III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

Sulfur dioxide is a colorless, irritant gas having a characteristic odor and taste. Its more important physical and chemical properties are presented in Table XI-1. [1,2] Potential occupational exposures are listed in Table XI-2. [3]

Sulfur dioxide has a number of important industrial uses. [4] It is used in many chemical processes including the manufacture of sodium sulfite, and as an intermediate in the manufacture of sulfuric acid. It is also used in refrigeration, bleaching, fumigating, and preserving operations, and as an antioxidant in the melting, pouring, and heat treatment of magnesium. Breathing-zone concentrations of sulfur dioxide in some magnesium foundries have reached concentrations in excess of 50 ppm. [4]

Exposures to sulfur dioxide are not limited to operations where it is used. It is generated as a byproduct from many industrial processes, including the smelting of sulfide ores, the combustion of coal or fuel oils containing sulfur as an impurity, paper manufacturing, and petroleum refining. [4]

NIOSH estimates that 500,000 persons in the work force could have potential exposure to sulfur dioxide.

Historical Reports

Comparatively few early historical reports are available of poisoning by sulfur dioxide. The first report of lasting harmful effects due to sulfur dioxide alone came from France in 1821. [5] There were many complaints of the irritant effect of the gas upon workers employing sulfur dioxide in the bleaching of textiles. There was a report from Germany in 1853 on the exposure of workers to sulfur dioxide during the process of drying sugar beets. [6] The gas was reported to cause pneumonia, gastritis, enteritis, and even vaginitis.

In 1893, the first measurements of occupational environmental concentrations of sulfur dioxide and its effects were reported by Lehmann from Germany. [7] Certain operations in the bisulfite papermaking industry contained from 6-30 ppm sulfur dioxide and the workers, alleged to have the appearance of good health, ignored its effects. However, the author [7] and his two assistants, unaccustomed to sulfur dioxide, reportedly experienced nasal irritation after 10 minutes exposure to 6.5 and 11.5 ppm and found 30-57 ppm decidedly disagreeable. It has since been shown that acclimatization to the subjective effects of sulfur dioxide does occur. [8,9]

In 1930, Rostoski and Crecelius [10] reported on the acute effects of overexposure to sulfur dioxide and probably other products of wood pulp bisulfite digestion following the explosion of a digester vessel. Of the 18 workers involved in the accident, one died 10 months and another 15

months later from intercurrent pulmonary infection. Three years later, 8 others were still incapacitated by radiologically confirmed chronic bronchitis and emphysema. Those who returned to work complained of dyspnea and bronchial catarrh. Greenwald [11] in 1954 believed that the serious results of this accident were not due to sulfur dioxide but to the wood and its products. Greenwald's 1954 report [11] represents an excellent review of the effects of sulfur dioxide inhalation up to that time.

Effects on Humans

The rapidity with which sulfur dioxide forms sulfurous acid on contact with moist mucous membranes explains its prominent biologic effect in man and animals, ie, severe irritation. The sulfur dioxide molecule itself is chemically reactive, but as all biologic systems function in an aqueous milieu, it is doubtful whether sulfur dioxide as such can exist in significant concentrations within living organisms. Sulfur dioxide is most likely absorbed as sulfurous acid or one of its ionization products and may undergo further biotransformation reactions in the body. The ultimate fate of practically all absorbed sulfur dioxide is apparently oxidation to sulfate ion, to be excreted principally as inorganic sulfate in the urine. [12]

(a) Occupational Exposures

(1) Acute Effects

Sulfur dioxide concentrations above 20 ppm have a marked irritant, choking and sneezing effect. [7,11] Acute exposure to

concentrations of about 50 ppm will promptly cause irritation of the nose and throat, rhinorrhea, and cough. These symptoms are sufficiently disagreeable that most persons would not tolerate them for more than 15 minutes. [11] Such exposure will cause reflex bronchoconstriction and possibly some increase in bronchial mucous secretion with increased pulmonary resistance to air flow. [13] These changes may be clinically manifested by high-pitched rales, and by a tendency to prolongation of the expiratory phase of respiration. [13]

If workers are exposed to catastrophic amounts of sulfur dioxide in a confined space, asphyxia will most probably result. If exposure is insufficient to cause death by asphyxia, a chemical bronchopneumonia with bronchiolitis obliterans may develop, which may be fatal after an interval of some days. Such a case was reported by Galea in 1964 [14] from an incident in a paper-pulp plant in Canada where a worker was exposed to a high, but unmeasured, concentration of sulfur dioxide for from 15-20 minutes and died 17 days later.

Romanoff [15] in 1939 reported the development of typical signs of bronchial asthma following acute exposures to unknown concentrations of sulfur dioxide. One man had frequently been exposed over a 10-year period to low concentrations of the gas in the course of his work. Following an unusually large exposure to leaking sulfur dioxide, the man developed asthma-like attacks which required hospitalization. It was suggested that he had become sensitized to the bacteria which had established a

suppurative bronchitis secondary to the inflammatory effects of the sulfur dioxide.

Sulfur dioxide gas is irritating to the eyes, producing burning discomfort and lacrimation, but actual injury from industrial exposure is rare. However, liquid sulfur dioxide from pressurized containers can produce severe burns to the cornea of the eye which may be deceptively painless for the first few hours or even days. The increased severity is due to the high concentration and is aggravated by the freezing effect of the rapidly evaporating liquid. Over the course of weeks or months, the cornea may become infiltrated and densely vascularized resulting in opacification and severe loss of vision. Only in the mildest cases would the initial corneal cloudiness be expected to clear completely. [16]

(2) Chronic Effects

Chronic exposure to sulfur dioxide is extremely widespread in industry, [4] with problems occurring in smelting operations, [17] paper manufacture, [18,19] and formerly in refrigerator production. [8] The most meaningful exposure-effect information is found in occupational epidemiologic reports and nonoccupational experimental studies; therefore, the presentation of epidemiologic findings at this point is considered desirable to best develop the subject.

(A) Epidemiologic Studies

In most industrial situations, exposures have occurred to a mixture of sulfur dioxide with some sulfuric acid aerosol, metallic oxides, or other gases or particulate matter. [18,19] In contrast, exposures to

relatively pure sulfur dioxide gas arising from the evaporation of liquid sulfur dioxide used as a refrigerant were reported in an epidemiologic study in 1932 by Kehoe et al. [8] The study included 100 men having a mean duration of employment exposure of 3.8 years (47 employees had from 4-12 years employment exposure) to atmospheric concentrations averaging 20-30 ppm (range 5-70 ppm) at the time of the study. Prior to 1927, the sulfur dioxide levels had been much higher, averaging 80-100 ppm. A control group of 100 men, age-matched with the exposed group, was selected from parts of the same plant where there was no known exposure to sulfur dioxide or to other known noxious gases, fumes, or dust. Each of the 200 subjects was questioned in detail as to the length and nature of his exposure to sulfur dioxide. In addition, urinalyses and chest roentgenograms were obtained.

