SECTION VII
EFFECTS OF INHALED TOXIC AGENTS

ACUTE AND CHRONIC RESPIRATORY EFFECTS OF EXPOSURE TO INHALED TOXIC AGENTS

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INTRODUCTION

This chapter covers the acute and chronic effects of exposure to inhaled toxic agents. The chemical agents discussed are hazardous primarily to the respiratory system. Some also affect distant organs or tissues. Examples of the latter are mercury and cadmium, which are toxic to kidneys. How extensively the respiratory system is involved, particularly following acute or accidental exposure, is determined largely by the concentration of the agent and duration of exposure. Other factors that may modify the individual's response include pre-existing heart or lung disease, prior long-term exposure to the same agent, level of activity during exposure, and age.

The symptoms and signs of mild exposure to irritant gases that are relatively soluble in aqueous solution (e.g., ammonia, chlorine, and sulfur dioxide) are likely to be confined to the upper airways within the head. In response a subject may experience one or more of the following: sneezing, nasal catarrh, unpleasant smell or taste, soreness of the throat, smarting of the eyes and lacrimation.

More intensive exposure extends the involvement to the central airways of the tracheobronchial tree. Cough, sputum, pain, or constriction of the chest—and in the event of bronchospasm—shortness of breath, and wheezing, may be prominent. If there is excessive production or retention of mucus, or if portions of the lining of the airways slough away, rhonchi may be heard. Spasm of the larynx may totally obstruct the airway requiring an immediate tracheotomy.

The most intense exposures damage the alveolar-capillary membrane or parenchyma of the lung. The consequence is edema. Depending on the amount of edema that forms, a subject may suffer extreme shortness of breath, dusky discoloration of the mucous membranes and nail beds (cyanosis), blood-tinged sputum mixed with foam, and collapse. Rales are heard over-lying the edema. sometimes initial evidence of edema is only vague and premonitory; consequently, the patient or examiner may underestimate the gravity of the condition.

The physiologic changes that occur are not unique to the chemical agent itself, but reflect the portion(s) of the respiratory system involved and the intensity of that involvement. If the laryngo-tracheo-bronchial tree is constricted, maximal ventilatory flow rates fall. Techniques are now available for making the important distinction between involvement of larger central airways and smaller peripheral airways. If constriction is peripheral, there is associated air-trapping. If, as usually happens, constriction is irregular in pattern, another group of tests can be used to show that the distribution of ventilation within the lung is uneven and abnormal, and that gas-exchange across the alveolar-capillary membrane is impaired. Impairment of gas-exchange leads to hypoxemia or retention of carbon dioxide (hypercapnea).

Chest pain and weakness from any cause tend to limit a subject's ability to inspire maximally. Consequently, any measurement that depends on a maximal inspiration—including the commonly used forced expiratory vital capacity (FVC) and 1-second forced expired volume ($FEV_{1.0}$)—will be affected apart from any changes imposed by narrow airways or stiffened lung parenchyma.

Edema reduces the subdivisions of lung volume, including total lung capacity (TLC) and vital capacity (VC). Edema also stiffens or reduces lung compliance and interferes with oxygen diffusion into the blood. Hypoxemia commonly follows edema. Chest x-rays are a useful means of assessing the amount and extent of edema.

Pollutant gases with relatively low solubility

in aqueous solution tend to shift their primary effect to the periphery of the respiratory system. Thus, ozone and nitrogen dioxide, in contrast to sulfur dioxide, are notable for the bronchiolar and parenchymal injury they produce at relatively low concentrations (1)(2). Sulfur dioxide, being more soluble, is likely to affect the upper airways and large central airways.

The effect of an irritant or toxic agent contained in an inhaled particle is intimately related to the aerodynamic behavior of the particle, since aerodynamic behavior is a determinant of where and how much deposition occurs within the respiratory system. Cadmium, vanadium, and sulfuric acid are examples of noxious agents that are inhaled in particulate form. A useful, concise review of the routes of entry and modes of action of gases, vapors, and particles was published by Stokinger (3).

The respiratory system has several means of clearing itself of infectious or inanimate particles. Most solid particles that deposit in the alveolar region are engulfed by macrophages, which are mobile cells that transfer the material to nearby terminal airways. A small, variable fraction of these particles may pierce the alveolar lining and either imbed in fixed tissues or be removed through lymphatics or blood vessels. The mucociliary system, beginning with the terminal bronchioles, carries particles from the nasal passages and from the lower airways toward the throat; the particles are then swallowed or expectorated. Cough is effective in clearing the central airways. The dosage to the lung of chemicals contained in solid particles is a complex function of ambient concentration, deposition rate, and clearance efficiency. The chemical agents discussed in this chapter all have the potential for impeding clearance and thereby influencing dosage.

Functional impairment is not synonymous with disability. For example, a specified reduction in ventilatory performance may not affect a sedentary worker, whereas it could disable a professional athlete. Disability may have a component that is hard to objectify. If there is uncertainty or dispute over disability and functional testing is to carry weight in the decision, it is preferable to rely as much as possible on tests that do not depend on voluntary performance.

It may be relatively simple to identify and describe the clinical and laboratory features of massive overexposure to a specific agent, but to detect the onset of subtle changes associated with prolonged low-level exposure and identify the cause with reasonable certainty is often difficult because laboratory findings upon which the diagnosis may rest are not always sharply divided between "normal" and "abnormal"; and because values may fluctuate within a healthy individual and differ widely among the population. To detect small deviations from normality, therefore, requires standards based on a control group that is similar to the workers at risk in terms of age, sex, race, and socioeconomic status. Detection of early abnormality improves with periodic testing, the latter being typical of so-called prospective studies, but this approach is not often used because of its expense and inconvenience. Once illness is established and the worker is removed from the offending environment, periodic testing becomes vital to determine the rate and extent of recovery or reversibility.

Above all, the detection of early or slowly progressive illness in a worker, along with identification of the cause, requires a careful, probing history. Information should be obtained about competing risks such as cigarette smoking and about variables such as socioeconomic status or nutritional habits that may alter the response to a specific hazard. Nonoccupational environments, including the home, may also contribute to specific airborne exposures, as with nitrogen oxides and carbon monoxide. Food, drink, and absorption through the skin may add to the total body burden of heavy metals. The current state of the art renders it difficult to predict the potential severity of future impairment from acute exposures and this difficulty is compounded by the usual lack of information about dosage in acute exposures. Such information gaps make case comparisons difficult. Consideration of how these independent variables may interact with an identified occupational risk can be vital to the clinical or epidemiological assessment.

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AMMONIA

Introduction

Among the gases considered in this chapter, the most soluble in water is ammonia (89.9 g/100 ml at 0°C). In solution, a strong alkali, ammonium hydroxide (aqua ammonia) is formed. The high solubility and strong alkalinity make ammonia especially irritating to the upper airways. The gas, which is colorless, has an easily recognized odor. It liquifies at -33.3°C.

Ammonia is used as a source of nitrogen in fertilizers (agriculture is a relatively frequent setting for accidental overexposure), as a commercial refrigerant, and in a wide variety of industrial and commercial activities. Table VII-1 of the NIOSH criteria document for ammonia lists 82 occupations that are implicated (9). It is estimated that over 3,000,000 workers are potentially at risk to the hazards of ammonia (8).

The current federal standard for ammonia is 50 ppm (35.7 mg/m^3) based on an 8-hour time-weighted-average (TWA). It has been recommended that the same numerical standard be expressed instead as a ceiling based on a 5 minute sampling period (9).

Acute Exposure, Human

Ammonia is unusual in that it is produced in the body (particularly in the oral cavity) and released continuously into respired air. The concentration of ammonia in air exhaled by mouth is on the order of 0.2 ppm (6). The hypothesis has been made that this endogenous ammonia may neutralize—and thereby mitigate—the effects of inhaled acid aerosols such as sulfuric acid (6).

