, and a threshold of about 1000 $\mu g/m^3$ (0.35 ppm).

Based on SO_2 chamber studies described herein the following conclusions are summarized:

- Population at risk

  The WHO-EU recommended guideline is set to protect the most susceptible individuals among the most susceptible population, namely exercising asthmatics not receiving medication.

- 10 minute sampling time

  The data suggest an exercising asthmatic's response to SO_2 begins within minutes, reaches a maximum in about 10 minutes, and does not increase with longer exposures (and may actually decrease with longer or repeated exposures). Further, bronchoconstriction may be reduced at rest compared with that experienced while exercising even if exposure continues.

- Healthy subjects, COPD patients, and resting asthmatics are not at risk of an adverse response to SO_2 exposure at concentrations as high as 1 ppm SO_2.

- The interpretation of the exposure-response relationships of exercising asthmatics, depends on the definition of an adverse effect. The WHO-EU definition is the most conservative one in the literature.

- The basis for inclusion of an uncertainty factor of two is unclear. The chamber studies include sensitive subjects, representative of the asthmatic population.

CONTENTS

1. INTRODUCTION

In 1987, the World Health Organization (WHO) concluded that "effects of clinical significance became evident in experimental exposure studies, of about 10 minute duration, involving exercising asthmatic patients, at concentrations of SO_2 from about 1,000 $\mu g/m^3$ (0.35 ppm) upwards." An uncertainty factor of two was introduced to account for the possibility that the most sensitive population had not been tested. Subsequent studies that included severe asthmatics support this conclusion. Based on these data, the WHO recommended that a value of 500 $\mu g/m^3$ (0.175 ppm) for 10 minutes should not be exceeded (WHO, 1995).

2. CHAMBER STUDIES

The WHO-EU recommended air quality guideline is based on results from experimental exposures of volunteers exposed in a chamber to known concentrations of SO_2 for periods of 5 minutes to several hours. The measured health effects are changes in lung function, either spirometry or airway resistance (AWR). The most important (and commonly reported) spirometric measures are Forced Expiratory Volume in 1 second (FEV_1) and to a lesser extent Forced Vital Capacity (FVC). **Table A** summarizes the results of chamber studies of volunteers exposed to SO_2 where spirometric results are reported. Studies measuring only AWR were not summarized in assessing exposure-response, although AWR and FEV_1 show similar patterns of response when both were measured).

3. EXPOSURE-RESPONSE

3.1. EXPOSURE-RESPONSE BASED ON REDUCTION OF FEV_1

The effects on FEV_1 of short-term exposure to SO_2 are summarized below (extracted from **Table A**). Studies are included only if the exposed volunteers are not wearing a mouthpiece or facemask (i.e., their breathing is unencumbered). The age range of the study populations is included. In all studies asthma medication was stopped prior to exposure.

Healthy Subjects. Among healthy subjects, several studies do not have pure non-exposed groups. The aged group in Rondinelli et al. (1987) was exposed to 1 mg/m^3 NaCl. The exposed and control groups in Stacy et al. (1981, 1983) are different groups. The only other non-healthy group studied besides asthmatics is patients with chronic obstructive pulmonary disease (COPD) (Linn et al., 1985a). Since SO_2 did not produce significant reductions in FEV_1 and these patients showed an SO_2 response similar to healthy subjects, they are included in the healthy subject group.

SO_2 Exposure (ppm)	Healthy and COPD Subjects: Δ FEV_1 % - Unencumbered Breathing				
	Control (0 ppm) (exercise)	SO_2 Exposure			Comments (references)
		Rest	Exercise	Exercise minus Control Value	
0.2	+0.5%	--	+1.2%	+0.7%	18-37 yrs (Linn et al. (1987)
0.2	+0.5	--	-0.5	0	18-32 yrs, atopics (Linn et al., (1987)
0.4	-0.9	--	-1.7	+0.8	49-68 yrs, COPD (Linn et al., 1985a)
0.4	+0.5	--	-0.5	0	Atopics (Linn et al., 1987)
0.4	+0.5	--	+1.4	+0.9	Linn et al. (1987)
0.5	-5.3	-2.7	-5.3	0	55-73 yrs (Rondinelli et al., 1987)
0.6	+0.5	--	-1.9	-1.4	Atopics (Linn et al., 1987)
0.6	+0.5	--	+1.4	+0.9	Linn et al. (1987)
0.75	+2.6	--	-2.1	+0.5	22-47 yrs (Stacy et al., 1981)
0.75	-1.2	--	-0.5	+0.7	Mean 24 yrs (Stacy et al., 1983)
0.8	-0.9	--	0	+0.1	COPD (Linn et al., 1985a)
0.99	+1.3	+0.3	-0.3	+1.4	20-35 yrs (Kulle et al., 1986)
1.0	-5.3	-2.6	-5.4	-0.1	55-73 yrs (Rondinelli et al., 1987)

There were 99 healthy and COPD patients exposed to SO_2 concentrations ranging from 0.2 ppm to 1 ppm, with some subjects exposed to multiple concentrations. Ages ranged from 18 to 73 years. The 10 normal nonsmokers studied by Rondinelli et al. (1987) showed the largest reduction of FEV_1 when exercising (-5%) and when exposed to 1 mg/m^3 NaCl (= control exposure). This decrement is similar to that observed when exposed to 1 ppm SO_2 plus 1 mg/m^3 NaCl and 0.5 ppm SO_2 plus 1 mg/m^3 NaCl.

Asthmatic Subjects - Unencumbered Breathing.

The severity of the asthmatic condition as well as age range of subjects is presented in the comments column. If severity is not known, the number of subjects on medication is provided (extracted from **Table A**).