The symptoms associated with exposure to sulfur dioxide were classified as: 1. initial symptoms, that is, those which developed during the period before acclimatization (discussed below); 2. symptoms arising from customary exposure with or without acclimatization; and 3. symptoms produced by heavy exposure. Initial symptoms were confined to the respiratory tract and consisted, in descending order of frequency of occurrence, of irritation to the upper respiratory tract, coughing, epistaxis, constriction in the chest, and hemoptysis. Symptoms associated with customary exposures were, in descending order of frequency, hacking cough, morning cough, nasal irritation and discharge, prolongation of common colds, and expectoration. The severity of these symptoms seemed to be related to individual variation; however, all subjects showed some

symptomatic evidence of irritation of the upper respiratory tract. Symptoms associated with severe exposure were chiefly an intensified form of those occasioned by the original customary exposure.

A statistically significant higher incidence of nasopharyngitis, alteration in the senses of smell and taste, and increased sensitivity to other irritants was elicited from the exposed group as compared with the controls. A significantly higher incidence of tendency to increased fatigue, of dyspnea on exertion, and longer duration of colds (although their frequency was no greater) was also noted. The acidity of the urine to methyl red was prominent in the exposed group. There was no significant difference in the incidence of chest roentgenographic abnormalities between the two groups. Slightly more than 4% of each group had "definite chest pathology." Acclimatization occurred in 80% of the exposed group. The mean length of time necessary for acclimatization was calculated to be 2.84 months (S.D. = 2 months). The high standard deviation emphasized the great variability in the time required for acclimatization to take place. Acclimatization was considered to be the acquired ability to withstand the customary basic exposure without experiencing a notable intensity of initial symptoms. Acclimatization is further discussed under Experimental Studies. It is of interest that 20% of the exposed group failed to become acclimatized to exposure, but, according to the report, nevertheless continued to work and to be exposed to sulfur dioxide. The authors believed that the human organism has a high degree of adaptability to a regular moderate exposure (presumably 20-30 ppm) of sulfur dioxide and that

it suffers no apparent injury from such an exposure. In the case of intense exposures, even though they occurred frequently, there was believed to be no evidence of damage of a serious or a permanent type.

Anderson [9] in 1950 reported on the effects of sulfur dioxide exposure in approximately 135 Iranian oil refinery workers. Usual exposures in the refining and special products areas were estimated at between 0-25 ppm. However, even though the buildings were open on all sides affording good ventilation in the warm climate, exposures varying between 60 and 100 ppm had been recorded during times when plant maintenance was relatively low. No significant differences were reported between exposed workers and reportedly nonexposed controls in weight, systolic blood pressure, or chest roentgenographic findings. An unexplained difference was reported in the mean vital capacity of exposed workers vs controls in the refining area; however, no differences were noted between exposed workers and controls in the special products area. The author claimed no evidence of adverse effects could be found as a result of the study although no mention was made of any incidence of pulmonary irritation, coughing, nasal irritation, etc, which are associated with sulfur dioxide concentrations at the exposure levels encountered.

Skalpe [18] in 1964 reported a study of sulfur dioxide exposure in 54 workers in 4 different paper-pulp mills in Norway. In addition, 56 nonexposed controls were studied from the same industry and districts. The study was stimulated by the fact that pulp mill workers very often complained of chronic cough; therefore, an attempt was made to determine

whether there was a higher incidence of respiratory disease in the pulp mill workers than in a comparable unexposed control group. Environmental measurements were taken with detector tubes at different times and sites at the 4 different pulp mills on a single day. Sulfur dioxide concentrations ranged from 2-36 ppm and were considered to represent general working conditions in the acid tower and digester plant of the 4 pulp mills. Special working procedures occurred, such as "blowing the digesters," for which concentrations up to 100 ppm resulted, lasting only a few minutes but during which, pulmonary irritation was so intense that gas masks had to be used. It was emphasized that workers had much heavier exposure than was indicated by the analyses. The mean durations of employment exposure were 6.8 years for the subjects under 50 years of age, and 20.3 years for those over 50 years. All subjects were questioned to determine the incidence of cough, sputum, dyspnea, and cigarette smoking habits.

A significantly higher frequency of cough, expectoration, and dyspnea on exertion was found in the exposed group, the difference from controls being 4 to 5 times the standard error in the age groups under 50 years and 2 times the standard error in the over-50-year groups. The average maximal expiratory flow rate was significantly lower in the exposed groups than in the control groups for men under 50 years of age. Beyond 50 years of age, there was no significant difference between the exposed and control groups. Vital capacity values showed no differences between exposed and control groups regardless of age. Cigarette smoking did not appear to have any significant influence.

It was surprising that the high frequency of symptoms of respiratory disease was the greatest in the age groups under 50 where employment exposure time had been shortest. According to the author, [18] the most likely explanation was that because respiratory disease was rare in the younger age groups, the effect of small external insults was easier to detect than in the older age groups where respiratory disease from other causes was more common and small additions would be less noticeable.

In 1967, Ferris et al [19] presented results on the incidence of chronic respiratory disease in 147 pulp mill workers together with 124 workers from a neighboring paper mill who served as controls. The exposed group from the pulp mill complex included workers from 3 separate subplants-- a Kraft mill, a sulfite mill, and a chlorine plant; therefore, exposures resulted from sulfur dioxide, chlorine, chlorine dioxide, hydrogen sulfide, and some organic sulfides including mercaptans. At the time of this study, only traces of chlorine and hydrogen sulfide were found although chlorine levels had been high in prior years (mean = 7.4 ppm, range 0 - 64 ppm). Mean concentrations of sulfur dioxide taken on 3 separate days on each of 3 prior years were 13.2, 4.05, and 2.06 ppm. Although not specified by the authors, it seems apparent from the type of operations involved, that, similar to Skalpe's report, [18] these concentrations represented general working conditions. Special procedures most likely occurred which resulted in exposure concentrations in excess of those reported. Ferris et al [19] found no statistical differences in the rates of chronic bronchitis and other respiratory diseases between the pulp

mill exposed workers and the paper mill controls, the prevalence of chronic nonspecific respiratory diseases being 32.5% and 27.4% for the pulp mill and paper mill groups, respectively. Interestingly, the incidence of respiratory disease found in both groups (approximately 30%) indicates that chronic respiratory disease was a problem and that the paper mill workers did not represent a satisfactory control group. This was substantiated by the authors, [19] since, during the course of the study, it became apparent that many of the men currently working in the paper mill had, in fact, been previously employed in the pulp mill. In many cases they had transferred from the pulp to the paper operation because they found the odors in the pulp plant to be so disagreeable. Also, wage scales were slightly higher on the paper machines so that a considerable amount of self-selection had taken place. A rather complicated comparison was also presented between pulp and paper mill workers and a local general male town population based on the incidence and type of smoking habits.

