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Current Toxicological Information as the Basis for Sulfur Oxide Standards

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The ambient air quality standard established in 1973 is 0.03 ppm annual average for sulfur dioxide and 0.075 mg/m³ for particulates. It is now generally believed that the toxicity of sulfur oxides in ambient air is significantly influenced by the coincident presence of particulates. Inhalation of 1 ppm of sulfur dioxide for 2 hr may produce alterations in pulmonary ventilatory function, both in normal and asthmatic subjects. Effects obtained at 0.5 ppm of sulfur dioxide are controversial and of questionable biological significance.

No clear evidence exists that sulfur dioxide or bisulfite causes mutagenicity in mammals, and it is concluded from a variety of animal experiments that long-term exposure to sulfur dioxide alone does not cause cancer.

Introduction

Since 1978, health effects and toxicity studies on sulfur oxides have been reviewed by scientists representing several organizations, including the National Research Council/National Academy of Science, the Environmental Protection Agency, the World Health Organization, the Natural Resource Defense Council and the American Iron and Steel Institute (*1-5*). This interest by various groups was brought about by the 1977 Clean Air Act amendments that mandate review by the Environmental Protection Agency of the scientific criteria for the establishment of air quality standards protective of health and welfare.

As new information on toxicity of air pollutants in general, and of sulfur oxides in particular, has become available, it is timely to review critically all of the scientific information in support of the standards in force since the early 1970s. Although the literature on toxicology of sulfur oxides exceeds 2000 original publications, this discussion focuses on those articles that are most relevant.

At the outset, it is important to point out that concepts of the toxicity of sulfur oxides have drastically changed during the past decade. It is now realized that the toxicity of sulfur oxides is influenced by the coincident presence of particulates and that air standards should be developed for both groups of pollutants, simultaneously or concurrently (*3-5*). The reasons for this conceptual change are as follows: (a) both sulfur oxides and particulates originate from such common emission sources as combustion of wood and other fuels and from less common sources, for example, volcanic eruptions; (b) levels of both are frequently concomitant in ambient air; (c) sulfur dioxide by itself in concentrations normally found in ambient air does not appear to be the cause of adverse human health effects; and (d) virtually all of the recent human health data suggest that health effects occur when sulfur oxides and particulates are interacting at very high concentrations of both.

The toxicological information on the combined effect of sulfur oxides and particulates is minimal (*6*). Thus, the discussion that follows is confined to the information on sulfur oxides alone.

The ambient air quality standards established in 1973 are as follows: 0.03 ppm annual average for sulfur dioxide and 0.075 mg/m³ for particulates. The criteria for the national ambient air quality standards for sulfur oxides and particulates are to be reviewed by the Administrator of the EPA, who has the choice of either changing the levels (as was done by relaxing the ozone standards in 1979) or maintaining them at the current levels.

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Inhalational Kinetics

Sulfur dioxide in the ambient air may be inhaled as a gas or it may enter into a variety of chemical and physical reactions with particulates that are present in the air. Depending on the aerodynamic properties of the particles, they may be deposited in the nasopharyngeal region, in the tracheobronchial passages or in the pulmonary alveolar area. It has been estimated that a nose-breathing person would have the following fractional deposition pattern: particles 5 μm in diameter or larger deposited mostly (i.e., 95%) in nasal and tracheobronchial regions; approximately 25% of particles 1 μm in diameter and 35% of particles 0.2 μm in diameter would reach the pulmonary alveoli (7); the remainder is impacted in the air passages or exhaled.

Sulfur dioxide as a gas in the inspired air or desorbed from inhaled particulates undergoes a series of chemical reactions (Fig. 1): (a) solution in water to form sulfurous acid ($H^+ + HSO_3^-$) which is absorbed into the blood stream through the pulmonary capillaries; (b) oxidation of bisulfite (HSO_3^-) to sulfate ($SO_4^=$), which is excreted in the urine; (c) reversibly combined with proteins; (d) irreversibly autoxidized with the formation of free radicals such as hydroxyl and superoxide; and (e) sulfonation of cytosine to form uracil, that is, deamination of cytosine (*8-14*).