SO_2 Exposure (ppm)	Asthmatic Subjects: Δ FEV_1 % - Unencumbered Breathing				
	Control (0 ppm) (exercise)	SO_2 Exposure			Comments (references)
		Rest	Exercise	Exercise minus Control Value	
0.1	not done	--	-3.0	?	12-18 yrs; 10/13 on medication (Koenig et al., 1990)
0.2	not available	--	-1.0	?	19-31 yrs; known SO_2 sensitive; 12/23 on regular medication (Linn et al., 1983b)
0.2	-1.6%	--	-4.1	-2.5	20-33 yrs, minimal/mild (Linn et al., 1987)
0.2	-8.4%	--	-9.5	-1.1	18-35 yrs, moderate/severe (Linn et al., 1987)
0.2	-2.2%	-3.5	--	--	18-45 yrs, mild allergic (Devalia et al., 1994)
0.25	not available	--	+4.2	?	18-30 yrs, mild (Linn et al., 1982)
0.25	-1.5	--	-1.9	-0.4	18-36 yrs; 8/10 atopic, 4/10 on medication (Schachter et al., 1984)
0.3	-5.0	--	-7.9	-2.9	19-36 yrs, mild (11/20 on medication) (Linn et al., 1988)
0.3	-14.5	--	-19.4	-4.9	18-50 yrs, moderate/severe (Linn et al., 1990)
0.4	not available	--	-0.4	?	Linn et al. (1983b)
0.4	-1.6	--	-10.7	-9.1	Minimal/mild (Linn et al., (1987)
0.4	-8.4	--	-17.9	-9.5	Moderate/severe (Linn et al., 1987)
0.5	not available	--	+0.5	?	Linn et al. (1982)
0.5	-1.5	--	-3.0	-1.5	Schachter et al. (1984)
0.6	not available	--	-12.8	?	Linn et al. (1983b)
0.6	-1.6	--	-18.4	-16.8	Minimal/mild (Linn et al., 1987)
0.6	-8.4	--	-25.3	-16.9	Moderate/severe (Linn et al., 1987)
0.6	-5.0	--	-19.6	-14.6	Linn et al. (1988)
0.6	-14.5	--	-30.2	-15.7	Linn et al. (1990)
0.75	not available	--	-7.5	?	18-30 yrs, SO_2 sensitive but none on medication (Linn et al., 1983a)
0.75	-1.5	--	-8.3	-6.8	Schachter et al. (1984)
1.0	-1.5	--	-13.7	-12.2	Schachter et al. (1984)
1.0	-1.6	--	-5.8	-4.2	20-30 yrs; mild, intermittent exercise (Kehrl et al., 1987)
1.0	-1.3	--	-8.0	-6.7	Continuous exercise (Kehrl et al., 1987)

There were a total of 109 asthmatic subjects tested, with ages ranging from 18 to 50 years. This does not include those studies where change in FEV_1 % for controls was unavailable. The range of SO_2 exposures was from 0.2 ppm to 1 ppm SO_2, and most studies exposed the same subjects to several concentrations of SO_2. The effects of exercise on FEV_1 ranged from a decrement of 1.3 to 1.5% (Schachter et al., 1984; Kehrl et al., 1987) to highs of almost -15% (moderate/severe asthmatics; Linn et al., 1990). The average of all study subject responses at a given concentration are shown below.

SO_2 Concentration (ppm)	n	Average % Change (FEV_1) in Asthmatics from SO_2 Chamber Studies	
		Exercise + SO_2	Corrected (Exercise - SO_2)
0.2	40	-7.3%	-1.7%
0.25	10	-1.9	-0.4
0.3	41	-13.8	-3.9
0.4	40	-15.0	-9.3
0.5	10	-3.0	-1.5
0.6	81	-23.8	-16.0
0.75	10	-8.3	-6.8
1.0	30	-9.2	-7.7

Some of the reduced response to SO_2 at 0.5 , 0.75, and 1 ppm SO_2 may be due to variability in sensitivity of the study population. Linn et al. (1987) exposed the same subjects to 3 concentrations of SO_2. These results (summarized below) show a more consistent exposure-response trend not affected by different conditions of exercise intensity, temperature and humidity, duration of exposure, intra-individual variation in sensitivity, methodology, etc.

SO_2 (ppm)	Study Population - Adjusted Δ FEV_1 % (Linn et al., 1987)			
	Normal	Atopic	Minimal/Mild Asthmatic	Moderate/Severe Asthmatic
0.2	+0.7	0	-2.5	-1.1
0.4	+0.9	0	-9.1	-9.5
0.6	+0.9	-1.4	-16.8	-16.9

These data show no difference in response between minimal/mild and moderate/severe asthmatics.

3.2. EXPOSURE-RESPONSE BASED ON PERCENT CHANGE IN AIRWAY RESISTANCE

Data from chamber studies can be presented in another way to estimate both exposure-response and the proportion of asthmatics likely to respond at a given SO_2 concentration. Horstman et al. (1986) exposed moderately exercising asthmatics to 0, 0.25, 0.5, and 1.0 ppm SO_2 for 10 minutes and measured AWR; a

100% increase in AWR was defined as the threshold for becoming an adverse effect and is an index of airway sensitivity [PC(SO_2)]. An exposure-response curve was then constructed so that the x-axis was SO_2 concentration at which there was a 100% increase in AWR greater than response to clean air, herein defined as, an adverse effect. The y-axis was cumulative percentage of subjects showing bronchial sensitivity to SO_2. The study population comprised 27 mild asthmatics age 18-35 years, who were not receiving corticosteroids, cromolyn, or desensitating therapy, and who were responsive to methacholine. Medication was withheld prior to exposure, and exercise was moderate to heavy, as ventilation was 42 litres/minute. The results are shown in **Figure 1** from Horstman et al. (1986). These data show the following distribution of an adverse response to SO_2 corrected for the effects of exercise in this asthmatic study population and estimated from **Figure 1**.

SO_2 Concentration (ppm)	PC (SO_2) = % with Adverse Response
0.25	0%
0.3	5%
0.4	13%
0.50	28%
0.75	46%
1.0	64%
2.0	90%

The authors conclude there is a wide range of sensitivity to SO_2 among subjects selected to be representative of young adults with mild asthma. Presenting the data in this manner allows for "assessment of the proportion of this population which might develop bronchoconstriction during ambient exposures to low concentrations of SO_2."

Bethel et al. (1985) exposed mildly asthmatic subjects to 0.25 ppm SO_2 at two different exercise intensities. AWR was increased 140% at the lower exercise level and 203% at the higher exercise level (11% and 89% of the subjects, respectively with greater than a 100% increase in AWR). The exercise-adjusted mean change in AWR% at lower and higher exercise and 0.25 ppm SO_2 were 66% and 37%, with $^1/_3$ and 0 individuals respectively showing an adverse response. The authors suggested that the bronchoconstrictor effects at higher exposure levels may overshadow the SO_2 effects. This dataset is also interesting in that at 0.25 ppm there is no adverse bronchoconstriction during heavy exercise, and a 33% adverse response rate among the same individuals at a reduced work rate.