(B) Carcinogenic Studies

Lee and Fraumeni, [17] reporting in 1969 on an excess in total mortality among arsenic exposed smelter workers, found as much as an 8-fold excess in instances of respiratory cancer as compared with that of the white male population of the same states. Their findings supported the hypothesis that inhaled arsenic is a respiratory carcinogen in man. At the same time, they showed a gradient in proportion to the degree of exposure to sulfur dioxide as well as the arsenic. Therefore, the influence of sulfur dioxide or unidentified chemicals, varying

concomitantly with arsenic exposure, could not be discounted. The study reported the mortality experience due mainly to malignant neoplasms of the respiratory system and diseases of the heart of 8,047 white male smelter workers during 1938 to 1963. Work areas were rated on a scale with respect to the level of sulfur dioxide exposure and members were classified in one of three exposure groups, that is, heavy, medium, or light work exposure areas. In general, the heavy sulfur dioxide exposure areas coincided with the medium arsenic exposure areas and the medium sulfur dioxide areas coincided with the heavy arsenic areas. Sulfur dioxide exposure and respiratory cancer mortality were positively correlated, with observed deaths ranging from 2 1/2 to 6 times expected in the light, medium, and heavy exposure groups (Table XI-3). Investigations revealed that persons with heavy exposure to arsenic and moderate or heavy exposure to sulfur dioxide were most likely to die of respiratory cancer. The overall excess of respiratory cancer could not be explained on the basis of other factors such as socioeconomic status, genetic susceptibility, availability of medical care, accuracy of death certificates, and urbanization. Furthermore, although smoking histories were not available for persons in the study, it was deemed highly unlikely that smoking alone would account for the excess respiratory cancer mortality observed. There was no reason to believe there was a positive relationship between amounts smoked and degree of arsenic and sulfur dioxide exposure in the smelters. Although no studies implicate sulfur dioxide as a carcinogen in man, it was postulated that perhaps sulfur dioxide or other chemicals in the work environment

possibly enhanced the suspected carcinogenic effect of arsenic or other unknown substances.

Two animal studies [20,21] have associated sulfur dioxide exposure with the incidence of bronchogenic carcinoma in conjunction with known carcinogens or animal strains having a high spontaneous incidence of lung carcinoma. The studies are discussed in the section under Animal Toxicity.

(C) Skin Hypersusceptibility

The incidence of skin reactions resulting from prolonged exposures to sulfur dioxide have been reported by Pirila in 1954 [22] and 1963. [23] The first report [22] involved a case of urticaria in a man working outdoors in a sulfate spirit mill where hot waste liquor was emptied into a reservoir several times daily. At such a time, the patient was exposed to the gases and, when using a gas mask, no skin reaction resulted; however, without the gas mask the skin eruptions occurred. When the patient was placed in a chamber and exposed to 40 ppm sulfur dioxide for 1 hour, the urticaria reappeared. In the second report, [23] a skin eruption resembling that resulting from a drug hypersensitivity occurred in a man working in an old building demolishing refrigerator machinery. Sulfur dioxide occasionally burst out in sufficient concentrations to cause him to evacuate the area. Three days after such an incident, the patient observed an eruption on his forearms which, during the following 5 days, spread to all the extremities and trunk. In addition, swelling of the eyelids resulted. No drugs had been used for 1 week prior to the onset of the eruption. Following topical treatment and oral antihistamines,

regression began and had entirely disappeared after 4 weeks. Later, the patient was exposed in a chamber to 10 ppm sulfur dioxide for 30 minutes. On the following day, lesions again appeared but were weaker than had been previously experienced. The eruption disappeared the following night. Another chamber exposure to 40 ppm sulfur dioxide for 10 minutes was given, after which the patient was permitted to breathe fresh air for an unspecified period and then returned to the chamber for another 10 minutes. On the following day, an eruption again developed which was more severe than to the 10 ppm exposure. Regression of the lesions followed in approximately 2 days. It thus seems that these 2 reported cases were due to a systemic allergic reaction. In the case of allergic individuals, it is extremely difficult to calculate a critical exposure concentration. The subject of sulfur dioxide-related hypersusceptibility is further discussed under Experimental Studies below.

Bronchial asthma has been reported by Romanoff [15] associated with chronic intermittent exposure to sulfur dioxide in the refrigeration industry. The affected individuals also had a predisposition to allergy.

(b) Experimental Studies

Many human experimental studies have been conducted in the past 2 decades concerning the effects of exposure to sulfur dioxide alone or in combination with aerosols of both soluble and insoluble particulates. Although the interest of most researchers has been with sulfur dioxide in the context of community air pollution, the experimental exposure levels have usually been in the range of industrial exposure levels. Most of the

effects studied have involved various aspects of respiratory mechanics, all related to pulmonary flow resistance. Unless otherwise stated, all the following experiments were performed on subjects not occupationally exposed to sulfur dioxide.

(1) Studies on Respiratory Mechanics

Sim and Pattle [13] in 1957 exposed healthy male volunteers to a wide range of sulfur dioxide concentrations either by facemask or by placing the subjects in an exposure chamber. The exposure levels were expressed as mg-minutes/cu m; however, by converting these to ppm for a 10-minute exposure (conducted with the facemask) and a 60-minute exposure (conducted in the chamber), results were as follows: at exposures above 50 ppm for 10 minutes or 9 ppm for 60 minutes (1330 mg-min/cu m), 50% of the subjects experienced an increase in airway resistance of more than 20% above normal accompanied with rhinorrhea and lacrimation. High pitched rales were noted over the larger bronchi for the 10-minute exposures and moist rales occurred over the lung periphery at the 60-minute exposures. At exposures to 30 ppm for 10 minutes or 5 ppm for 60 minutes (800 mg-min/cu m), little change was noted clinically or in lung resistance to air flow.

Several investigators have exposed subjects to sulfur dioxide concentrations at 5 ppm.

Frank et al [24] in 1964 reported an average 39% increase in pulmonary flow resistance above control levels within 10 minutes of exposure to 5 ppm sulfur dioxide in 11 men. Rates of recovery to baseline

varied after cessation of exposure but the group still showed residual effects after 15 minutes.

Nadel et al [25] in 1965 found that inhalation of 4-6 ppm sulfur dioxide for 10 minutes in 7 healthy subjects caused an increase in airway resistance. This effect was completely prevented by prior subcutaneous injection of atropine, suggesting a reflex bronchoconstrictive effect.