The toxicity attributed to sulfur dioxide occurs through the last three of these mechanisms. However, there is no accurate estimation of the proportion of these three potentially toxic reactions relative to the formation and urinary excretion of sulfate ion; nor is there any practical means of identifying the sulfate derived from inhaled sulfur dioxide separately from that ingested in food or water. Extensive critical studies in animals with the use of labeled sulfur would be desired to assess the fate of inspired SO_2, but the information available is limited.

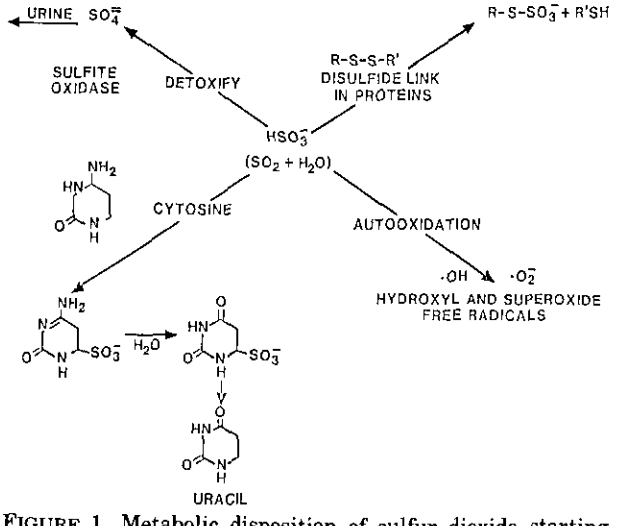

FIGURE 1. Metabolic disposition of sulfur dioxide starting with the formation of bisulfite ion.

Table 1. Summary of results of human exposure to low levels of sulfur dioxide.

SO_2 (120 min), ppm		Positive	Negative
0.5	Odor perception	1 study	1 study
	Reduced ventilatory function, normal subjects	1 study	6 studies
	Reduced ventilatory function, resting asthmatics	2 studies	1 study
1.0	Odor perception	—	1 study
	Reduced ventilatory function, normal subjects	5 studies	2 studies
	Reduced ventilatory function, resting asthmatics	2 studies	—

The Lung as Primary Target Organ

Human Studies

There is general agreement that the inhalation of sulfur dioxide exerts its primary toxicity on the respiratory system, specifically the lung. The epidemiologic studies relative to the health effects of exposure to sulfur oxides and particulates have been vigorously debated in the literature, most recently by Holland et al. (*2*).

From the toxicology standpoint, the results of controlled human exposure studies can offer some definitive, as well as controversial, statements (Table 1). There is a consensus among scientists that the inhalation of 1 ppm sulfur dioxide for approximately 2 hr may produce alterations in pulmonary ventilatory function, both in normal and asthmatic subjects (*15-23*). On the other hand, the results of human exposure to 0.5 ppm are more controversial, since there are three studies that show a positive influence on ventilatory function (*13-24*) and six studies that do not show such effects (*19, 25-29*). The ability to perceive odor at either level of sulfur dioxide is highly variable (*30-32*).

The author agrees with the above stated generalization that, in controlled human expo-

sure, the minimal concentration that influences pulmonary ventilatory function is approximately 1 ppm of sulfur dioxide. The effect of 2-hr inhalation is a transient and reversible decrease in ventilatory function. There is no proof that this low level of sulfur dioxide provokes acute asthmatic attacks independent of this transient effect on pulmonary ventilatory function. The past episodes of acute exacerbations of asthma, occurring in London, New York City and Danora, were characterized by excessively high levels of sulfur oxides (>10 ppm).

Jaeger et al. (*24*) reported a decrease in ventilatory function of asthmatics exposed to 0.5 ppm of sulfur dioxide. The late H. A. Bouhuys pointed out that the exposure was with mouth breathing and that the slight effect seen in a few of the asthmatics studied was less than the normal variation seen in these patients over time (*33*). More recent studies by Boushey, using lower concentrations of sulfur dioxide, show that exercise increases sulfur dioxide-induced bronchoconstriction in subjects with mild asthma (*34*). Koenig's reports (*20, 21*) are on adolescent asthmatics inhaling sulfur dioxide with saline aerosol. Unfortunately, sulfur dioxide alone was not tested. The airway response can only be explained by the effects of sulfurous acid solution dissolved in the aerosol. Furthermore, the subjects wore nose clips and were, therefore, necessarily mouth-breathing, a situation that has little parallel with real life.