The threshold for detection of ammonia by smell varies as reported by different investigators (9). Most of these reports provide inadequate information about test methods. Fifty ppm is known to impart a strong smell (10). Brief exposure to 100 ppm increases nasal air flow resistance, thought to be attributable to vascular congestion, edema, and increased mucus secretions (7). This effect is perceived as "stuffiness."

There are two sources for our knowledge of the respiratory effects of acute exposure to ammonia: controlled laboratory studies and accidents. In laboratory experiments, mild irritation of the eyes, nose, and throat is provoked by 50 ppm but not by 25 ppm (5)(13). Among the subjects tested, "experts" familiar with the reported effects of ammonia and of the opinion that "it will do little or no harm" have expressed fewer complaints than have "nonexperts" (13). Nonexperts could not tolerate exposure to 140 ppm for 2 hours, chiefly because of an urge to cough. Neither group showed any impairment of function as measured by VC and $FEV_{1.0}$. Acclimation to 50 ppm developed within one week (5). One hundred ppm became easily tolerated within 2 to 3 weeks of repeated exposure.

In an earlier laboratory study, volunteers were exposed to 500 ppm of ammonia for 30 minutes by oro-nasal mask (11). Aside from the expected irritation of the skin beneath the mask and of the upper airways, the most significant physiologic response was hyperventilation and an associated increase in respiratory rate. (By contrast, sensory irritants typically reduce respiratory rate in rodents; see also Chlorine (1).) There was no coughing, however, exposure to 1,000 ppm of ammonia caused immediate coughing.

Together, these studies offer little evidence of physiological abnormalities in the lower airways among healthy subjects either in response to 500 ppm for 30 minutes or to lower concentrations for intervals lasting up to several weeks.

Massive accidental exposure to ammonia can be rapidly fatal. Concentrations in the range of 700 ppm to 1,700 ppm can be incapacitating due to extreme lacrimation and coughing (5). The eyes, skin, and all levels of the respiratory tract may be severely inflamed. The clinical and physiologic abnormalities associated with acute, extensive injury to the respiratory tract have been outlined in the Introduction to the chapter.

The pathologic changes that may develop are described in the report of a fatality occurring 60 days following exposure to anhydrous ammonia (12). The report provides a tabulation of autopsy findings of other authors. Severe damage at every possible level within the respiratory system is mentioned, ranging from purulent oro-pharyngitis to edema, hemorrhage, and

Table VII-1

OCCUPATIONS WITH POTENTIAL EXPOSURE TO AMMONIA

Acetylene workers
Aluminum workers
Amine workers
Ammonia workers
Ammonium salt makers
Aniline makers
Annealers
Boneblack makers
Braziers
Bronzers
Calcium carbide makers
Case hardeners
Chemical laboratory workers
Chemical manufacturers
Coal tar workers
Coke makers
Color makers
Compressed gas workers
Corn growers
Cyanide makers
Decorators
Diazo reproducing machine operators
Drug makers
Dry cleaners
Dye intermediate makers
Dye makers
Electroplaters
Electrotypers
Explosive makers
Farmers
Fertilizer workers
Galvanizers
Gas purifiers
Gas workers, illuminating
Glass cleaners
Glue makers
Ice cream makers
Ice makers
Ink makers
Lacquer makers
Latex workers
Maintenance workers (janitors)
Manure handlers
Metal extractors
Metal powder processors
Mirror silverers
Nitric acid makers
Organic chemical synthesizers
Paper makers
Perfume makers
Pesticide makers
Petroleum refinery workers
Photoengravers
Photographic film makers
Plastic cement mixers
Pulp makers
Rayon makers
Refrigeration workers
Resin makers
Rocket fuel makers
Rubber cement mixers
Rubber workers
Salt extractors, coke oven by-products
Sewer workers
Shellac makers
Shoe finishers
Soda ash makers
Solvay process workers
Stablemen
Steel makers
Sugar refiners
Sulfuric acid workers
Synthetic fiber makers
Tanners
Tannery workers
Textile (cotton) finishers
Transportation workers
Urea makers
Varnish makers
Vulcanizers
Water base paint workers
Water treaters
Wool scourers

Adapted from NIOSH.

consolidation of the parenchyma.

Chronic Exposure, Human

No epidemiological studies adequately designed to test the (possible) harmful respiratory effects of chronic, low-grade occupational exposure to ammonia have been reported. This is surprising in view of the large, diverse population of workers potentially at risk. Available reports have been judged inadequate (9). One personal communication from an official of the Division of Occupational Hygiene in Massachusetts refers to the odor and slight sensory irritation associated with levels of ammonia at or below 45 ppm in proximity to refrigeration equipment; there is no mention of any clinical or physiologic assessment.

As noted under Acute Effects, informal evidence suggests that acclimation of the upper airways to the sensory irritation of ammonia, and particularly of the sense of smell, is common.

Animal Effects

There have been several histologic studies of the lungs and other tissues following repeated exposure of animals to ammonia. None were combined with physiologic measurement.

Coon et al., in a screening procedure, exposed rats continuously to about 365 ppm of ammonia for 90 days (3). About one-fourth of the animals developed mild nasal discharge; a smaller fraction had slight increases in blood leucocytes suggestive of an infection; and the lungs and kidneys of the entire group showed "nonspecific circulatory and degenerative changes." Lower concentrations of ammonia (220 ppm or less) over the same or slightly longer period of time had no histologic or hematologic effects. Concentrations of about 635-640 ppm caused eye and nasal irritation, labored breathing and death in a majority of the animals within 65 days, when the experiment was terminated. (Among the other species exposed to these concentrations, about one-fourth of the guinea pigs died and no deaths were reported among rabbits or dogs.) In another study involving exposure of guinea pigs to about 170 ppm for up to 12 weeks, evidence was found of structural changes in a number of abdominal organs but not in the lungs (14).

There is evidence that ciliary beat rate, and by implication mucociliary clearance, is depressed in an excised rabbit tracheal preparation directly exposed to ammonia for several minutes, beginning at about 100 ppm (4); that bacterial clearance from the lungs may be impaired after 2 hours of exposure to an estimated 50 ppm of ammonia; and that the prevalence of infectious disease in rat lungs caused by *Mycoplasma pulmonis* is related to the concentration of ammonia in the range of 25 ppm to 250 ppm, when the gas is administered over a 4 to 6 week period (2).

Recommendations

Further studies on the possible effects of ammonia on lung clearance are warranted in animals and, if possible, in human subjects. These studies should include concentrations of the gas at or near the present standard of 50 ppm.

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CADMIUM

Introduction

Several forms of cadmium are hazardous to workers, including the elemental metal, oxide, chloride, and sulfate salts. All occur as respirable dusts, and the metal also vaporizes if heated. At the melting point of cadmium (321 °C), the concentration of the vapor may exceed 560 mg/m³ (3). On an equal weight-basis, the vapor is considered more toxic than the dust.

Cadmium is usually recovered as a by-product in the processing of zinc, copper, and lead ores. Most of the approximately 5,000 tons of cadmium used annually in the United States are for electroplating and production of alloys. It is estimated that nearly 2,000,000 workers are potentially at risk to cadmium (18). A partial list of these occupations is shown in Table VII-2, revealing the rich variety of uses made of the metal (22).

The federal standard for cadmium fume is 0.1 mg/m³ based on an eight-hour time-weighted-average (TWA); the ceiling concentration is 0.3 mg/m³. There is a separate eight-hour standard for the dust of 0.2 mg cadmium/m³, together with a ceiling concentration of 0.6 mg/m³.

NIOSH has recommended that the standards for fumes and dusts be consolidated into a single total particulate standard of 40 μg/m³ (TWA), and that the ceiling be lowered to 200 μg/m³ (0.2 mg/m³) based on a 15-minute sampling period (19). The rationale underlying the first recommendation is that fumes represent small particles without a precise definition of size, form a continuum with larger dust particles, and all may be sampled together. Because cadmium is volatile at high temperature, workers in heated environments may be exposed to hazardous concentrations of the vapor that could pass undetected by the popular sampling method which relies on cellulose ester membrane filters.