Snell and Luchsinger [26] in 1969 found a statistically significant decrease in maximum expiratory flow from the level of one-half vital capacity in 9 men exposed to 5 ppm.

Melville [27] in 1970 reported on changes in specific airway conductance of 49 healthy volunteers exposed to 5 ppm sulfur dioxide (also to 2.5 and 10 ppm) for 1 hour. An observed decrease in specific airway conductance was more pronounced with mouth breathing than with nose breathing at the 2.5 and 5 ppm exposure levels. At 10 ppm, there was no significant difference between the decrease in specific airway conductance for nose and mouth breathing. At 5 ppm, there was no further decrease in specific airway conductance after the first 5 minutes of exposure. According to the author, these experiments suggested that at sulfur dioxide levels up to 5 ppm, the nasal passages effectively absorb some of the inhaled sulfur dioxide and thereby diminish the stimulation of sensitive receptors in the larynx, trachea, and bronchi. Since continued exposure to sulfur dioxide resulted in no significant change in specific airway conductance after 5 minutes, a response was suggested aimed at maintaining an optimal compromise between airway diameter and work of breathing.

The following studies have measured exposure responses to sulfur dioxide concentrations at 1 ppm.

Amdur et al [28] in 1953 showed an increase in respiratory rate of 3-4 breaths/minute, an increase in pulse rate of 8-9 beats/minute, and a decrease in tidal volume of about 25% below control levels during the first 2 minutes of an 11-minute exposure to 1 ppm sulfur dioxide in 4 healthy adult men. During the remainder of the exposure period, the tidal volume increased again but stabilized at about 15% below control values. Subsequent studies by others [13,29] have failed to confirm these findings at the 1-ppm level.

Frank et al [29] in 1962 reported no detectable change in pulmonary flow resistance or peak flow rate in 10 out of 11 healthy male adults. The one subject who did show a response consistently had the highest preexposure control values of the group for pulmonary flow resistance. He had no history of respiratory illness and was a moderate smoker.

Snell and Luchsinger [26] in 1969 reported a small but statistically significant decrease in maximum expiratory flow from the level of one-half vital capacity for a group of 9 physicians and technicians.

Burton et al [30] in 1969 failed to find any immediate physiologic effect on pulmonary flow resistance to sulfur dioxide levels averaging 2.1 ppm ±0.19 (range 1.2-3.2 ppm) in 10 healthy male volunteers, half of them smokers.

Weir et al [31,32] exposed 4 groups of 3 healthy young adult males continuously for 120 hours to low levels of sulfur dioxide. At levels of

0.3 ppm and 1 ppm sulfur dioxide, no dose-related changes were observed in subjective complaints, clinical evaluation, or pulmonary function measurements. At 3.0 ppm, there was evidence of significant but minimal reversible decreases in small airway conductance and compliance.

(2) Hypersusceptibility

Studies have detected the presence of susceptible individuals who appear to overreact to concentrations of sulfur dioxide which, in most persons, elicit much milder responses. [13,29,30,33,34] Burton et al [30] in 1969 estimated that such "hyperreactors" may occur in 10-20% of the healthy young adult population. The hyperreactive responses occur with single exposures to sulfur dioxide. Apparently many such persons voluntarily transfer or remove themselves from surroundings involving sulfur dioxide exposure as was indicated in the study by Ferris et al.[19] This may be extremely difficult or virtually impossible for some individuals for various socioeconomic reasons. The mechanism of this hyperreactivity is unknown.

(3) Acclimatization

Acclimatization refers to the physiological adjustment exhibited by an individual to environmental changes, in this case to changes produced by sulfur dioxide. Such an adjustment to the environmental stimulus does not necessarily imply a beneficial effect even though the stimulus may become less objectionable to the individual upon continuous or repeated exposure.

Several studies have shown evidence of rather rapid physiological compensation to the effects of sulfur dioxide, especially on respiratory mechanics. [8,28,29,33] Kehoe et al [8] reported that acclimatization occurred in 80% of the sulfur dioxide-exposed group studied. The specifics of the study have been discussed under Epidemiologic Studies.

Amdur et al [28] in 1953 reported that 2 men who customarily worked in atmospheres containing 10 ppm sulfur dioxide or more showed no changes in respiration rate, tidal volume, or pulse rate to 5 ppm exposures.

Frank et al [29] showed that an initial coughing and sense of irritation in the throat and chest to 5 ppm and 13 ppm of sulfur dioxide tended to subside after 5 minutes, at a time when an increase in pulmonary flow resistance was maximal. The coughing and irritation presumably remained diminished for up to 30 minutes, the longest duration of exposure.

Acclimatization is considered to be mediated through depression of tracheobronchial nerve reflexes [27,29] along with a direct action of sulfur dioxide on bronchial smooth muscle as demonstrated in animals. [35-37] Whether mucosal secretion is an additional factor is not certain. It is questionable whether acclimatization to sulfur dioxide is desirable from a health standpoint in the occupational environment. Melville [27] emphasized the fact that although workers exposed to high sulfur dioxide concentrations showed no physical disability, it should not be accepted as proof that sulfur dioxide has no harmful effects, since a prolonged decrease in specific airway conductance might eventually compromise pulmonary function. Also, Haggard [38] in 1923 stated that the apparent

tolerance in workers exposed to sulfur dioxide was due to mucus in the upper air passages which acted as a protective coating. In his opinion, depression of the reflex merely removed one measure of protection.

(4) Interaction with Aerosols

The possible presence of sulfur dioxide-aerosol interaction in man and animals (see Animal Toxicity) has been investigated with conflicting results.

Frank et al [24] in 1964 reported changes in pulmonary flow resistance in 12 healthy male adults during exposure to 3 levels of sulfur dioxide: 1-2 ppm, 4-6 ppm, and 14-17 ppm alone, and then combined with 12-24 mg/cu m of sodium chloride aerosol having a geometric mean diameter of 0.15 micron. No evidence of augmentation was detected at any of the concentrations studied. Moreover, no statistically significant changes in pulmonary flow resistance occurred during exposure to 1-2 ppm sulfur dioxide, with or without added aerosol.

Snell and Luchsinger [26] in 1969 were unable to detect significant differences between 0.5, 1.0, and 5 ppm sulfur dioxide and either distilled water aerosol or normal saline aerosol, on expiratory flow rates and total respiratory resistance in 9 healthy young adults. The aerosol concentrations were not stated directly. Only particle (droplet) sizes in the range between 0.3 micron and 10.0 microns could be counted with the aerosol photometer being used.

Burton et al [30] in 1969 exposed 10 young healthy male adult subjects, half of them cigarette smokers, to sulfur dioxide concentrations

alone from 1.2-3.0 ppm and then combined with sodium chloride aerosol (0.25-micron mean diameter) at concentrations ranging from 2.0-2.7 mg/cu m. Pulmonary flow resistance and airway resistance were measured. No significant effects were noted on pulmonary flow resistance with sulfur dioxide alone or mixed with the sodium chloride aerosol.