The subject of mouth breathing with nose clipping needs additional comment. Human exposure studies consisting of this artificial maneuver are difficult to interpret because the inspired air bypasses the protective and conditioning mechanism of the nose. The mouth is less likely to modify the inspired air so that air pollutants such as sulfur dioxide penetrate more deeply into the air passages than they would under natural circumstances.

Animal Studies

The potentiation of the airway effects of sulfur dioxide by saline (sodium chloride) aerosol was first demonstrated by Amdur in the 1960s (*35, 36*). In guinea pigs, the inhalation of 2 ppm sulfur dioxide caused an increase in airway resistance of 20%, and the addition of saline aerosol elicited a response of 55%. The potentiation was seen only with high levels of aerosols (10000 mg/m^3) but not with lower levels (4000 mg/m^3). Solutions of other salts (manganous chloride, ferrous sulfate, sodium orthovanadate) also potentiated the response to sulfur dioxide—all through formation of sulfuric acid, a known irritant.

It should be recognized that potentiation of the bronchoconstrictive effect of 2 ppm sulfur dioxide by saline aerosol can only be demonstrated in guinea pigs. The phenomenon cannot be seen in cats or dogs with levels higher than 2 ppm. Amdur warned in her own publication that "the stress of techniques used has rendered the animals more sensitive to low grade irritant exposure." Others have criticized the design of Amdur's experiments as using very high levels of humidity, which are rarely encountered in the natural setting.

The fundamental question is the significance of bronchospasm in the pathogenesis of lung disease. The airway response is an indication of a defense mechanism and there is positive proof that when sulfur dioxide is administered continuously for months, at levels exceeding 2 ppm, the lungs do not develop persistent pathologic changes (Table 2). Alarie et al. exposed guinea pigs and monkeys continuously for 18 months and found no histopathologic changes in the lung (*37, 38*). The following exposures gave negative results: 0.13 ppm, 1.0 ppm or 5.1 ppm sulfur dioxide, with or without fly ash particulates. The minimal concentration that caused histopathological lesions in the lung was 10 ppm of sulfur dioxide.

A chronic study in dogs, reported by Lewis et al. (*39*), consisted of exposure for 670 days. The animals exposd to 5.1 ppm showed abnormal pulmonary function, though no clear-cut histopathological changes were observed.

It should be stated that lung cancer was not seen in the chronically exposed animals described above. Laskin et al. (*40, 41*) conducted three series of experiments consisting of long-term expo-

Table 2. Summary of long-term animal exposure to low levels of sulfur dioxide.

SO_2, ppm	Exposure 16-23 hr/day		Pulmonary toxicity	
			Negative	Positive
0.13	Guinea pigs	12 months	1 study	—
0.13	Monkeys	18 months		
0.42 ($+H_2SO_4$) (Aerosol)	Dogs	18 or 36 months	1 study	—
1.0	Guinea pigs	12 months	1 study	—
1.0	Monkeys	18 months		
5.1	Guinea pigs	12 months	1 study	—
5.1	Monkeys	18 months		
5.1	Dogs	7.5 or 20 months	—	1 study
10.0 (+B(a)P)	Hamsters	23 months	—	1 study
	Rats	23 months		

sure to sulfur dioxide alone or in combination with benzo(a)pyrene. Their first series, using hamsters exposed 6 hr/day, 5 day/week for 98 weeks, was totally negative in terms of lung carcinogenicity. Their second series was also negative when rats were exposed to 10 ppm sulfur dioxide alone (Table 3). However, 24% of rats exposed to a combination of sulfur dioxide and benzo(a)pyrene developed lung neoplasms. The third series consisted of lifetime exposures with the following results: negative for lung carcinogenicity following exposure to sulfur dioxide alone, and the presence of lung neoplasm in 20% or fewer of rats exposed to both sulfur dioxide gas and benzo(a)pyrene.