4. INTERPRETATION OF WHO DEFINITION OF ADVERSE EFFECT LEVEL

It appears that the WHO defined an adverse effect as a greater than 5% reduction in the average FEV_1 among study subjects, or a greater than 100% increase in AWR among individual study subjects. There were two studies that included severe asthmatics (Linn et al., 1987, 1990), and these studies appear to include the most sensitive subjects. Using WHO's assumed definition of "adverse" as described above, these studies suggest no adverse effect at 0.3 ppm (-4.9% change in FEV_1) and an adverse effect at 0.4 ppm (-9.5% change in FEV_1). The WHO conclusion of a threshold of about 0.35 ppm probably comes from these data.

The study by Horstman et al. (1986) shows the distribution of sensitivity to SO_2 among what is thought to be a representative sample of young adults with mild asthma. The "threshold" is about 0.3 ppm for about 5% of the asthmatic population studied; asthmatics represent perhaps 2-3% of the general population (Linn et al., 1987).

5. ISSUES ASSOCIATED WITH DEFINITION OF ADVERSE EFFECTS

A key question in developing an air quality guideline for SO_2 is what percentage change in FEV_1 and/or AWR should be considered an adverse effect? At present, there is no consensus among the scientific community as to what degree of change in FEV_1 and AWR should be considered adverse. The short-term reductions in these measures occur within minutes of first exposure, and are transient and reversible within minutes (Stacy et al., 1981; Koenig et al., 1983; Schachter et al.,1984). Schachter et al. (1984) showed that 40-minute exposure of exercising asthmatics at SO_2 concentrations of 1 ppm produced significant decrements in FEV_1 only at 1 minute and 5 minutes after exposure ended. Linn et al. (1984a) exposed asthmatics to 0.6 ppm for 6 hours on two successive days (5 minutes heavy exercise at beginning and end of each 6-hour period). AWR returned to pre-exposure values about an hour after exercise even though SO_2 exposure continued. A similar pattern, but slightly less severe airway obstruction was observed on the second day. Sheppard et al. (1983) found that short, repeated exposures to 0.5 ppm SO_2 over a day can reduce airway reaction to SO_2. Horstman et al. (1988) suggest the minimal exposure time necessary for significant bronchoconstriction to occur is 2 minutes with maximal responses achieved within 5 minutes and minimal increases beyond 10-minutes exposure.

The American Thoracic Society (ATS, 1985) suggests that interferences with normal activity should be considered an adverse effect. However, it is not clear where on the continuum of effects measurable changes in airway obstruction become an adverse effect.

The National Institute of Health criteria for exercise-induced asthma is a 15% or greater reduction in FEV_1. An individual reduction in FEV_1 of 15-20%, corrected for the effects of exercise alone, has been suggested as adverse, while reductions greater than 40% have been defined as incapacitating (Lippmann, 1988). Three studies of asthmatic patients seeking emergency medical treatment had average FEV_1 decrements of 60-80% (US EPA, 1994), which is clearly an adverse effect. Another definition of adverse effects used is a 100% increase in airway resistance (AWR) above that produced by exercise alone. To be adverse, the airway obstruction should be accompanied by moderate or severe symptoms (Horstman et al., 1988). The US Environmental Protection Agency (US EPA) suggests that AWR increases of 200% or more are of likely clinical concern.

The estimates of clinically significant physiological effects cannot be extrapolated directly to the results of chamber studies for two major reasons. First, FEV_1 results of the SO_2 chamber studies are mostly expressed as average reductions which have been recalculated to determine average percent reduction (i.e., the level of FEV_1 reduction for each individual study subject was not reported). Second, the incidence and severity of symptoms are not reported in a consistent form that can be used to assess adversity.

As mentioned previously, it appears that the WHO defined an adverse effect as an average reduction in FEV_1 of greater than 5% among all study subjects. This reduction is very likely to be conservative, as FEV_1 normally varies by 3% or less from blow to blow in the same individual, and 7 to 8% for asthmatics from hour to hour (Rodan et al., 1995). US EPA (1994) indicated the range of normal variation often experienced by asthmatics during a given day could be up to 10 to 20% lower FEV_1 and a 40% higher AWR in early morning versus afternoon due to daily circadian variation.

Lebowitz et al. (1987) addressed the question of what reduction in group mean is greater than expected and not due to just normal variability and diurnal change. Assuming lung function changes are normally distributed, the diurnal (within a day) coefficient of variation can be multiplied by 1.65 (2 standard deviations) to obtain the limit of normal daily changes. The coefficient of variation of FEV_1 for healthy subjects is 3-5%, and for obstructive patients is 7-10% (Lebowitz et al., 1987, Rodan et al., 1994). Thus, the percent reduction in FEV_1 that is different from normal variation is about 5 to 8% for normal persons and 11 to 17% for subjects with airway obstruction.

Note that a mean reduction in FEV_1 in a group of SO_2 exposed subjects may be greater than the cut-off point (e.g., 5% for healthy subjects) yet not statistically different because the variability in the group mean is not known, and the standard deviation of the group mean is usually not provided and cannot be calculated.

Changes in AWR for exposure-response trends are not considered here except for the study by Horstman et al. (1986) where individual AWR responses are reported. The authors use an increase in AWR of 100% above the effects of exercise as the measure of response. However, as with FEV_1, there is no strong consensus among the scientific community as to the level of AWR increase that should be considered adverse. US EPA (1994) estimated a 100% increase in AWR roughly corresponds to a 12 to 15% decrease in FEV_1.

6. PROTECTIVE EFFECT OF NOSE-BREATHING

Nose breathing provides more protection against SO_2 effects compared with mouth breathing (Kirkpatrick et al., 1982). Linn et al. (1982) found no significant bronchoconstriction of exercising asthmatics exposed to 0.50 ppm SO_2 during unencumbered breathing. However, in a pilot study reported in the same publication, exposure by mouthpiece showed a "substantially greater tendency to bronchoconstriction with 0.5 ppm SO_2". Linn et al. (1982) suggest two reasons for the differences: 1) the mouthpiece compromises the SO_2 scrubbing ability of the upper respiratory tract, or 2) the main study subjects had less reactive airways than the pilot study subjects. Linn et al. (1983a) showed that bronchoconstriction among asthmatic volunteers was about 3 times greater for mouthpiece exposure compared with unencumbered breathing under conditions of heavy exercise and exposure to 0.75 ppm SO_2. No difference was observed when exposed to clean air. These data suggest option (1) of Linn et al. (1982) is most likely.