Acute Effects

Several possible mechanisms for the toxicity of cadmium have been proposed. One is that cadmium inhibits a number of oxidative enzymes, perhaps by displacing essential metals such as zinc from their structure (9). Second, that cadmium promotes the formation of metallothionein, a protein said to contribute to toxicity. The precise effect of metallothionein on normal protein synthesis is unknown. Third, based on *in vitro* evidence, that cadmium depresses the alpha-1-antitrypsin level of blood (4)—alpha-1-antitrypsin acts as a curb on trypsin, a lysin thought to play a role in the development of emphysema. This observation has not been confirmed (26).

Most cases of acute intoxication have been associated with welding, brazing, or soldering (22). The manifestations of toxicity are chiefly respiratory. The onset of symptoms may be delayed several hours, or until the worker has left the scene of exposure. The severity of exposure determines the extent of respiratory involvement, and consequently, the symptoms, signs, and prognosis. Slight exposure is attended by drying and irritation of the upper airways, sneezing, and a metallic taste. Cough and chest pain signal involvement of the lower airways. Involvement of the parenchyma leads to edema. Shortness of breath and cyanosis are then likely to dominate the clinical picture. Pulmonary edema may occur within hours of severe exposure and persist for days or weeks.

Symptoms of systemic intoxication, i.e., headache, nausea, vomiting, chills, muscular aches, diarrhea, and weakness, may follow shortly upon the onset of respiratory complaints. The clinical picture may simulate that of an acute infection, or be mistaken for metal fume fever,

Table VII-2
OCCUPATIONS WITH POTENTIAL EXPOSURE TO CADMIUM

Alloy makers	Incandescent lamp makers
Aluminum solder makers	Jewelers
Auto mechanics	Lithographers
Battery makers, storage	Lithopone makers
Bearing makers	Metalizers
Braziers and solderers	Paint makers
Cable and trolley wire makers	Paint sprayers
Cadmium-compound collecting-bag handlers	Pesticide makers
Cadmium platers	Pharmaceutical workers
Cadmium smelters	Photoelectric cell makers
Cadmium vapor lamp makers	Pigment makers
Cadmium workers	Plastic products makers
Ceramics, pottery makers	Sculptors, metal
Copper-Cadmium alloy makers	Small arms ammunition makers
Dental amalgam makers	Smoke bomb makers
Electric instrument makers	Solder makers
Electrical condenser makers	Textile printers
Electroplaters	Welders, cadmium alloy
Engravers	Welders, cadmium-plated objects
Glass makers	Zinc mining, smelting and refining workers*
Hobbyists, metal	

*Mineralogically, cadmium and zinc occur together.

Adapted from Blejer (1971, Appendix A, II)

particularly among welders. Systemic intoxication may be accompanied by proteinuria, perhaps a reflection of injury to renal tubules.

The mortality rate in the presence of pulmonary edema may reach 15-20%. The lethal dose of cadmium is estimated to be about 2,500 mg-min/m^3 (19), and fatalities have been reported following exposure to 40-50 μg/m^3 for one hour (23). While recovery from edema generally appears to be complete within weeks, shortness of breath and impaired pulmonary function persist for years in some instances.

Chronic Effects

Exposure to cadmium is not limited to occupational setting. Cadmium contaminates ambient air, drinking water, food, and cigarettes. Generally, the concentrations in ambient air and water are low. The average dietary intake is estimated to be about 30-50 μg/day (14), of which only 10% or less is absorbed from the intestines (5). Absorptive rates from the gut can be increased by nutritional deficiencies in calcium or vitamin D or by disorders of iron metabolism. This increase is held largely responsible for the occurrence of Itai-Itai, a painful cadmium-induced disease of bone found in women from a particular locale in Japan (6). There are roughly 35 μg of cadmium in each pack of cigarettes. Measurements of the amount inhaled in smoke may vary from about 10% to 70% (13) (17). Assuming that the cadmium-containing smoke particles range in diameter from 0.01 μg to 0.5 μg, about half the inhaled dose would be expected to be retained by the lung.

The body eliminates cadmium mostly in urine. Normally this amounts to about 1 to 2 μg/day, so that the total body burden tends to increase with age. To what extent these additional sources of cadmium may contribute to the adverse effects of chronic occupational exposure, particularly involving the kidneys where accumulation of the metal is relatively high, is uncertain. (Cadmium also accumulates in hair; the analysis of hair may be useful in showing that exposure to the metal has occurred, but not to assess the magnitude of uptake (1)).

With chronic exposure to cadmium, nasal passages become inflamed, and there is loss of the sense of smell owing to damage to the olfac-

tory nerve. The teeth show yellow discoloration. How seriously the lungs are affected is a matter of controversy. Several investigators have stated that cadmium causes emphysema (7)(10)(12). A recent study found no evidence to support this concept and indeed questioned its soundness (26). In the latter study, 18 workers who had been exposed for at least 22 years to cadmium dust (average: 32 years) were compared with control subjects in terms of respiratory symptoms, chest films, and a comprehensive battery of functional tests. The two groups were matched in age, height, weight, socioeconomic status, and smoking habits. Since 1972, total cadmium concentrations in the workplace had ranged from 50 $\mu g/m^3$ to 356 $\mu g/m^3$; while concentrations were presumed to have been higher in earlier years, these data were not accessible. Both groups gave evidence of narrowing of small airways that appeared to be related largely to smoking. The authors concluded that chronic exposure to cadmium "does not represent a major hazard for the lung."

Others have suggested that emphysema cases attributed to chronic cadmium exposure may have resulted from one or more past acute intoxications (14). This would accord with findings in animal experimentation, which show that one or repeated exposures to high concentrations of cadmium chloride may eventually produce an emphysematous lesion (25).

Fibrosis of the lung has been reported among workers chronically exposed to cadmium; this evidence is based on radiographic changes in lung appearance, and a reduction in FVC without any obstruction to flow as measured by $FEV_{1.0}$ and maximal mid-expiratory flow (MMEF) (24). In animals, cadmium-induced fibrosis is thought to be a forerunner of emphysema by causing distortion of small airways and adjacent parenchyma (25).

Of all organs, the kidney is the most commonly affected by chronic exposure to cadmium. Evidence of renal failure, however, is rare. Proteinuria, comprising both small (molecular weight under 40,000) and large molecules, is not uncommon among exposed workers (13). The percentage affected increases with duration of exposure, approaching unity within three decades (19). It is uncertain to what extent this form of renal injury and the hypertension associated with cadmium intoxication may be related. The association between elevated levels of renal cadmium at autopsy and a history of hypertension has been reported by several investigators (21).

Anemia and painful demineralization of bone (osteomalacia) have been associated with chronic exposure to cadmium; the latter particularly in association with excessive dietary intake (21). Evidence for an increased incidence of prostatic carcinoma is equivocal (11).

Animal Toxicology

High doses of cadmium chloride aerosol (0.1% solution, aerosol mass concentration unspecified) are injurious chiefly to the bronchioles and adjacent parenchyma (25). There is an acute, edematous reaction, followed by growth of granulation tissue and scarring (25). The scarring distorts and destroys tissue, imparting the appearance of human emphysema of the centrilobular type. It has not been determined whether low concentrations of cadmium aerosols administered over long periods of time may also provoke fibrosis and emphysema in the same species of animals.

Hypertension has been produced in rats with long-term, low-level cadmium feeding, particularly in a species that is genetically predisposed to systolic hypertension (20)(21). The effect is seen in the absence of overt damage to the kidney and may reflect increased reabsorption of sodium by the kidney or a direct effect on the tone of vascular smooth muscle.

Cadmium chloride causes fibrosarcoma when injected into connective or muscle tissue (8). These tissues are mesodermal in origin. The cells implicated in prostatic carcinoma, which was reported to occur more often than expected in one survey of workers exposed to cadmium for a minimum period of one year, is endodermal (specifically epithelial) in origin. Epithelial carcinoma has not been produced in animals with cadmium.

Selenium protects against the testicular necrosis caused by cadmium in animals (6).