The positive observations by Laskin et al. have been interpreted as suggesting that sulfur dioxide gas is a cancer-promoting agent or a cocarcinogen to benzo(a)pyrene. The results have been questioned because of the limited number of animals, the inadequate design and the questionable statistical significance of the results. Furthermore, the exposed rats, including the controls, exhibited a high incidence of pneumonia (A. Sellakumor, personal communication).

In view of these shortcomings, the Laskin study does not provide such evidence of any cancer-producing role of sulfur dioxide. One statement can be unequivocally made: sulfur dioxide alone is not a carcinogen based on the observations of Alarie et al. in guinea pigs and monkeys, Lewis et al. in dogs, and Laskin et al. in rats. In a recently completed, but yet unpublished, NIOSH-sponsored study in Cincinnati, Ohio, rats were exposed to 5 ppm sulfur dioxide, 5 days/week, 7 hr/day, for a duration of more than 12 months. There was no evidence of carcinogenicity or cocarcinogenicity in this study.

The mutagenicity of biosulfite in some *in vitro* preparations does not necessarily apply to inhalation of sulfur dioxide. Bisulfite is a transient metabolite and is quickly oxidized to sulfate. It is, therefore, questionable whether a sufficient concentration persists in the cells to simulate the conditions of the *in vitro* studies.

No clear evidence exists for mutagenicity in mammals due to sulfur dioxide or bisulfite (*5, 14*). However, because of the deamination of cytosine in high concentrations of bisulfite previously described, there has been speculation that the sulfur oxides might be mutagenic. At very high concentrations of bisulfite in acid solutions, point mutations in Salmonella were detected, while there was no clear-cut evidence of mutagenicity at low concentrations or at neutral pH (*5, 14*). The relevance to inhaled sulfur dioxide as a mutagen is not clear. Cell toxicity, rather than mutagenicity, is observed when cultures of animal and human cells are exposed to bisulfite (*5, 14, 42*). Negative results are seen when using the dominant lethal assay (*14, 43, 44*) as well as when Drosophila are exposed to bisulfite (*45*). There are limited data showing that 0.01 M bisulfite inhibits mitosis in human lymphocytes (*14, 46*).

Summary

A variety of animal experiments show that long-term exposure to sulfur dioxide alone is not a cancer-causing condition (*37-39*). The experiments reported by Laskin et al., because of shortcomings in design, do not prove that sulfur diox-

Table 3. Summary of results of long-term exposure of rats to low levels of sulfur dioxide and particulates.[a]

	Exposure	Incidence of lung cancer, %	
Rats exposed 5 days/week for 98 weeks			
Air controls	—	0/3	0
SO_2 (10 ppm)	6 hr/day	0/3	0
SO_2 (3.5 ppm) + B(a)P	1 hr/day	2/21	9.5
SO_2 (10 ppm) followed by SO_2 (3.5 ppm) + B(a)P	6 hr/day 1 hr/day	5/21	24.0
Rats exposed 5 days/week lifetime			
Air controls		0/15	0
SO_2 (10 ppm)	6 hr/day	0/15	0
B(a)P	1 hr/day	1/30	3.3
SO_2 (10 ppm) followed by B(a)P	6 hr/day 1 hr/day	2/30	6.7
SO_2 (4 ppm) + B(a)P	1 hr/day	4/45	8.9
SO_2 (10, ppm) followed by B(a)P + SO_2 (4 ppm)	6 hr/day 1 hr/day	9/46	19.6
All B(a)P = 10 mg/m^3			

[a]Data of Laskin (*40*).

ide may serve as a cocarcinogen to benzo(a)pyrene (A. Sellakumar, personal communication).

In long-term exposure experiments, the minimal concentration that causes pulmonary lesions that are non-neoplastic in nature is 5 ppm sulfur dioxide in dogs (*29*) and 10 ppm in monkeys and guinea pigs (*37, 38*). On the basis of transient changes in pulmonary function, the threshold concentration in man is 1.0 ppm. The studies showing a response to 0.5 ppm are inconclusive because they were derived from asthmatic subjects with nose clips (*24*).

It is anticipated that sulfur dioxide will continue to interest investigators in designing animal experiments relating to cocarcinogenic and mutagenic potential of air pollutants in general. Epidemiologic studies designed to correct the deficiencies of those reported to date and to answer the question of human toxicity need to be initiated as soon as possible.

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