Therefore, the exposure-response effects of SO_2 for freely breathing subjects is considered the more appropriate estimate of SO_2 effects. For this reason, studies are not included in evaluating exposure-response where mouth only breathing is necessary because of inhalation via mouthpiece or facemask (Koenig et al., 1980, 1981, 1982a,b, 1983, 1987, 1989, 1990; Hackney et al., 1984; McManus et al., 1989).

7. EXERCISE

Asthmatics are particularly susceptible to exercise-induced bronchoconstriction (EIB). Exercise alone in the SO_2 chamber studies reduces FEV_1 of asthmatics from less than 1% to 15%. The air temperature and humidity in chamber studies are such that they minimize EIB.

Cold air and hot dry air inhaled during exercise can significantly reduce FEV_1. Eschenbacher et al. (1992) provide an example of the effects of temperature and humidity on FEV_1 among exercising healthy and asthmatic subjects. The largest effects were from cold air and hot dry air; however, breathing the air while resting had little or no effect on FEV_1 as summarized in the table below:

Chamber Conditions	Δ FEV_1 %			
	Asthmatics		Normal Healthy Subjects	
	Rest	Exercise	Rest	Exercise
Cold, dry	-1	-18	-1	+2
Cold, humid	-4	-20	+1	+2
Hot, dry	+3	-16	+2	+2
Hot, humid	-1	-2	+3	+6
Normal ambient	-1	-7	0	+3

Noviski et al. (1987) showed that for asthmatic children FEV_1 was reduced 36% and 31% after 6 minutes exercise in room air (25°C) and cold (0°C) dry air, respectively. As exercise intensity increases, bronchoconstriction also increases (Bethel et al., 1983).

The effect of exercise alone on FEV_1 under certain extreme conditions of temperature and humidity could be considered an adverse effect. Air conditions may also potentiate the effects of SO_2. Sheppard et al. (1984), for example, showed that SO_2 causes bronchoconstriction at lower concentrations when inhaled in dry air compared with humid air, although the differences were small. Temperature of the air was of little importance. Consistent with greater effects of low humidity is the finding of Linn et al. (1986) that high temperatures and high humidity tend to mitigate the bronchoconstriction effects of 0.6 ppm SO_2 in exercising asthmatics. Linn et al. (1984b,c) showed that hot humid air plus exercise did not produce significant EIB. However, bronchoconstriction increased as temperature dropped from 38°C to -6°C, and the effects of SO_2 at cold temperature were additive.

8. MEDICATION

The withholding of medication prior to exposure may increase hyperreactivity of the airways. However, some asthma medications reduce the bronchoconstrictive effects of SO_2, and some do not. Theophylline does not appear to provide effective protection against EIB, but metaproternol does. Linn et al. (1990) showed that 10 minutes heavy exercise of moderate/severe medicine-dependent asthmatics (mostly taking theophylline) resulted in 12-15% reduction in FEV_1 whether medication was withheld or not. Administration of metaproternol (MP) prior to exercise plus SO_2 exposure resulted in an increase in FEV_1. Koenig et al. (1987) showed that albuterol prevented the bronchoconstrictive effects of SO_2.

Ipratropium bromide (IP) acts as a bronchodilator, increasing FEV_1 even when exposed to SO_2, but not exercising; however, IP does not completely block the bronchoconstrictive action of SO_2 in exercising asthmatics (McManus et al. 1989). Tan et al. (1982) showed that IP blocked the airway conductive response to 20 ppm among resting atopic subjects (allergic to 2 allergens and history of rhinitis), but was only partially successful in 4 of 9 asthmatic subjects exposed to 10 ppm SO_2. Previous treatment with clemastine blocked the effect of 10 ppm SO_2 for 2 of 7 asthmatics. Disodium cromoglycate (cromolyn) was effective in blocking SO_2 bronchoconstriction for both the atopic and asthmatic subjects. Snashall and Baldwin (1982) showed that sodium cromoglycate (SCG) and atropine significantly inhibited the effect of 8 ppm SO_2 in most normal and asthmatic subjects tested. Atropine did not inhibit the bronchoconstrictive effect in normal persons with hyperreactive airways or in several asthmatics. Sheppard et al. (1981) also found that cromolyn inhibited bronchoconstriction of exercising healthy and asthmatic subjects exposed to SO_2, although they found that atropine was successful in both asthmatic and non-asthmatic subjects they tested.

Metaproternol is clearly effective in preventing SO_2-induced bronchoconstriction among asthmatics. It was shown to be very effective, with about a 10% increase in FEV_1 after exposure to 0.6 ppm SO_2 (Linn et al., 1988, 1989). Albuterol is only slightly less effective (Koenig et al., 1987). However, the effect of withholding normal medication on airway reactivity to SO_2 is not clear, and probably depends on the medication being used. Linn et al. (1990) suggest it makes little difference, but more study is needed.

9. SUMMARY

The data presented in this report are summarized with regard to the recommendations of WHO-EU.

- Population at risk

  The WHO-EU recommended guideline is set to protect the most susceptible individuals among the most susceptible population, namely exercising asthmatics not taking medication.

- 10-minute sampling time

  The data suggest an exercising asthmatic's response to SO_2 begins within minutes, reaches a maximum in about 10 minutes, and does not increase with longer exposures (and may actually decrease with longer or repeated exposures). Further, bronchoconstriction may be reduced at rest compared with that experienced while exercising even if exposure continues.

- Definition of adverse effect level and existence of a threshold

  The data suggest that concentrations as high as 1.0 ppm SO_2 do not cause significant airway obstruction among healthy subjects and patients with COPD, even when exercising, or among resting asthmatics. Among exercising asthmatics, the threshold depends on the definition of adverse effect that is used. As discussed in the body of the report, there is currently no consensus among the scientific community as to the degree of change in FEV_1 and/or AWR that should be considered adverse.

- An uncertainty factor of two was applied in 1987 at the NOAEL of 1000 $\mu g/m^3$ (0.35 ppm) to allow for the possibility that the most sensitive population may not have been tested. This uncertainty factor was maintained in the 1994 re-evaluation as further studies with more sensitive subjects have supported this assumption.