Recommendations

Evidence suggests cadmium is more toxic as a vapor than as a particle. Therefore, assurance is needed that air-monitoring methods be sensitive to both physical forms of the metal. This is particularly important in heated environments where the vapor pressure of cadmium may be high.

Enough vexing questions remain concern-

ing the possible adverse effects of low-level, prolonged exposure to cadmium to warrant continued longitudinal studies of exposed workers. The type and severity of lung disease that may occur, and the possible relation between chronic exposure and the incidence of hypertension and of specific types of neoplasm are unresolved.

In animals the nature of the structural and functional changes that may be produced by chronic exposure to low levels of cadmium should be defined more clearly.

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CHLORINE

Introduction

Chlorine is the most abundant halogen and among the most reactive of all elements. It is a yellow-green gas at ambient temperature and liquifies at low temperature (boiling point, 1 atmosphere = -34 °C) or elevated pressure (boiling point, 5 atmospheres = 10.3 °C). It has a conspicuous, pungent odor, is about 2.5 times heavier than air, and therefore tends to accumulate in dependent sites. Such sites may become extremely hazardous in the event of accidental leaks within confined spaces. Liquid chlorine is a strong irritant that inflames the skin, eyes, and mucous membranes upon contact.

NIOSH has estimated that about 15,000 persons have the potential for exposure to chlorine at work (9). Table VII-3 illustrates the number and variety of these occupations. (Emissions from photographic manufactories may also contaminate nearby community air, as in regions of Niagara Falls, Rochester and Syracuse, New York(9)).

The present federal standard for chlorine is 1 ppm (~3 mg/m³), based on an 8-hour time-weighted-average (TWA). NIOSH has recommended a ceiling concentration be established of 0.5 ppm based on a 15-minute sampling period (9).

Acute Exposure, Human

Upon absorption into tissue fluids, chlorine undergoes a series of reactions to produce hydrochloric acid (HCl), hypochlorous acid (HOCl), and nascent oxygen (O). Each of these chemicals damages biologic tissue.

The threshold for detecting chlorine by odor ranges widely among individuals, is inconsistent from one occasion to another and becomes blunted within minutes of the onset of exposure (9). Generally, the average concentration cited in primary references has been under 1 ppm, having ranged as low as 0.012 ppm; at odds with these findings is the statement in the *Handbook of Chemistry and Physics* which states that "As little as 3.5 ppm can be detected as an odor" (7).

The consequences of accidental over-exposure to chlorine gas are well documented, although specific information about the concentrations inhaled by victims is meager. The symptoms and signs associated with acute inflammation of the eyes, entire respiratory system, and skin were enumerated in the Introduction to this chapter. In addition, the teeth may be damaged or discolored. Death may be caused by asphyxia from laryngospasm or massive pulmonary edema. Other nonspecific symptoms include headache, dizziness, anxiety, nausea, and vomiting.

The effects of a single accidental exposure vary in duration. It may be difficult to distinguish between disability arising from psychologic trauma or anxiety and that due to intrinsic respiratory injury. This has been particularly true of retrospective studies carried out on military personnel gassed by chlorine in World War I (5).

Chester et al. could find decreased ventilatory function in only 3 of 55 workers in a chlorine gas plant who had been accidentally exposed one or more times to concentrations in excess of 1 ppm (3). Ambient or background concentrations of chlorine in the plant averaged less than 1 ppm (99% of all samples). Overexposure was defined as an undetermined dose, severe enough to require oxygen therapy. The clinical findings indicated an obstructive ventilatory defect, which cleared rapidly. Earlier, Kowitz et al. described a similar type of obstructive defect in 11 longshoremen hospitalized after an accidental exposure to chlorine, but with a different outcome (8). Here the obstruction increased over the next two years of follow-up. A

Table VII-3
OCCUPATIONS WITH POTENTIAL EXPOSURE TO CHLORINE

Aerosol propellant makers	Iron dezincers
Alkali salt makers	Laundry workers
Aluminum purifiers	Methyl chloride makers
Benzene hexachloride makers	Paper bleachers
Bleachers	Pesticide workers
Bleaching powder makers	Petroleum refinery workers
Bromine makers	Phosgene makers
Broom makers	Photographic workers
Carpet makers	Plastic makers
Chemical synthesizers	Pulp bleachers
Calcium chloride makers	Rayon makers
Chlorinated solvent makers	Refrigerant makers
Chlorinated hydrocarbon insecticide makers	Rubber makers
	Sewage treaters
Chlorine workers	Silver extractors
Color makers	Sodium hydroxide makers
Disinfectant makers	Submarine workers
Dye makers	Sugar refiners
Ethylene glycol makers	Sulfur chloride makers
Ethylene oxide makers	Swimming pool maintenance workers
Flour bleachers	Tetraethyl lead makers
Fluorocarbon makers	Textile bleachers
Gasoline additive workers	Tin recovery workers
Gold extractors	Vinyl chloride makers
Ink makers	Vinylidene chloride makers
Iodine makers	Water treaters
Iron detinners	Zinc chloride makers

Adapted from NIOSH (1976, Table XIII-2)

defect in the diffusing capacity of the lungs, present at the first examination, also worsened. Unlike the workers in the gas plant, the longshoremen had not worked in an environment characterized by relatively low concentrations of chlorine (< 1 ppm) (3). Whether exposure to low levels of chlorines induces tissue adaptation, which may have contributed to the salutary outcome in the gas plant workers, is unknown.

The following statement appears in another report: "(the) prevailing chemical view is that significant permanent damage does not result from acute exposure to chlorine gas" (11); and the findings in this same study support this viewpoint. Still, a more tenable and prudent view is that while most victims of accidental exposure appear to recover completely, clinically and physiologically, some retain evidence of persistent damage that may even grow worse in time. The importance of factors such as age, previous state of health, and smoking habits as an influence(s) on the outcome is not yet understood.

Chronic Exposure, Human

Information about the pulmonary hazards of intermittent, long-term exposure to low concentrations of chlorine is ambiguous. Ferris et al. found no difference in respiratory symptoms or ventilatory function between workers in a pulp mill exposed an average of about 20 years to both sulfur dioxide and chlorine and a control group from a nearby paper mill (5). "Considerable self-selection" occurred since many workers who found the odors of the pulp mill disagreeable transferred to the paper mill. Within the pulp mill the men exposed principally to chlorine plus chlorine dioxide had more shortness of breath and slightly lower ventilatory performance than did those exposed principally to sulfur dioxide. The air monitoring was too limited to characterize dosage.

Perhaps surprisingly, both groups showed lower prevalences of respiratory disease than did the male population in the community at large. This finding suggested the workers were not representative of the general population.

The most comprehensive study in North America is that by Patil et al. of 600 workers from 25 plants that manufactured chlorine (10). Concentrations on a time-weighted-average ranged between 0.006 ppm and 1.42 ppm (mean: 0.146 ▲ 0.287). Few workers were exposed to over 1 ppm and the average duration of exposure was 10.9 years. Comparison was made with unexposed personnel from the same plant: there was no difference between the two groups in ventilatory function, frequency of colds, shortness of breath, chest pain, abnormal chest x-rays, or abnormal electrocardiograms. The exposed workers tended to report more anxiety, dizziness, and fatigue, and had more tooth decay, which alone among all the parameters tested was interpreted as showing a correlation with dose.

There is no evidence that chlorine is a carcinogen.

Animal Effects

With few exceptions, studies on animals have resorted to lethal concentrations of chlorine. There is virtually no information about the effects of low concentrations of the gas, administered acutely or chronically. An exception is the study of Barrow et al. (2) who exposed mice to concentrations ranging from 0.7 ppm to 38.4 ppm of chlorine for 10 minutes and measured the percentage of change in respiratory rate. This method offers a simple, quantitative means of comparing the irritancy of airborne pollutants. Chlorine slowed the breathing rate, which was judged to be evidence of sensory irritation to the upper airways, particularly the nasal mucosa. (An increase in rate, as occurs with ozone (1), is considered evidence of irritation to the tracheobronchial airways and parenchyma of the lung.) The threshold for sensory irritation from chlorine was about 0.9 ppm. This was interpreted by the authors to mean that the current standard of 1 ppm represents an upper acceptable limit.