In contrast, Toyama [39] in 1962 reported evidence of synergism between sulfur dioxide in a wide range of concentrations (1.6-56.0 ppm) and 7.4 mg/cu m sodium chloride aerosol (0.22 micron mean diameter) in 13 healthy male adults as measured by pulmonary flow resistance. Inhalation for 5 minutes to sodium chloride aerosol alone produced no differences from prior control values in any of the subjects. Five-minute inhalation of sulfur dioxide, 30 minutes after the aerosol exposures, produced changes in pulmonary flow resistance which varied according to the concentration of sulfur dioxide employed. Concentrations from 1.6-5 ppm consistently showed about 5% increase in pulmonary flow resistance; thereafter, values increased regularly for increased sulfur dioxide concentrations. For example, an approximate 10-ppm sulfur dioxide concentration resulted in a 10% increase in pulmonary flow resistance, 30 ppm sulfur dioxide in a 30% increase, and 56 ppm sulfur dioxide in a 50% increase. After recovery to control values (generally 30 minutes) the sulfur dioxide-aerosol combination, inhaled for 5 minutes, produced an average 20% increase in pulmonary flow resistance above that observed for sulfur dioxide inhalation alone.

In a later study in 1964, [40] Toyama claimed evidence of synergism between sulfur dioxide in concentrations from 3-40 ppm and dust obtained from the Kawasaki, Japan, area and dispersed at 10-50 mg/cu m. Ten young adult males were tested for increases in pulmonary flow resistance by procedures described above. Wide individual differences in response were noted including a detectable response to the inhalation of the dust alone.

Animal Toxicity

Although a considerable amount of experimental work has been reported on exposure of animals to sulfur dioxide, much of the information has been duplicated by human experiments, especially at exposure levels which are pertinent to the development of an occupational exposure standard. Therefore, rather than include all animal studies in this discussion, only those experiments are presented which have not been studied in humans but which may be applicable to the occupational exposure situation.

In general, man is considered to be more sensitive than other mammals to the effects of sulfur dioxide in ranges commonly employed experimentally [11] with the possible exception of the domestic cat. [41] The effect of sulfur dioxide on all mammals is qualitatively the same--that of respiratory and mucous membrane irritation and reflex bronchoconstriction with increased airway resistance.

(a) Inhalation

Dalhamn and Sjoholm [42] in 1963 found that 5-minute exposures to 1,150-7,700 ppm sulfur dioxide (20-30 mg/liter) produced arrested ciliary activity in rabbit trachea in vitro. Ciliary movements in the rabbit trachea in vivo were frequently arrested after 15 minutes exposure to 200 ppm sulfur dioxide. [43] The same series of experiments failed to demonstrate synergism between sulfur dioxide and carbon black particles mostly below 5 microns in size.

Dalhamn [44] in 1956 reported morphologic changes in rats as determined by electron microscopy. Rats exposed to 10 ppm sulfur dioxide for 3-10 weeks showed severe morphologic changes in the epithelium and lamina propria of the upper respiratory tract with evidence of abnormal cell proliferation. These changes were unaffected by differences in the duration of exposure nor did the changes appear to have regressed in rats examined about 4 weeks after exposure to sulfur dioxide had ceased.

Fraser et al [45] in 1968 reported no alteration in ciliary activity in rats exposed to 1 and 3 ppm sulfur dioxide, either with or without concomitant exposure to graphite dust (1.5 micron median diameter, 1 mg/cu m concentration). Also, on microscopic examination of lung sections, they found no alteration in the ratio of dust-laden cells to the total number of alveolar cells.

Reid [46] in 1963 exposed young rats to 300-400 ppm sulfur dioxide for 5 hours/day, 5 days/week for 6 weeks. An increase in mucin-containing cells was found in the large bronchi and the cells were observed in

peripheral bronchioles where they are not normally found. There was evidence of increased mucous secretion but no signs of increased invasions by infective microorganisms. The excess of mucin-containing cells persisted for at least 3 months after the termination of exposure.

Spiegelman et al [47] in 1968 exposed 3 miniature donkeys to sulfur dioxide concentrations ranging from 26-713 ppm for periods of 30 minutes and studied bronchial clearance of radioactive monodisperse ferric oxide particles. They found no alteration in the rate of bronchial clearance at sulfur dioxide levels below 300 ppm. At higher levels, impairment of bronchial clearance was attributed in part to the increase in mucous secretion.

Rylander [48] in 1969, using aerosols of killed radioactive and viable Escherichia coli, demonstrated no impairment of the bacterial elimination mechanisms (mechanical clearance, phagocytosis, etc) in guinea pigs exposed to 10 ppm sulfur dioxide, 6 hours/day for 20 exposures.

Alarie et al [49] in 1970 reported on essentially continuous exposure of guinea pigs, 22 hours/day, 7 days/week for 1 year to about 0.1, I, and 5 ppm sulfur dioxide. Pulmonary function measurements including tidal volume, respiratory rate, minute volume, dynamic compliance, pulmonary flow resistance, and carbon monoxide uptake indicated that no detrimental changes could be attributed to sulfur dioxide. In addition, hematological and microscopic tissue studies failed to show any adverse effects on body weight, growth, and survival. In a subsequent study, Alarie et al [50] in 1972 reported on the effects in young cynomalgus

monkeys of long term (78 weeks) 24-hour/day exposure to concentrations of sulfur dioxide of about 0.1, 0.6, 1, and 5 ppm. Control groups exposed to fresh air were also included. Evaluations were made on mechanical properties of the lung, distribution of pulmonary ventilation, diffusing capacity of the lung, arterial blood tension, lung histology, hematological and blood biochemical indices, and organ histology. No deleterious effects could be attributed to concentrations of 0.1-1.28 ppm sulfur dioxide. After 30 weeks of the regulated exposure to the 5 ppm concentration, an accidental overexposure occurred for 1 hour to something between 200 and 1,000 ppm sulfur dioxide. Thereafter, the group was maintained on pure air for the remainder of the experimental period. The accidentally exposed group showed deterioration in pulmonary function which persisted during the remaining 48 weeks of observation despite the discontinuation of sulfur dioxide exposure. Microscopic examination of the pulmonary tissues of this one group showed scattered foci of alveolar proteinosis and numerous alveolar macrophages. The alveolar walls were moderately thickened and infiltrated with histiocytes along with moderate hyperplasia of the bronchial epithelium. Eight of the 9 animals involved had moderate bronchiectasis and bronchiolectasis.