  It is unlikely that the subjects with most severe disease have been tested, as they are probably excluded because of their inability to exercise and/or the large adverse effect of EIB. It is not always obvious *a priori* who are the most sensitive subjects. For example, the correlation of sensitivity to methacholine and SO_2 is not very high, and is not a good predictor of sensitivity to SO_2. Horstman et al. (1986) show a wide range of sensitivity to SO_2 among exercising asthmatics ranging from about 0.30 ppm to a high of about 10 ppm. However, sensitivity may also be a function of exercise intensity (Sheppard et al., 1981; Noviski et al., 1987). For example, as ventilation increased the response to SO_2 also increased (Sheppard et al., 1981). On the other hand, Bethel (1985) showed that higher exercise intensity produced more increases in airway obstruction but less adverse responses to the same concentration of SO_2. Also, it is not clear that severe asthmatics are more sensitive than mild asthmatics. Linn et al. (1987) showed no difference in adjusted change in FEV_1 % between mild asthmatics and moderate/severe asthmatics at 0.2 and 0.4 ppm SO_2. Linn et al. (1988, 1990) showed no difference at 0.3 ppm SO_2; Linn et al. (1987, 1988, 1990) also did not find a difference at 0.6 ppm SO_2.

There appear to be few data that provide a useful estimate of variability in sensitivity within the spectrum of all asthmatics. Horstman et al. (1986) appears to be the only dataset assessing variability among mild asthmatics at different exposure levels. If mild asthmatics are similar to severe asthmatics, then these data would apply to the severe asthmatic as well, which WHO-EU seems to assume include the most sensitive.

A problem with the chamber studies is that the subjects are not representative of the actual population. In this context they are not representative because normal medication is interrupted. It is also not reported whether subjects routinely exercise or not. To be representative, the subjects in the chamber studies should be drawn from the population of mild to moderate asthmatic who regularly exercise with enough intensity to increase ventilation rates. Their normal medication prior to exercise should not be discontinued. The possible non-representativeness of the sample suggests a potential bias to spuriously increase the magnitude of the response.

In sum, an appropriate uncertainty factor is not clear based on the data. The chamber studies include sensitive subjects, which arguably may be representative of the asthmatic population. If so, no safety factor may be necessary.

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Table A

Selected Chamber Studies of Acute Changes in Spirometry when Experimentally Exposed to SO_2

Reference	Subjects	SO_2 Exposure	% Change in FEV_1, FVC	Comments
Koenig et al. (1980)	9 asthmatics age 14-18 yrs requiring medical therapy; EIB after 6 min exercise; medication withheld prior to exposure	60 min exposure at rest; PFT measured at 30 and 60 min (n = 5 for NaCl alone); exposure via face mask (mouth breathing)	Δ FEV % 30 minutes / 60 minutes Air +3.2% / -0.5% 1 mg/m^3 NaCl +4.8 / +1.0 1 mg/m^3 NaCl + 1 ppm SO_2 +1.2 / +2.4	No exposure to SO_2 alone; NaCl is submicron, and alone has no effect; NaCl + SO_2 may affect small airways
Koenig et al. (1981)	8 adolescent asthmatics age 14-18 yrs with EIB; requiring medical therapy; medication withheld on day of exposure unless medication needed; same subjects as Koenig et al. (1980)	30 min exposure at rest (post-rest) followed by 10 min exposure during moderate exercise; NaCl MMD = 0.9 µm (GSD = 2.0); exposure via mouthpiece	Δ FEV_1 % Post-rest / Post-exercise (Immediately / 14 minutes) Air +5.3% / +0.3% / +2.5% 1 mg/m^3 NaCl +9.7 / +7.9 / +5.9 n = 4) 1 mg/m^3 NaCl + 1 ppm SO +5.5 / -23.4* / -13.1* *p <0.5	No delayed clinical effects occurred during subsequent 2 days; no exposure to SO_2 alone; Koenig et al. (1982a) suggest added effect of NaCl when SO_2 is added
Stacy et al. (1981)	31 healthy male volunteers age 22-47 yrs, without skin response to ≥7 skin allergens; Control n = 15 exposed to air; Exposed n = 16 exposed to 0.75 ppm SO_2	Total of 2 hrs exposures: 45 min at rest + 15 min exercise (post-exercise), and last hr at rest	Δ FEV_1 % Post-exercise / End-exposure / 24-hrs Post-exposure Control +2.6% / +1.2% / +2.1% 0.75 ppm SO_2 -2.1 / -0.7 / +0.2 Δ FVC % Control +0.6 / -0.2 / +0.2 0.75 ppm SO_2 +0.4 / -0.2 / -0.6	Authors conclude: subjects with positive allergen skin tests more reactive than skin test negative subjects; no significant health hazard to normal subjects under test conditions
Koenig et al. (1982a)	8 healthy adolescents age 12-14 yrs; without allergies or EIB or sensitivity to methacholine and normal PFT	30 min exposure at rest (post-rest) followed by 10 min exposure during exercise (measured 2-5 min and 18 min post-exercise); mouth breathing via mouthpiece	Δ FEV_1 % Post-rest / Post-exercise (2-5 minutes / 18 minutes) 1 mg/m^3 NaCl +1.0% / -4.0% / -3.3% 1 ppm SO_2 -1.9 / -6.5* / -3.2 NaCl + SO_2 -3.2* / -5.4* / -4.5 *p <0.5	No exposure to air alone; authors conclude asthmatic adolescents much more sensitive than healthy adolescents, and show no subjective symptoms at these concentrations

Table A (Cont'd)

Selected Chamber Studies of Acute Changes in Spirometry when Experimentally Exposed to SO_2