Recommendations

Accidental exposure to high concentrations of chlorine are likely to recur in view of the ubiquity of the gas. NIOSH should encourage and facilitate the use of sophisticated, follow-up studies of victims, including tests for assessing the caliber of small airways and the elastic recoil of the lung.

Research undertaken on animals should be directed toward assessing the effects of low-grade, prolonged exposure on the structure and function of the lung. Whatever adaptation to the gas develops with repeated exposures should be determined.

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HYDROGEN SULFIDE

Introduction

Hydrogen sulfide (H_2S) is a colorless gas at ordinary temperatures and liquefies at low temperatures (boiling point = -61.8°C) or elevated pressures. The gas is inflammable, explosive and, like cyanide, may be lethal at high concentrations within a few breaths. The soluble salts of hydrogen sulfide are toxic also.

Drilling, mining, smelting, and processing of both fossil fuels and metallic ores, plus a variety of other unrelated industries, may involve hazardous exposure to sulfides. The gas is released whenever sulfur-containing organic matter undergoes decomposition by bacteria. Accordingly, sewers, septic tanks, trucks that transport chemical wastes, fishing boats, fumaroles, sulfur springs and various other settings, may serve as pockets for the gas. About 125,000 workers are estimated to be potentially at risk (8). A partial list of the occupations involved is shown in Table VII-4.

The present federal standard for hydrogen sulfide is 20 ppm (1 ppm = ~1.4 $\mu g/m^3$ at 25 °C, 760 mm Hg), described as a "ceiling concentration determined for an eight-hour day" (8). The standard also specifies a peak concentration of 50 ppm not to exceed 10 minutes (8).

Acute Toxicology

The toxicity of hydrogen sulfide is attributable to both biochemical and direct irritative actions. In tissue liquids the gas dissociates into hydrosulfide (HS^-) and sulfide ($S^=$) ions, which by inactivating a number of respiratory enzymes, interfere with cellular metabolism of oxygen (4)(5)(11). As a consequence, the respiratory center in the brain may cease function, causing apnea and sudden death. Biochemical recovery accompanies the conversion of sulfide to innocuous sulfate ions. As a surface irritant, hydrogen sulfide primarily affects the eyes and respiratory system.

Dose-response relations: Hydrogen sulfide is detectable by smell at about 25 ppb (parts per billion); at 3-5 ppm, the smell becomes offensive (8). The olfactory sense is rapidly fatigued by increasing concentrations of the gas so that the individual is likely to be unaware of continuing exposure.

Inflammation of the cornea of the eye has been reported in workers in Germany exposed to as low as 10 ppm for 6 to 7 hours (8)(10). The simultaneous presence of either carbon disulfide or formaldehyde in the air in these studies may have played contributory roles. A British study associated eye irritation with concentrations of 150 ppm or higher (2). Among the eye symptoms described were pain, blurred vision, and colored halos surrounding light. Inflammation of the conjunctiva and cornea accompanied the symptoms.

There may be evidence of central nervous system stimulation or depression beginning around 200 ppm. At about 500 ppm, hydrogen sulfide produces hypocapnic hyperventilation through stimulation of chemoreceptors in the carotid body, and cardiac arrhythmias (6)(7). At higher concentrations these effects are likely to be disabling; 1,000 ppm can cause apnea within seconds.

Central nervous system involvement may be associated with headache, mental confusion, agitation, dizziness, somnolence, coma, and convulsions (3). There may be nausea and vomiting.

The entire respiratory system may be acutely inflamed. Frothy, at times bloody, secretions may obstruct the airways and require suction or intubation. In one survey, pulmonary edema was reported in 20% of the victims (3). Chest pain, shortness of breath, cough, and cyanosis, are likely to accompany the edema.

A number of case reports of accidental exposure by inhalation have been summarized in the NIOSH criteria document (8). Burnett et al. analyzed in detail 221 cases of acute intoxication among workers in Alberta, Canada. Most occurred in the natural gas, oil, and petroleum industries—typically in confined spaces—and required hospitalization (3). Almost all of the deaths (6%) occurred before hospital arrival. Among the survivors (94%), recovery was complete with little or no evidence of long-term effects. The following have been cited as sequela in other case reports: epilepsy, acoustic nerve damage, and amnesia (8). Burnett et al. also described cases of severe physical injury following loss of consciousness, and drowning has been reported elsewhere (8).

Treatment: Successful treatment hinges on how rapidly the victim is removed from the contaminated environment and supportive measures

Table VII-4

OCCUPATIONS WITH POTENTIAL EXPOSURE TO HYDROGEN SULFIDE

- Animal fat and oil processors
- Animal manure removers
- Artificial-flavor makers
- Asphalt storage workers
- Barium carbonate makers
- Barium salt makers
- Blast furnace workers
- Brewery workers
- Bromide-brine workers
- Cable splicers
- Caisson workers
- Carbon disulfide makers
- Cellophane makers
- Chemical laboratory workers, teachers, students
- Cistern cleaners
- Citrus root fumigators
- Coal gasification workers
- Coke oven workers
- Copper-ore sulfidizers
- Depilatory makers
- Dyemakers
- Excavators
- Felt makers
- Fermentation process workers
- Fertilizer makers
- Fishing and fish-processing workers
- Fur dressers
- Geothermal-power drilling and production workers
- Gluemakers
- Gold-ore workers
- Heavy-metal precipitators
- Heavy-water manufacturers
- Hydrochloric acid purifiers
- Hydrogen sulfide production and sales workers
- Landfill workers
- Lead ore sulfidizers
- Lead removers
- Lithographers
- Lithopone makers
- Livestock farmers
- Manhole and trench workers
- Metallurgists
- Miners
- Natural gas production and processing workers
- Painters using polysulfide caulking compounds
- Papermakers
- Petroleum production and refinery workers
- Phosphate purifiers
- Photoengravers
- Pipeline maintenance workers
- Pyrite burners
- Rayon makers
- Refrigerant makers
- Rubber and plastics processors
- Septic tank cleaners
- Sewage treatment plant workers
- Sewer workers
- Sheepdippers
- Silk makers
- Slaughterhouse workers
- Smelting workers
- Soap makers
- Sugar beet and cane processors
- Sulfur spa workers
- Sulfur products processors
- Synthetic-fiber makers
- Tank gaggers
- Tannery workers
- Textiles printers
- Thiophene makers
- Tunnel workers
- Well diggers and cleaners
- Wool pullers

NIOSH (1977, Table XIV-2)

are instituted. Resuscitation, including mouth-to-mouth breathing, and establishment of a patent airway may be life-saving.

Nitrites have been shown to be effective in countering the enzymatic effects of sulfide in animals, and in one case of severe poisoning of a worker (12)(13). Nitrite converts the oxyhemoglobin (HbO_2) of red blood cells to methemoglobin; methemoglobin traps toxic sulfate ions forming sulfmethemoglobin; the latter is restored within hours to oxyhemoglobin while the sulfur is excreted in an oxidized state. Nitrites may be inhaled from ampules or injected intravenously.

Oxygen therapy is useful whenever pulmonary edema or depressed ventilation impede the uptake of oxygen by the blood.

Chronic Toxicity

There is little evidence that repeated exposure to low concentrations of hydrogen sulfide causes persistent or cumulative adverse effects. The majority who were exposed to daily levels that could exceed 20 ppm experienced a variety of complaints involving changes in personality, intellect, and memory; eye and respiratory irritation; and gastrointestinal disorders (1). Neurologic changes reflecting damage to the brain or spinal cord were present in the more seriously affected workers. One individual had difficulty in maintaining equilibrium several years following an acute exposure to an unspecified concentration. Sudden and sustained interference with the delivery or metabolism of oxygen by the brain tissue could result in permanent damage.