In conjunction with a nitrogen dioxide study, Lewis et al [51] in 1969 reported changes in pulmonary function in female beagles exposed to approximately 5 ppm sulfur dioxide alone or combined with about 0.8 mg/cu m sulfuric acid mist for 21 hours/day for 225 days. The dogs exposed to sulfur dioxide alone or combined with sulfuric acid showed increased

pulmonary resistance and decreased lung compliance. The dogs exposed to both sulfur dioxide and sulfuric acid showed, in addition, a decrease in residual volume, possibly due to a greater degree of lung fibrosis.

Prokhorov and Rogov [52] reported the histopathological and histochemical effects of prolonged exposures of rabbits to 76 ppm sulfur dioxide alone and combined with 182 or 364 ppm carbon monoxide for 3 hours/day for 13 weeks. Exposure to sulfur dioxide alone resulted in edema of the myocardial muscle fibers, capillary enlargement, and numerous perivascular hemorrhages. These changes were more pronounced following simultaneous exposure to carbon monoxide. Exposure to sulfur dioxide alone led to dystrophic changes in the round cells and Kupffer cells of the liver and the epithelium of the renal convoluted tubules. In the lungs, sulfur dioxide gave rise to alveolar epithelial cell proliferation.

Bushtueva [53] in 1962 exposed 6 guinea pigs to 1 mg/cu m (0.4 ppm) sulfur dioxide alone continuously for 5 days. No observable differences were noted between the exposed guinea pigs and unexposed controls.

Lee and Danner [54] in 1966 reported exposing guinea pigs to concentrations of 7-310 ppm sulfur dioxide for 2 1/2 hours. Among other changes, it was found that hemoglobin concentrations increased approximately 10% immediately after exposure to sulfur dioxide. The increase in hemoglobin concentration appeared linear with increasing sulfur dioxide concentrations between 7 and 20 ppm, but thereafter the linearity ceased.

Barry and Mawdesley-Thomas [55] in 1970 reported the effect of sulfur dioxide (300 ppm, 6 hours/day for 10 days) on the enzyme activities of rats by histochemical techniques applied immediately post-mortem to sections of the lungs. They reported a marked increase in acid phosphatase activity in the free alveolar cells throughout the lung parenchyma. It was suggested that in rats, acid phosphatase in alveolar macrophages is associated with the catabolism and removal of mucopolysaccharide and increases in response to the excess mucous secretion induced by sulfur dioxide.

Studies have been conducted [56,57] to investigate the possibility that exposures to sulfur dioxide might increase susceptibility to, or the severity of, respiratory infections in animals. Goldring et al [56] in 1967 failed to demonstrate any such increase in respiratory infections in the hamster between sulfur dioxide at (650 ppm, 3 hours/day for 75 days) and inoculated influenza virus. Navrotskii [57] in 1959 described an "immuno-biological reactivity" of rabbits following exposure to 6.8-8.5 ppm sulfur dioxide for 2 hours/day for 5 1/2 to 8 1/2 months. Agglutination and blood complement titers were determined by intravenous injections of typhoid vaccine. Both titers were "acutely depressed" in the exposed rabbits.

(b) Interaction with Aerosols

In the industrial situation, the inhalation of sulfur dioxide is regularly associated with varying amounts and qualities of aerosol suspensions dispersed as particulate solids or liquids. A considerable amount of animal experimental work has been conducted, [41,43,58-61] often with conflicting results, investigating sulfur dioxide-aerosol interactions with a variety of particulate matter of differing particle sizes and concentrations.

Dalhamn and Strandberg [43] in 1963 reported the effect of 100 ppm sulfur dioxide adsorbed onto activated carbon on ciliary movements in the rabbit trachea in vivo. The effects noted did not differ from those of 100 ppm sulfur dioxide alone, and the effects were less than those observed for 200 ppm sulfur dioxide alone despite the finding of a significant catalytic conversion of sulfur dioxide to sulfuric acid on the carbon particles.

Amdur and Underhill [58] in 1970 studied the effects on airflow resistance of combined exposures to sulfur dioxide (1.5-26 ppm) and iron oxide dust (geometric mean diameter, 0.076 micron) at concentrations of 1.0-24.0 mg/cu m in guinea pigs. No evidence of potentiation was found. Similarly, guinea pigs were exposed to a combination of sulfur dioxide (0.16-0.80 ppm) with open-hearth dust (geometric mean diameter, 0.037 microns) at concentrations ranging from 0.12-0.72 mg/cu m. No significant difference was found between the combinations and corresponding concentrations of sulfur dioxide alone.

Battigelli et al [59] in 1969 reported monitoring the surface microflora from the nasal turbinates, stem bronchi, and from lung homogenates of rats following long-term exposure (12 hours/day, 7 days/week, for 4 months) to 1 ppm sulfur dioxide combined with 1 mg/cu m of graphite dust. Separate groups of rats were also exposed to the graphite dust alone and to fresh air (controls). In addition, weight curves, hematocrit, and post-mortem microscopic studies of the respiratory structures were made. No meaningful differences were found between the 3 groups of rats.

Corn et al [41] in 1972 measured pulmonary flow resistance and lung compliance in 20 healthy adult male cats before and after exposure to 20 ppm sulfur dioxide alone and in combination with sodium chloride aerosol (10 mg/cu m, arithmetic mean diameter, 0.25 micron). Only 2 of the 20 cats, the "reactors," showed any significant increase in pulmonary flow resistance.

There is also animal experimental evidence that potentiation of effects does occur with combinations of sulfur dioxide and certain particulate aerosols. Amdur [60] in 1960 reported on studies in which the increase in pulmonary flow resistance of unanesthetized guinea pigs exposed to about 100 ppm sulfur dioxide was augmented by 10 mg/cu m sodium chloride aerosol (mean particle diameter, 0.04 micron). However, the same concentration (10 mg/cu m) of 2.5 micron sodium chloride aerosol had no such synergistic effect.

Amdur and Underhill [61] in 1968 reported studies on airflow resistance in guinea pigs exposed to approximately 20 ppm sulfur dioxide together with a large variety of both soluble and insoluble particulates namely: sodium chloride, potassium chloride, manganous chloride, ammonium thiocyanate, ferrous sulfate, sodium orthovanadate, activated and spectrographic carbon, manganese dioxide, iron oxide fume, open hearth dust, fly ash, and triphenyl phosphate. The greatest potentiation of the response to sulfur dioxide was observed with sodium chloride, potassium chloride, and ammonium thiocyanate in that order. The effects noted were found to correspond with the sulfur dioxide solubilities in solutions of these salts. Soluble salts of manganese, ferrous iron, and vanadium, known to catalyze the oxidation of sulfur dioxide to sulfuric acid, potentiated the response to sulfur dioxide. The potentiation occurred more rapidly and at much lower concentrations of aerosol than with sodium chloride. The insoluble aerosols were completely ineffective in intensifying the response to sulfur dioxide.