Reference	Subjects	SO_2 Exposure	% Change in FEV_1, FVC	Comments
Koenig et al. (1982b)	8 atopic (allergic rhinitis) adolescents age 13-17 yrs with hyperactive airways but not asthmatics; EIB (>15% to FEV after 6 min exercise) and positive response to methacholine	30 min exposure via mouthpiece at rest + 10 min exposure while exercising (not enough to produce EIB); NaCl MMD = 0.9 µm (GSD = 2.0)	Δ FEV_1 % Post-rest / Post-exercise Air alone: +0.7% / +1.0% 1 mg/m^3 NaCl: 0 / -4.4 1 ppm SO_2 (n = 5): -4.7 / -21.9 SO_2 + NaCl: -1.7 / -17.7	Study group estimated to constitute 35% of allergic persons <18 yrs; no statistically significant difference in SO_2 alone and SO_2 + NaCl; effects largely occurred after exercising
Linn et al. (1982)	24 mild asthmatics 18-30 yrs; none on regular medication	1 hr exposure to 0.25 and 0.50 ppm SO_2 with alternating 10 min moderate exercise	Only post-exposure FEV_1 and FVC available, so % change from 0 ppm available; Δ PFT % estimated as change from baseline PFT Δ FEV_1 % / Δ FVC % 0 ppm: 2.81 litres / 3.61 litres 0.25 ppm: +4.2% / +2.6% 0.50 ppm: +0.5% / +0.7%	Authors conclude no meaningful effect of SO_2 on airways or symptoms; 0.25 ppm SO_2 possibly more favourable than clean-air; no pre-exposure spirometry values
Linn et al. (1983a)	23 asthmatics 18-30 yrs; screened to include SO_2 sensitive subjects; no routine use of asthma medication	mouthpiece vs. unencumbered breathing; 10 min exercise at 0.75 ppm SO_2	Δ FEV_1 % (Unencumbered / Mouthpiece); Δ FVC% (Unencumbered / Mouthpiece) Air: ? / -2.2% / ? / +0.1% 0.75 ppm SO_2: -7.5% / -23.2 / -5.5% / -9.6 Post-exposure values compared to post-exposure for air and unencumbered breathing	Authors conclude mouthpiece breathing can compromise upper-respiratory defences against SO_2 compared to natural breathing, and should be taken into account in using data for air quality risk assessment
Linn et al. (1983b)	23 asthmatics 19-31 yrs; screened to include SO_2 sensitive subjects; 12 on regular asthma medication	5 min heavy exercise; no medication prior to exposure	0 ppm (post-exposure value): Δ FVC +3.98 liters; ΔFEV$_1$ +3.07 liters Δ FVC % / Δ FEV_1 % 0.2 ppm: -0.3% / -1.0% 0.4 ppm: -0.4 / -4.0 0.6 ppm: -3.2* / -12.8* *p <0.05	Changes based on differences between post-exposure clean air and SO_2 exposure days, so day-to-day variation not accounted for and change at 0 ppm not reported

Table A (Cont'd)

Selected Chamber Studies of Acute Changes in Spirometry when Experimentally Exposed to SO_2

Reference	Subjects	SO_2 Exposure	% Change in FEV_1, FVC	Comments
Koenig et al. (1983)	9 asthmatics age 12-16 yrs under medical care for asthma; EIB, elevated IgE and positive inhalant skin-test reactions	30 min exposure via mouthpiece at rest (post-rest), 10 min exposure with moderate exercise (post-exercise); MMD of NaCl = 0.9 µm	Δ FEV_1 % Post-rest; Post-Exercise (2-3 minutes; 18 minutes) 1 mg/m^3 NaCl: -2.9%; -4.4%; -0.7% 0.5 ppm SO_2 + NaCl: +3.9; -15.0*; -2.4 1 ppm SO_2 + NaCl: -1.1; -22.9*; -14.4 *p <0.05	Responses are reversible, and duration of effect is related to exposure, so return to baseline is quicker at lower concentrations and is seen with SO_2 alone but not 1 ppm SO_2 + NaCl; exposure via mouthpiece (oral) produced similar changes as exposure via face mask (oronasal)
Stacy et al. (1983)	Normal healthy males; different subjects for each exposure; average age ~24 yrs; n = 10 subjects exposed to air, 11 subjects exposed to SO_2	Total of 4 hrs exposure; 15 min exercise at 1 hr 45 min and at 3 hrs 45 min	Δ PFT at 2 Hours: Δ FEV_1 %; Δ FVC %; Δ PFT at 4 Hours: Δ FEV_1 %; Δ FVC % Air (n = 10): -1.2%; -1.4%; -2.5%; -2.5% 0.75 ppm SO_2: -0.5; +0.4; -1.2; -0.6	Neither SO_2 nor the combination of SO_2 and sulphate particulates produced any significant effect on FEV_1 or FVC at 2 hrs, 4 hrs, or 24 hrs after exposure
Hackney et al. (1984)	17 asthmatics selected for sensitivity to SO_2; 7 taking bronchodilators; medication stopped on test day	10 min exercise; 0.75 ppm SO_2; exposure via mouthpiece	Δ FEV_1 % 0.75 ppm SO_2: -19.7%	Effect of exercise (0 ppm SO_2) on FEV_1 not tested; effect of SO_2 on AWR 3 x greater than effect of exercise. similar statistical significance of SO_2 on AWR and FEV_1. No increased AWR after 1 hr exposure to SO_2

Table A (Cont'd)

Selected Chamber Studies of Acute Changes in Spirometry when Experimentally Exposed to SO_2

Reference	Subjects	SO_2 Exposure	% Change in FEV_1, FVC	Comments
Schachter et al. (1984)	10 asthmatics, 18-36 yrs; 4 on medication, and stopped prior to exposure; 8 with atopic history; predicted FEV_1 = 83%; 10 normal subjects, 23-38 yrs; 3 atopic; predicted FEV_1 = 102%	Protocol 1: 40 min exposure, first 10 min includes moderate exercise Protocol 2: 40 min exposure, no exercise	Protocol 1 (exercise): Asthmatics 0 ppm SO_2: 0% >20% Reduction Post-exposure; -1.5% Δ FEV_1 % Post-exposure; +0.8% Δ FEV_1 % 10 min Post-exposure 0.25: 0%; -1.9; -1.5 0.5: 0%; -3.; -3.9 0.75: 20%; -8.3*; -4.2 1 ppm: 30%; -13.7*; -5.7 Protocol 2 (no exercise): Asthmatics 0 ppm, 1 ppm SO_2: No change in FEV_1 at either concentration, immediate post-exposure Normal Subjects: no significant reductions at any exposure for either protocol	Daily variation in mean baseline FEV_1 ~7% (2.56 - 2.75 L); changes in AWR similar to FEV_1
Roger et al. (1985)	28 mild asthmatics 19-34 yrs; selected for sensitivity to methacholine; 6/28 EIB, 18/28 with cold air-induced asthma; medication stopped prior to exposure	75 min including 3 10-min exercise periods (42 l/min)	0 ppm, 0.25, 0.5, 1 ppm: No statistically significance changes; actual values not reported	Bronchoconstriction (AWR) greatest after first exercise and progressively less after repeated exercise; spirometry ~12 min after last exercise, and since bronchoconstriction is transient may explain lack of effect
Linn et al. (1985)	24 COPD patients 49-68 yrs; mean FEV_1/FVC = 47%; 20 on bronchodilators; medication stopped 4 hrs prior to exposure	60 min exposure, with exercise 0-15 min and 30-45 min (18 l/min), similar to most vigorous normal activity	0 ppm: Δ FVC % +1.8%; Δ FEV_1 % -0.9% 0.4 ppm: -1.4; -1.7 0.8 ppm: +0.4; 0	No convincing evidence of physiological or clinical effects of SO_2 either as group means or individually; not even slight response in spirometry implies COPD less reactive than asthmatics and not susceptible population