Animal Studies

Animal studies have been useful in correlating the dose of hydrogen sulfide with lesions produced in the cerebellum, basal ganglia, and cornea; in demonstrating the cardiac malfunction and arrhythmias produced by the gas; and in clarifying the mechanism of hydrogen sulfide toxicity and the palliative effects of nitrites. There is little unambiguous information on the effects that chronic exposure to low concentrations of hydrogen sulfide may have on behavior, vision, the neurophysiologic and cardiorespiratory systems.

Recommendations

A registry of acute hydrogen sulfide intoxication cases should be established, especially those requiring hospitalization. A standardized form of reporting should prove feasible for large industries. Among the benefits of the registry would be the accumulation of information about the efficacy of different forms of treatment, incidence of persistent clinical disorders, and factors governing prognosis.

Early institution of effective treatment is often critical. All potentially exposed workers should be familiar with proper procedures to be followed and approved methods of resuscitation as well as the danger of rendering assistance in contaminated areas. Consideration should be given to installing first aid units containing ampules and injectable forms of nitrite plus a supply of oxygen close to potentially hazardous settings.

Surveys of workers potentially at risk to repeated exposure to low concentrations of hydrogen sulfide are warranted as are additional animal studies of the potential consequences of long-term exposure of animals to low concentrations.

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MERCURY

Introduction

Three chemical forms of mercury pose occupational hazards: elemental of atomic mercury, inorganic salts, and organic salts. This discussion is confined to the metallic element and inorganic salts.

Elemental mercury, a liquid, vaporizes readily at ambient temperatures. Exposure by inhalation occurs with both the vapor and the inorganic salts as dusts. It was estimated that at least 1,100,000 workers are potentially at risk of exposure to mercury vapor and inorganic salts (10). Their occupations are listed in Table VII-5.

Mercury may also be taken up by ingestion and absorption through the skin. Generally, elimination of the metal from the body proceeds slowly so allowance should be made for cumulative effects from combined occupational and nonoccupational sources. Contaminated fish foods have been incriminated as a source of methyl and ethyl organic mercury.

The standard for inorganic mercury recommended by NIOSH is 0.05 mg/m³ based on a time-weighted-average (TWA) concentration for an eight-hour workday (11). The standard defines "inorganic mercury" to include elemental mercury, all inorganic mercury compounds, and organic mercury compounds exclusive of methyl and ethyl (monoalkyl) salts. There is a National Emission Standard for mercury from stationary sources ranging from 2.3 to 3.2 kg per 24-hour period depending on the facility or process involved (5); there is no equivalent ambient air standard.

Kinetics, Mechanism of Effect

Following inhalation, mercury vapor diffuses rapidly into the plasma and red blood cells and is distributed to most body tissues (1)(3). The elemental state carries no ionic charge and is soluble in lipids. These properties facilitate rapid passage across cell membranes and localization within nerve tissue (7)(9). Once mercury has been oxidized to a charged ionic state (Hg_2^{++} or Hg^{++}), passage across the blood-brain barrier is impeded. The kidney then becomes the principal site for storage and elimination (12).

Largely on the basis of *in vitro* studies, the toxicity of mercury has been attributed primarily to chemical links that are formed with sulfhydryl groups (-SH) present in all proteins (2)(7). Mercury binds with other cellular components also, including amines, phosphoryl, and carbonyl groups. As a consequence, the permeability of cell membranes and the function of a variety of enzyme functions may be altered (8).

Clearance of mercury from the brain is slower than from other tissues. The half-life (time required for one-half to be eliminated) for the total body burden is about two months (6). The extent to which total body burden is reflected in blood or urine concentrations is arguable. Correlations among the concentrations of metal in air (an index of exposure), blood, and urine may be statistically significant for large populations, particularly after chronic exposure to elemental mercury (14), but they break down frequently within individuals. A confounding factor is the tendency for urine concentrations to change on the basis of metabolic activity and diet, independent of body burden. Blood is thought to be a more reliable indicator of body burden than urine (4). There is poor correlation between chronic exposure to inorganic mercury salts and urine concentrations (6).

Mercury is also concentrated in the roots of hair. Since hair tends to grow at a steady rate of roughly 1cm/month the distribution of the metal along the strands of hair becomes a means of relating the magnitude of exposure to specific periods of time. Generally, mercury is about 250 to 300 times more concentrated in hair than in blood (6).

Table VII-5

OCCUPATIONS WITH POTENTIAL EXPOSURE TO MERCURY

Amalgam makers	Fur processors
Bactericide makers	Gold extractors
Barometer makers	Histology technicians
Battery makers, mercury	Ink makers
Boiler makers	Insecticide makers
Bronzers	Investment casting workers
Calibration instrument makers	Jewelers
Cap loaders, percussion	Laboratory workers, chemical
Carbon brush makers	Lampmakers, fluorescent
Caustic soda makers	Manometer makers
Ceramic workers	Mercury workers
Chlorine makers	Miners, mercury
Dental amalgam makers	Neon light makers
Dentists	Paint makers
Direct current meter workers	Paper makers
Disinfectant makers	Percussion cap makers
Disinfectors	Pesticide workers
Drug makers	Photographers
Dye makers	Pressure gauge makers
Electric apparatus makers	Refiners, mercury
Electroplaters	Seed handlers
Embalmers	Silver extractors
Explosive makers	Switch makers, mercury
Farmers	Tannery workers
Fingerprint detectors	Taxidermists
Fireworks makers	Textile printers
Fungicide makers	Thermometer makers
Fur preservers	Wood preservative workers

NIOSH (1973, Table XII-5)

Acute Effects, Humans

Most cases of acute intoxication are either accidental (e.g., following rupture of a large mercury-containing receptacle in a confined space) or the consequence of attempted suicide. If the vapor has been inhaled, the clinical picture will generally reflect injury to the lung (chest pain, cough, shortness of breath) plus general toxemia (fever, chills, profound weakness, anorexia, and joint pain). In nonfatal cases, recovery is rapid and may be complete within 24 hours.

If intoxication follows ingestion of inorganic salts, the site of injury shifts to the abdominal organs. Gastroenteritis (abdominal pain, nausea, vomiting, bloody diarrhea) and renal insufficiency, which may culminate in shutdown, are likely to prevail. Evidence of general toxemia may also be present.

Chronic Effects, Humans

Chronic intoxication chiefly affects the central nervous system. The clinical picture is termed "erethism." Headache and various personality changes are described, including increased irritability, depression, paranoia, insomnia, and loss of memory and mental acuity (2)(13). Mercury may remain unsuspected as the cause of symptoms if the onset is gradual. Motor disturbances also occur. Tremors of the limbs, particularly of the hands, are often an early sign of chronic intoxication. Use of the limb aggravates the tremor. Muscular coordination can become impaired.

Smith et al. found evidence of early erethism in some workers at chloralkli plants where ambient levels of elemental mercury ranged from 0.05 mg/m^3 to 0.10 mg/m^3 (TWA) (12)(13). At

concentrations above 0.1 mg/m³, tremors and abnormal reflexes occurred with increasing frequency and severity as a function of dose. The authors concluded that dose-response relations below 0.1 mg/m³ were not sufficiently sensitive to warrant concern. (Some unexposed control subjects also had symptoms identified with early erethism.)

Other sites of involvement are the oral cavity (inflammation of the buccal lining and gums, excessive salivation), kidneys (proteinuria, which may lead to the syndrome of nephrosis), skin (rashes), and various changes of a nonspecific nature (anorexia, weight loss, weakness, anemia).

Treatment: Chelating agents, including BAL, d-penicillamine, and dithrocarbonate, have been administered to accelerate the excretion of mercury in urine and sweat. Despite the severe toxicity and disability associated with prolonged exposure to mercury, removal of the patient from the offending environment combined with chemical treatment have at times led to dramatic recovery (16).

Recommendations

The excretion rate of mercury from the body may be modified by metabolic factors. It is not possible to reliably predict the amount of mercury accumulated in an individual from knowledge of air concentrations and time spent in the offending atmosphere (other sources, principally dietary, may also complicate the analysis). Therefore, some method of periodic surveillance of potentially exposed workers should be considered. Admittedly, the earliest evidence of mercurial toxicity is likely to be subjective, even vague. But the appearance of such complaints should merit thorough neurologic examination, combined perhaps with blood and urine analyses.