(c) Absorption, Distribution, Fate, and Excretion

Much animal experimentation has involved the use of sulfur dioxide labeled with radioactive sulfur (35S). [12,37,62-66] Over a wide range of sulfur dioxide levels (1 to several hundred ppm), and in all animal species studied, a high proportion of inhaled sulfur dioxide was found to be absorbed in the nasal passages and only slightly less in the oral and nasopharyngeal cavities. [62,63] In the dog, Frank et al [62] in 1959 reported nasal uptake exceeding 99% of $^{35}SO_2$ whereas uptake by breathing

through the mouth averaged more than 95%. Similarly, Strandberg [63] reported 90-95% uptake in the supratracheal portion of the upper respiratory tract in rabbits. In dogs, a small proportion of sulfur dioxide absorbed by the upper respiratory mucosa was desorbed back into the expired air. [62] Results obtained by Balchum et al in cats [37] and dogs [64] demonstrated that absorbed sulfur dioxide was carried by the bloodstream, lymphatics, and other body fluids to all tissues of the body. Frank et al [65] surgically isolated the head and upper neck of the dog from the remainder of the respiratory system and provided ventilation through the nose with air containing 22 ppm of $^{35}SO_2$. Ninety-five percent of the administered sulfur dioxide was found to be absorbed by the mucosa and $^{35}SO_2$ rapidly appeared in the expired air from the lungs. The expired $^{35}SO_2$ could not have reached the lower respiratory tract in the inspired air and its presence in the lungs was presumed to be via the pulmonary capillaries into the alveolar air. A small fraction of sulfur dioxide entering the blood of dogs remained in simple physical solution, or at least in reversible chemical solution, reportedly as free sulfite and bisulfite ion. However, in vitro experiments with rabbit blood and serum indicated that most, if not all, dissolved sulfite reacted reversibly with disulfide bonds present in the plasma proteins forming "S-sulfonate" groups. [67] Bystrova [66] in 1957, working with inhaled ^{35}S-labeled sulfur dioxide and also intravenously injected labeled sodium sulfite in cats, demonstrated that ^{35}S from either source was incorporated into the protein fractions of the blood and other organs. Balchum et al [64] in

1960 found that in dogs exposed experimentally to 35SO2, the hilar lymph nodes, and in one instance the abdominal lymph nodes, contained a considerable proportion of the retained 35S, considering their size. The majority of the 35S was concentrated in the trachea, bronchi, lungs, hilar lymph nodes, kidneys, and esophagus. The ovaries, stomach, and brain were intermediate and substantially lower in activity and the liver, spleen, and heart muscle were least, apparently having a 35S content as a result of diffusion from the blood or perhaps due to the blood they contained. Yokoyama et al [12] in 1971 reported that dogs exposed to 22 and 50 ppm 35S-labeled sulfur dioxide demonstrated more 35S in the plasma than the red blood cells, that more than half of the plasma 35S was dialyzable, ie, in the inorganic ionic form, and that most of the nondialyzable fraction was associated with alpha globulins. Most of the urinary 35S was in the form of inorganic sulfate.

(d) Carcinogenesis

In certain instances, irritant substances are associated with polycyclic hydrocarbon carcinogens. Laskin et al [20] in 1970 reported the induction of squamous cell carcinomas in rats given inhalation exposures to sulfur dioxide in combination with benzo(a)pyrene, a known carcinogen in animals. Previously, inhalation experiments with polycyclic hydrocarbons, including benzo(a)pyrene, had failed to duplicate human-type lung cancer in animals although surgically implanted benzo(a)pyrene-impregnated threads and pellets in the lung had produced squamous cell carcinoma which metastasized to the lymph nodes, pleura, and kidneys. [20] Exposures of

rats to 10, 51, 105, and 567 ppm sulfur dioxide alone were given for 6 hours/day, 5 days/week for periods up to 16 weeks. Rats exposed to 567 ppm demonstrated marked gross pulmonary damage, clinical symptoms, and death while these observed effects were absent at 10 ppm. Tracheitis was found in virtually all animals at all levels of exposure. The combined sulfur dioxide with benzo(a)pyrene studies were carried out with 24 rats and 20 hamsters. The animals were exposed to 10 ppm sulfur dioxide for 6 hours/day, 5 days/week, while an equal group, serving as a control, lived in a prefiltered fresh-air atmosphere. Animals from each group were then given combined carcinogen-irritant exposures (10 mg/cu m benzo(a)pyrene-3.5 ppm sulfur dioxide) for 1 hour/day, 5 days/week for a period which spanned 794 days. The rats showed findings of squamous cell carcinomas as listed in Table XI-4 but, interestingly, no significant pathology was reported to be found in the hamsters. Sulfur dioxide, a pulmonary irritant, and benzo(a)pyrene, when inhaled singly by rats, have failed to produce bronchogenic carcinomas. A "promoting" effect for sulfur dioxide is suggested by these experiments; however, the data are minimal and a question remains as to whether such an effect is specific for sulfur dioxide or whether such a "promoting" effect may be shared by other pulmonary irritants when inhaled in conjunction with known or suspected carcinogens.

Peacock and Spence [21] in 1967 reported exposing 35 male and 30 female spontaneous tumor-susceptible mice to 20 ml/minute sulfur dioxide for 5 minutes (500 ppm), 5 days/week for about 300 days. An approximately

equal number of control mice were also included. The observed distribution of tumors (malignant and nonmalignant) was not shown to be statistically different from those of the controls. However, it was concluded that the sulfur dioxide exposures accelerated the onset of neoplasia in the susceptible mice as a result of the initial, essentially inflammatory reaction caused by the sulfur dioxide. The effects noted by the authors [21] were not considered to be sufficient to justify the classification of sulfur dioxide as a chemical carcinogen.