Table A (Cont'd)

Selected Chamber Studies of Acute Changes in Spirometry when Experimentally Exposed to SO_2

Reference	Subjects	SO_2 Exposure	% Change in FEV_1, FVC	Comments
Kulle et al. (1986)	20 healthy adults age 20-35 yrs, non-smokers with normal spirometry, not on medication, no history of allergic rhinitis	4 hrs exposure with 15 min exercise (~35 l/min) at beginning and end of 4 hrs period; PM = activated carbon MMD = 1.5 µm (GSD = 1.5) (517 µg/m^3); SO_2 concentration = 0.99 ppm; Control exposures = mean of before and after exposure day	Δ FEV_1 % 17 minutes (post exercise) / 2 hours / 4 hours Control (air) +1.7% +1.3% +2.1% 0.99 ppm SO_2 -0.3 +0.3 +0.8 Post-exposure (air) +0.3 +0.5 +1.3 Mean air +1.0 +0.9 +1.7 --- Control (air) 0 +0.8 +3.0 0.5 mg/m^3 carbon +0.8 +1.6 +1.6 Post-exposure (air) +2.4 +2.2 +3.8 Mean air +1.2 +1.5 +3.4 --- Control (air) +1.6 +2.2 +2.7 SO_2 + carbon -0.8 +1.3 +0.8 Post-exposure (air) +0.8 +0.5 +1.3 Mean air +1.2 +1.35 +2.0	No effect on FVC or FEV_1; 1% of SO_2 adsorbed onto respirable carbon; which may explain why no important differences between SO_2 alone and SO_2 + carbon; small reduction after first 15 min of exercise/exposure to SO_2 and SO_2 + carbon, but not carbon alone; no significant decrements during second exercise period at exposure completion (4 hrs)
Kehrl et al. (1987)	10 mild asthmatics, 20-30 yrs; excluded persons insensitive or very sensitive to SO_2; FEV_1/FVC = 76%; preselected for mild-moderate broncho-constriction after 10 min exercise + 1 ppm SO_2; medication stopped prior to exposure	60 min exposure plus: 1) 3 10-min intermittent exercise, 2) 30-min continuous exercise; exercise = brisk walk up slight incline (~41 l/min)	Δ FVC % / Δ FEV_1 % Intermittent exercise 0 ppm -2.4% -1.6% 1 ppm -1.4 -5.8* Continuous exercise 0 ppm -2.0 -1.3 1 ppm -2.6 -8.0* *p <0.05	Somewhat attenuated response (AWR) after second or third exercise; refractory period similar to that of exercise-induced bronchoconstriction
Rondinelli et al. (1987)	10 normal non-smokers 55-73 yrs (117% predicted FEV_1)	30 min rest (post-rest) + 10 min moderate exercise with 1 mg/m^3 NaCl; 1 mg/m^3 NaCl + 0.5 ppm SO_2; 1 mg/m^3 NaCl + 1 ppm SO_2	Δ FEV_1 % Post-rest / Post-exercise 1 mg/m^3 NaCl -2.6 -5.3 NaCl + 0.5 ppm SO_2 -2.7 -5.3 NaCl + 1 ppm SO_2 -2.6 -5.4	Differences between text and table results; calculation shows no effect of SO_2 + NaCl

Table A (Cont'd)

Selected Chamber Studies of Acute Changes in Spirometry when Experimentally Exposed to SO_2

Reference	Subjects	SO_2 Exposure	% Change in FEV_1, FVC			Comments
				Δ FEV_1 %		
				20 minutes	60 minutes	% Unable to Perform Exercise	
Linn et al. (1987)	24 normal subjects age 18-37 yrs; mostly no allergies; no substantial EIB	1 hr-exposure, (30 min = exercise to 43 l/min ventilation); alternating 10 min rest/exercise); exposed twice to same regime with average % change calculated; medication withheld from all subjects on medication	0 ppm 0.2 ppm 0.4 ppm 0.6 ppm	+0.5% +1.2 +1.4 +1.4	+1.05% +1.4 +0.15 +0.95	0% 2%	Variation of baseline FEV_1 between exposures (high-low/low) = 1.2%
	21 atopics age 18-32 yrs; multiple allergies but normal baseline PFT and no EIB (exercise-induced bronchoconstriction)		0 ppm 0.2 ppm 0.4 ppm 0.6 ppm	+0.5% -0.5 -0.5 -1.9	-0.5% +0.3 -0.9 -0.8	2.5% 0	1.1% variation of baseline FEV_1
	16 minimal/mild asthmatics age 20-33 yrs; multiple allergies, normal baseline PFT; most no EIB; no regular medication		0 ppm 0.2 ppm 0.4 ppm 0.6 ppm	-1.6% -4.1 -10.7 -18.4	-0.4% -1.6 -5.4 -11.4	9% 15%	~2-3% of general population; 1.7% variation in baseline FEV_1
	24 moderate/severe asthmatics age 18-35 yrs; multiple allergies, 10 with reduced baseline FEV_1; all had activity restrictions and regular medication		0 ppm 0.2 ppm 0.4 ppm 0.6 ppm	-8.4% -9.5 -17.9 -25.3	-9.5% -9.8 -14.1 -20.9	10% 12	~<1% of general population; 3.8% variation in baseline FEV_1

Table A (Cont'd)

Selected Chamber Studies of Acute Changes in Spirometry when Experimentally Exposed to SO_2