The ease with which elemental mercury penetrates the placenta and concentrates in fetal tissue should be the basis for protecting pregnant workers from all known exposures to this agent.

Continued toxicologic research into the metabolic, biochemical, and functional changes produced by all chemical forms of mercury, with an eye toward improving the early detection of intoxication, is to be encouraged.

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OSMIUM TETROXIDE

Introduction

Osmium has only limited commercial use. Its principal forms of production are as metallic osmium and osmium tetroxide, also called osmic acid (OsO_4). Osmium tetroxide is toxic. It occurs in crystalline and amorphous states, melts at 40 to 41 °C, and is soluble in water and alcohol. It is highly volatile (vapor pressure at 26 °C = 10 mm Hg); the odor given off is brusque and offensive.

The metal is biologically inert and extremely dense (specific gravity = 22.48). With other metals of the platinum group, particularly iridium, it forms alloys noted for their hardness.

The most recent published estimate of osmium production in the United States is for 1971 and amounts to about 140 lbs. (5). NIOSH has estimated that only about 100 workers are potentially at risk in the production of osmium tetroxide. It is used principally in histology laboratories to fix and stain tissue, and the personnel of these laboratories constitute the principal population-at-risk. The second major use of osmium is in the drug industry as a catalyst in the production of steroid hormones. The alloy has only a small market in the electrical industry and in the manufacture of such miscellany as phonograph needles, engraving tools, and bearings.

The federal standard for osmium tetroxide is 2 $\mu g/m^3$ based on an eight-hour time-weighted-average (TWA) and 40-hour workweek. There is no standard for metallic osmium.

The properties that distinguish osmium tetroxide as a fixative are responsible for its toxicity. It reacts with lipids, nucleic acids, and proteins. The structure and function of proteins are thereby altered. As a consequence, a variety of enzyme systems may be damaged or destroyed (2).

There are more case reports of acute poisoning from osmium tetroxide dating to the last century than the present one. The two principal sources of "new" clinical information are articles by Brunot (1), and McLaughlin and coworkers (3); Brunot's contribution is contained in a footnote to a study on rabbits in which he describes his own symptoms following inadvertent exposure.

Osmium tetroxide vapors irritate the surfaces of the skin, eyes, and respiratory tract. The subject may have smarting of the eyes, lacrimation, and see halos around lights. Corneal ulcers may occur. (A case of blindness was reported in the last century.) Seven workers who were engaged in refining osmiridium and were exposed to vapors estimated to range from 133 $\mu g/m^3$ to 640 $\mu g/m^3$, developed conjunctivitis that subsided within one day (3).

Among all respiratory irritants, osmium vapors appear to strike with the most dramatic intensity. The odor and sense of nasal irritation are powerful and virtually indistinguishable. Depending on the degree of exposure, all strata of the respiratory system may be involved. Cough has been the most frequent symptom (3). More severe exposure may cause a sense of chest constriction coupled with difficulty in breathing (1).

Headache behind or above the eyes is relatively common (3). The skin may be blackened at the site of contact, owing to reaction of the osmium with lipids.

A therapeutic oddity has been the injection of 1% osmium tetroxide into the joints of patients with rheumatoid arthritis and related disorders (4). The absence of any reported systemic side-effects may be taken as evidence that the action of osmium was confined to the local tissues.

Chronic Effects

No data are available on the possible effects of periodic or repeated exposure to osmium tetroxide among workers who produce it or laboratory personnel who use it.

Animal Toxicology

Acute toxicologic studies on animals confirm the severe, widespread injury to the respiratory system and eyes produced by osmium tetroxide.

Recommendations

The hazard associated with the production and use of osmium tetroxide should be minimal if recommended procedures are followed, caution is observed, and adequate ventilation is provided. No recommendations for research are offered.

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OXIDES OF NITROGEN

Introduction

The term oxides of nitrogen as used in federal occupational standards is reserved for nitric oxide and nitrogen dioxide (23). Both gases are by-products of a variety of combustive processes associated with high temperature. Typically they co-exist together although their relative concentrations vary widely, depending on the nature of the combustive process. For example, nitrogen dioxide may comprise over 50% of the mixture formed by a blast of dynamite, but less than 10% of that formed from an oxyacetylene torch (23). Since nitrogen dioxide is the more toxic gas, such variations have important implications for health. Unfortunately, the gases are not differentiated in many reports of occupational exposure.

It is estimated that about one million workers are potentially at risk to repeated exposure of low concentrations of nitrogen oxides (22). A partial list of the occupations is contained in Table VII-6. A small fraction of this total, which includes silo workers, welders, and firefighters, is subject to acute toxicity from sudden high concentrations—or "boluses"—of the gases (10)(21)(27). The general population may be exposed to nitrogen oxides in community air or indoors near gas stoves (24)(31). Tobacco smoke is a source of intense exposure to both nitric oxide and nitrogen dioxide (3).

The present federal occupational standard for nitrogen dioxide is 5 ppm, based on an eight-hour averaging time (TWA). NIOSH has recommended an alternative ceiling concentration of 1 ppm (sampling time unspecified). The occupational standard for nitric oxide is 25 ppm, based on an eight-hour averaging time.

The national ambient air quality standard for nitrogen dioxide is 0.05 ppm (100 mg/m^3) annual arithmetic mean.

Toxicity

Mechanism: Comprehensive reviews of nitrogen oxides toxicology are contained in recent monographs and in the criteria document prepared by EPA (12)(24)(29). Several mechanisms

Table VII-6

OCCUPATIONS WITH POTENTIAL EXPOSURE TO OXIDES OF NITROGEN

Braziers	Medical technicians
Dentists	Metal cleaners
Dye makers	Nurses
Fertilizer makers	Organic chemical synthesizers
Food and textile bleachers	Photoengravers
Garage workers	Physicians
Gas and electric arc welders	Silo fillers
Jewelry makers	Sulfuric acid makers

Adapted from NIOSH (1977, p.426)

of toxicity have been postulated, including: (a) combination with water to form nitric acid, a powerful irritant; (b) direct oxidation of lecithin and unsaturated fatty acids, which constitute major elements of cell membranes; and (c) formation of free radicals, which in turn oxidize unsaturated fatty acids in cell membranes and may also denature elastin and collagen, the structural proteins of lung. Nitric oxide and nitrogen dioxide combine with hemoglobin to form a variety of nitroxy-hemoglobin complexes and methemoglobin (5). The latter, which is the major end-product, is physiologically inactive.

Acute Effects, Human

As with healthy subjects, patients with chronic bronchitis and asthma have shown little or no functional changes following exposure to 0.5 ppm (15) or 1.0 ppm (13) for several hours; mild irritative symptoms were most frequent among the asthmatics (15). The threshold concentration causing lung function changes in volunteers exposed acutely to low concentrations of nitrogen dioxide is about 1.5 ppm (29). Concentrations in the range of 1.5 to 5.0 ppm may cause the following: narrowing of both central and peripheral airways; stiffening and reduced diffusing capacity of the lung, which probably reflects an abnormal distribution of ventilation and possible swelling of the alveolar-capillary membrane; and a slight fall in the partial pressure of oxygen physically dissolved in arterial blood (Pa_{O_2}) without, however, any essential change in the saturation of hemoglobin with oxygen (Sa_{O_2}) in either healthy subjects or patients with chronic bronchitis (30). These functional changes may be associated with symptoms of irritation, including cough. Typically, responses are short-lived. There is also evidence that as little as 0.1 ppm of nitrogen dioxide may render the airways in some asthmatic subjects more reactive to carbachol, a pharmacologic bronchoconstrictor (25), but questions regarding the validity of this observation have been raised and confirmation of the experimental results is in order. There is no evidence that low levels of nitrogen dioxide alter the pulmonary functional response to other pollutants, whether gases or particles.