Correlation of Exposure and Effect

It is well documented that persons engaged in occupations involving significant exposures to sulfur dioxide consistently demonstrate injury associated with damage to the respiratory tract. [8,10,11,19] Acute occupational exposure concentrations are difficult to establish because of their sudden unanticipated occurrences. Exposure to unknown but probably high concentrations of sulfur dioxide have caused death by asphyxia or bronchopneumonia with permanent damage [14]; asthma-like attacks have also been reported. [15] Single or repeated exposures are irritant to the nose and throat producing choking sensations, rhinorrhea, and cough. [7,11]

Because sulfur dioxide is often associated with other environmental contaminants in occupational situations, [18,19] it is difficult to attribute observed effects to the compound itself. One exception, however, is the relatively old (1932) but pertinent epidemiologic study reported by Kehoe et al [8] on workers in the refrigeration industry because exposure

occurred to relatively pure sulfur dioxide being used as a refrigerant. Environmental concentrations averaging 20-30 ppm (range 5-70 ppm) obtained at the time of the study were associated with symptomatic evidence of irritation of the upper respiratory tract. A significantly higher incidence of nasopharyngitis, alteration in the senses of taste and smell, and an increased sensitivity to other irritants was elicited from the exposed group as compared with the controls. In addition, a significantly higher incidence of tendency to increased fatigue or dyspnea on exertion, along with longer duration of colds (although their frequency was no greater), was also noted. Skalpe [18] reported essentially the same findings in Norwegian paper pulp mill workers exposed to 2-36 ppm sulfur dioxide under general working conditions. Special procedures, such as "blowing the digesters," resulted in potential exposure concentrations up to 100 ppm. The study of Anderson [9] in oil refinery workers and Ferris et al [19] in pulp mill workers reported no differences between exposed workers and controls. However, Anderson's study [9] considered changes in body weight, systolic blood pressure, or chest roentgenographic findings. No mention was made of the possible incidence of pulmonary irritation or cough. Similarly, the pulp mill study of Ferris et al, [19] found no statistical differences between the exposed group and the controls; however, although the prevalence of chronic nonspecific respiratory diseases was extensively evaluated, the disease incidence in both the exposed pulp mill group and the paper mill controls was approximately 30% paper mill workers did not represent a satisfactory control group.

All of the occupational exposure studies share a common weakness in that sulfur dioxide data are meager and direct exposure correlation with observed effects is generally not possible because mixed exposures to materials such as chlorine and organic sulfites in wood operations, [18,19] and metal or metal-like compounds [17] in smelting operations, are the rule. In general, however, it may be concluded that usual working conditions have involved exposures to sulfur dioxide concentrations of about 10-30 ppm with frequent short term exposures up to 100 ppm.

Most human experimental exposure studies have involved various aspects of respiratory mechanics related to airway or pulmonary flow resistance in subjects not occupationally exposed to sulfur dioxide. Controlled exposures at concentrations of 9 ppm for 60 minutes have produced increases in airway resistance accompanied by rhinorrhea and lacrimation. [13] At concentrations of about 5 ppm, increases in pulmonary flow resistance [24,25] and decreases in maximum expiratory flow [26] have been observed. Melville [27] reported decreases in small airway conductance at 2.5 and 5 ppm sulfur dioxide exposure levels. In addition, at sulfur dioxide concentrations up to 5 ppm, sensitivity to stimulation of receptors in the larynx, trachea, and bronchi was diminished. At sulfur dioxide concentrations of 1 ppm, Amdur et al [28] reported increases in respiratory rate and pulse rate, and a decrease in total volume of about 25% below control levels during the first 2 minutes of an 11-minute exposure in 4 subjects. Frank et al [29] and Sim and Pattle [13] failed to confirm these findings in subsequent studies. At 1 ppm sulfur dioxide,

most investigators have reported negative dose-related findings in human studies of changes in respiratory mechanics. [29,30-32] Weir et al [31,32] reported significant but reversible decreases in small airway conductance and compliance at exposure levels of 3 ppm sulfur dioxide but found no changes at 1 ppm.

Animal experiments provide information on the effects produced by prolonged sulfur dioxide exposure under controlled conditions for relatively prolonged periods of time. Young rats exposed to 300-400 ppm sulfur dioxide [46] for 5 hours/day, 5 days/week for 6 weeks showed cellular proliferation in the large bronchi and bronchioles along with increased mucous secretion. The excess cells persisted for at least 3 months after termination of the exposure. This condition was believed [46] to represent an induced chronic bronchitis in the rats. In rabbits, exposures to 76 ppm sulfur dioxide [52] for 3 hours/day for 13 weeks resulted in capillary enlargement with perivascular hemorrhaging and alveolar epithelial cell proliferation. In young monkeys, [50] an accidental 1-hour overexposure to between 200 and 1000 ppm sulfur dioxide in young monkeys following 30 weeks of continuous exposure to about 5 ppm, produced progressive deterioration in pulmonary function with eventual development of moderate bronchiectasis and bronchiolectasis. Exposure of rats to 10 ppm sulfur dioxide for 3-10 weeks showed morphologic epithelial changes in the upper respiratory tract with abnormal cell proliferation. [50] These changes reportedly persisted in rats examined 4 weeks after exposure had ceased. Exposure levels of 5 ppm in dogs [51] exposed 21

hours/day for 225 days showed increased pulmonary resistance and decreased lung compliance. In guinea pigs and monkeys, [49,50] no detrimental changes were observed following continuous exposures of 1 year for the guinea pigs and 30 weeks for the monkeys. At 1 ppm exposures, no alteration in alveolar ciliary activity in rats was found [45] following exposures of 12 hours/day, 7 days/week for 4 months. In guinea pigs, [53] following continuous exposure to 0.4 ppm for 5 days, no observable differences were noted between exposed animals and unexposed controls.

In summary, no changes were noted in animals to exposure concentrations of 0.4 ppm and 1 ppm. Extended sulfur dioxide exposures to 5 ppm appeared to produce measureable pulmonary changes and exposures to 10 ppm and greater seem to produce progressive pulmonary damage which may result in extended tissue changes.

There is evidence that a rather rapid physiological compensation (acclimatization) occurs to the effects of sulfur dioxide, especially on respiratory mechanics. [8,28,29,33] Kehoe et al [8] found wide variability in the time required for acclimatization to develop (mean 2.84 months, S.D., 2 months). Acclimatization occurred in 80% of Kehoe's [8] exposed group and has been reported at exposure levels of 5 ppm. [28,29] It is believed to be mediated through depression of tracheobronchial nerve reflexes [27,29] along with a direct action on bronchial smooth muscle. [35-37] Differences of opinion exist as to whether acclimatization has been beneficial in the occupational environment. Melville [27] stated that

a prolonged decrease in airway conductance might eventually compromise pulmonary function.

Sulfur dioxide interaction with aerosols has received considerable attention in both human [24,26,30,39,40] and animal experimental work. [41,43,58-61] Interaction with insoluble aerosols such as activated carbon, iron oxide (Fe2O3) and graphite dust have generally proved ineffective in potentiating the effects produced by sulfur dioxide alone. [43,58,59] Toyama, [40] however, reported potentiated activity with a sulfur dioxide-stack dust aerosol. Amdur and Underhill [61] in 1968 reported potentiation of activity of sulfur dioxide by sodium chloride, potassium chloride, and ammonium thiocyanate. The potentiation was proportional to the solubility of sulfur dioxide in each of the compounds. In addition, it was found that soluble salts of manganese, ferrous iron, and vanadium also produced potentiated sulfur dioxide-aerosol activity. These metal ions are known to promote the catalytic conversion of sulfur dioxide to sulfuric acid. [61] Attempts to produce potentiation with insoluble salts were ineffective.