Reference	Subjects	SO_2 Exposure	% Change in FEV_1, FVC	Comments
Koenig et al. (1987)	10 adolescent allergic subjects with EIB but without asthma; age 13-17 yrs; EIB = ≥15% reduction FEV_1 after 6 min exercise at >85% maximum O_2 consumption	10 min exposure via mouthpiece with exercise that did not elicit EIB (34 l/min)	Δ FEV_1 % Air: placebo -1.3% Air: albuterol (bronchodilator) -3.9 0.75 ppm SO_2: placebo -14.3 0.75 ppm SO_2: albuterol -4.2	Albuterol prevented SO_2-induced bronchoconstriction (-0.3% after subtraction of effect of air); -13% decrease FEV_1 after subtracting effect of exercise
Linn et al. (1988)	20 mild asthmatics age 19-36 yrs, 11 on medication to relieve symptoms or before exercise/pollen exposure; all had hyper-reactive airways to methacholine, cold air, exercise, or SO_2; 9 on asthma medication, withheld prior to exposure	10 min exposure with continuous exercise (50 l/min volume); 3 pretreatment conditions: 1) none 2) placebo 3) bronchodilator = metaproterenol (MP)	Δ FEV_1 % Treatment Prior to Exposure: None / Placebo / Bronchodilator 0 ppm: -5.0% (2) / -2.5% (2) / +14.6% (1) 0.3 ppm: -7.9 (2) / -6.4 (2) / +12.1 (0) 0.6 ppm: -19.6 (7) / -13.2 (3) / +10.4 (0) Δ FEV_1 %, mean pre-exposure FEV_1 assumed to be 2.8 l Δ FVC % and AWR showed similar pattern to Δ FEV_1 % ( ) = number taking broncholilator MP post-exposure	Within 30 min post-exposure symptoms and FEV_1 mostly returned to pre-exposure values; authors conclude typical bronchodilator usage by asthmatics likely to reduce response to ambient SO_2
McManus et al.(1989)	9 non-allergic asthmatics ≥55 yrs without respiratory disease; all on medication, which was stopped prior to exposure; ipratropium bromide and placebo also administered prior to exposure to 1 ppm SO_2	20 min exposure via mouthpiece at rest; 10 min exposure while exercising; at ~26 l/min; PFT was measured 30 min after exposure and exercise (= recovery); same protocol as Rondinelli et al. (1987)	Δ FEV_1 %:Table Post-resting / Post-exercising / Recovery Air: -2.4% (-1.6, 0.8) / -2.8% (-2.5, 1.1) / -1.4% 0.5 ppm: -4.1 (4.6, 1.9) / -6.5 (7.0, 2.0) / -3.4 1 ppm: -6.8 (8.5, 5.4) / -12.0 (-13.1, 5.6) / -8.2 1 ppm SO_2: Treatment Prior to Exposure Placebo -2.0% -5.2% -6.2% Bronchodilator +3.6 -3.6 -3.2 (% FEV_1 calculated from baseline after pretreatment) ( ) = Δ FEV_1 % and SEM from text; other values calculated from table	Authors comment that non-allergic asthmatics are more sensitive than healthy adults, there is large variation in response, and while ipratropium bromide improves baseline PFT, it does not reduce the proportionate response to SO_2

Table A (Cont'd)

Selected Chamber Studies of Acute Changes in Spirometry when Experimentally Exposed to SO_2

Koenig et al. (1989)	9 allergic adolescents with EIB age 12-18 yrs; 5/9 also had mild/moderate allergic asthma	40 min exposure (30 min at rest, 10 min moderate exercise of 32 l/min) via mouthpiece	Δ FEV_1 % Post-exposure Air: -1.8% 0.1 ppm SO_2: -2.3	There are preliminary results as 15 subjects are planned and final conclusions "must wait for conclusion of the study"
Linn et al. (1990)	21 moderate/severe medication-dependent asthmatics 18-50 yrs; 16 on theophylline, and usually added medication, e.g., β-adrenergic bronchodilators	10 min heavy exercise (50 l/min) during exposure to 0, 0.3, 0.6 ppm SO_2 and low, normal, and high medication low = medication withheld prior to exposure; normal = usual medication; high = normal medication + metaproterenol	Post-exercise Δ FEV_1 % (estimated from graph) SO_2 / Medication: Low / Normal / High 0: -14.5% / -12.2% / +15.2 0.3 ppm: -19.4 / -16.8 / +13.0 0.6 ppm: -30.2 / -29.1 / +9.5	Normal medication of metaproterenol provides similar protection for moderate/severe asthmatics as in mild non-medication dependent asthmatics (Linn et al., 1988). Theophylline improves baseline PFT but not effective against EIB or effects of SO_2
Koenig et al. (1990)	13 adolescents with allergic asthma and EIB age 12-18 yrs; 10/13 on regular medication; but withheld prior to exposure	45 min intermittent exercise (30 min at rest 15 min exercise of ~30 l/min) 120 ppb O_3 or air exposure, followed by 15 min 0.1 ppm SO_2 via mouthpiece and exercise	Δ FEV_1 % 2-3 min Post-exercise / 7-8 min Post-exercise 45 min air/ 15 min 0.1 ppm SO_2: -3.0% / -1.3% 45 min 120 ppb O_3/ 15 min 0.1 ppm SO_2: -7.7 / -3.0	Response to SO_2 may have been exaggerated because of exposure via mouthpiece; effect of exercise not measured, and cannot differentiate effects of exercising vs. SO_2
Devalia et al. (1994)	8 mild asthmatics with allergy to house dust mites, age 18-45 yrs; baseline FEV_1 ≥70% predicted; not on medication	6-hrs exposure at rest	Δ FEV_1 % (S.E.) / Δ FVC % (S.E.) Air: -2.2 (3.0) / -4.1 (2.0) 0.2 ppm SO_2: -3.5 (3.8) / -1.9 (3.0)	SO_2 exposure did not significantly increase sensitivity (p = 0.51) to allergen inhalation

Table A (Cont'd)

Selected Chamber Studies of Acute Changes in Spirometry when Experimentally Exposed to SO_2

AWR	-	airway resistance
COPD	-	chronic obstructive pulmonary disease
EIB	-	exercise-induced bronchoconstriction
Exercise	-	expressed as ventilation (l/min)
FEV_1	-	forced expiratory volume in 1 second
FVC	-	forced vital capacity
GSD	-	geometric standard deviation
MMAD or MMD	-	mass mean aerodynamic diameter (µm)
PFT	-	pulmonary function test
Δ PFT %	-	$\frac{\text{(post-exposure pre-exposure)}}{\text{pre-exposure}} \times 100$
PM	-	particulate matter
SE	-	standard error
Shaded area	-	>5% mean reduction after subtraction of effects at 0 ppm

FIGURE 1

Distribution of individual airway sensitivity to SO_2 [$PC(SO_2)$].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