Irritation of conjunctival surfaces has been associated with open arc-welding, in which concentrations of nitrogen oxides were estimated to range from 4 to 20 ppm (21). More massive exposures may cause shortness of breath, cough, weakness, and chest pain, followed by lung edema after intervals ranging from hours to days. Methemoglobinemia may contribute to the hypoxemia associated with both bronchospasm and edema.

With massive accidental exposure, the entire length of the respiratory system may become involved. Pneumonia may supervene; persistent cough and sputum may develop; and inflammation of the bronchioles may progress to obstruction and emphysema-like changes of the neighboring airspaces. While most cases of accidental overexposure recover with little or no apparent functional impairment, the damage associated with obliterative bronchiolitis is likely to be permanent (1)(12). Lethal exposures have been associated with "silage gas poisoning" and with the massive concentrations of nitrogen oxides that may be released by burning plastics and nitrocellulose (11)(18).

Chronic Effects, Human

Information about possible effects of prolonged low-level exposure to nitrogen oxides in industry or in polluted communities is both sparse and equivocal. One study drew the conclusion that workers exposed to nitrogen oxides in a German chemical plant had clinical and laboratory findings consistent with emphysema; the data presented, however, do not appear to support the conclusion (17). Increased rates of respiratory illness, particularly in children living near plants producing TNT in Chattanooga, Tennessee have been attributed to nitrogen dioxide in ambient air (29). Two major criticisms have been directed against these studies, namely that the technique (Jacobs-Hockheiser) used to analyze nitrogen dioxide was unsatisfactory, and that the adverse health effects could have been caused by other ambient pollutants known to have been present. A British study concluded that female children in homes with gas stoves were subject to more respiratory illness than their counterparts in homes without gas stoves. Nitrogen dioxide was suggested as the responsible agent, although no airmonitoring was done (2). This finding has not been confirmed in a more recent study in the United States sponsored by the American Gas Association (19).

Finally, there is physiological and postmortem evidence for an increased prevalence of emphysema among British coal miners exposed

to "nitrous fumes" from shot firing, particularly associated with the use of Hydrox shells in 1959-60 (14). (The bulk of the charges in these shells consists of nitrates; the shells have been banned from the mines since 1962.) The concentration of nitrous fumes in coal mine headings following shot-firing are reported to range up to several hundred ppm if ventilation is low. Such levels are known to cause severe parenchymal damage in animal lungs.

Animal Effects

Inhalation studies on laboratory animals have provided graphic descriptions of structural lesions that may be produced by acute, subacute, and chronic exposure to different concentrations of nitrogen dioxide, as well as associated biochemical and functional derangements (12)(24)(29). As with other respiratory irritants, the extent and severity of effects are dose-related, so that any anatomic level and respiratory cell type may be subject to injury. Among the effects noted have been impaired clearance of particulate matter, impaired resistance to infection, altered mechanical performance (static and dynamic compliance, resistance of the airways to gas flow), and uneveness in the distribution of ventilation within the lung (4)(8)(9)(16). Which of these functional attributes may be most sensitive to the gas or most likely to show adaptation with repeated exposure is not readily apparent.

Evidence of histologic damage, or of increased capillary permeability that may predispose to edema are seen in rodents at concentrations of about 0.5 ppm (26). Mice exposed to 0.5 ppm of nitrogen dioxide for 3 to 12 months develop bronchiolar inflammation and changes in surrounding airspaces—changes interpreted as being consistent with early focal emphysema (2). Inflammation and thickening of the walls of the bronchioles and alveoli is seen in rats exposed to 2.0 ppm continuously for 33 months and in monkeys exposed to this same concentration for 14 months (6)(7).

There is no convincing evidence that nitrogen dioxide is a teratogen, mutagen, or carcinogen.

Recommendations

Prospective clinical-physiological studies are needed of workers who might be repeatedly exposed to low levels of nitrogen oxides. Emphasis should be given to measurements useful in detecting early emphysema, including lung volume and its subdivisions, small airway function, and when feasible, static lung compliance. A careful assessment of other possible confounding sources of nitrogen oxides, including cigarette smoke, indoor (residential) air, and community air is necessary in such studies.

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Table VII-7

OCCUPATIONS WITH POTENTIAL EXPOSURE TO OZONE

Air treaters	Organic chemical synthesizers
Arc welders	Sewage treaters
Cold storage food preservers	Textile bleachers
Industrial waste treaters	Water treaters
Liquor agers	Wax bleachers
Odor controllers	Wood agers
Oil bleachers	Flight attendants on commercial aircraft

(NIOSH, 1977)

OZONE

Introduction

Ozone (O_3), an allotropic form of oxygen, is colorless, highly reactive, and unstable. Its sources and the populations potentially at risk to its toxic action are diverse. Formed secondarily in photochemical smog, ozone may exceed federal ambient air quality standards with regularity in urban communities and be transported hundreds of miles downwind. (In 1973, maximal hourly average oxidant concentrations equaled or exceeded 0.2 ppm on 100 or more days at air monitoring stations in Pasadena, Pomona, and Azusa, California (17).) Natural sources, represented chiefly by the periodic downdraft of ozone from the stratosphere, may produce ground levels of 0.04-0.05 ppm, with occasional spikes to 0.08 ppm or higher (20). Exposure to stratospheric ozone is most likely to occur in unsealed, high altitude aircraft. Indoor levels may reach about 40-70% of outdoor levels, depending on the type and degree of ventilation in the building and the materials used in furnishings (fabrics adsorb ozone) (1). Homes or offices may generate low levels of ozone intermittently through ultraviolet light and a variety of machines and equipment using high voltages: common examples are electrostatic air cleaners and continuously operated copying machines (1). A listing of occupations associated with exposure to ozone is shown in Table VII-7. It is estimated that about one million workers may be at risk (16).

The federal occupational standard for ozone is 0.1 ppm (195 $\mu g/m^3$) based on a time-weighted-average concentration for an 8-hour workday and 40-hour workweek.

The National Ambient Air Quality Standard, based on a maximum one-hour level, has recently been set at 0.12 ppm (235 $\mu g/m^3$). The previous standard of 0.08 ppm was for photochemical oxidants measured as ozone. (Ozone is the major, but not the most reactive oxidant in photochemical smog.).

Effects

Mechanism: Ozone shares similar mechanisms of effect with nitrogen dioxide, a less toxic oxidizing gas. Among the basic modes of biochemical damage postulated for ozone are: oxidation of polyunsaturated fatty acids, especially in cell membranes; formation of free radicals; formation of secondary toxic compounds through oxidation of lipids; oxidation of sulfhydryl compounds (17)(21). Changes in lung mechanics and ventilatory performance may occur reflexly (stimulation of nerve receptors) or through the release of histamine from injured mast cells located in the epithelium of the airways.

Human Effects, Acute

Information about the acute effects of ozone has come from four sources: controlled laboratory studies of volunteers, surveys of workers such as welders, accidents, and studies of the general population exposed to ambient pollution. Under laboratory conditions, the odor threshold is 0.02 to 0.05 (12). As concentration increases between about 0.2 ppm and 2 ppm, symptoms proceed from upper to lower airways and intensify. There may be irritation of the eyes, nose, and throat, substernal tightness, cough, and shortness of breath. (Ozone, however, is not considered responsible for the eye irritation experienced in photochemical smog (21)). Headache and lassitude, suggestive of systemic or a generalized effect, occur occasionally.

The threshold for functional impairment is slightly higher than for symptoms of discomfort. No changes in ventilatory performance (FVC,

$FEV_{1.0}$) are seen in normal subjects following several hours of exposure to 0.25-0.3 ppm of ozone, to which intermittent light exercise and heat stress are added (8)(21). There are slight average reductions in FVC and $FEV_{1.0}$ at 0.37 ppm of ozone, attributable principally to subjects with evidence of hyperreactive airways which are not statistically significant. Exposure to 0.15 ppm of ozone during vigorous exercise (65% of maximal oxygen uptake) elicits a change in ventilatous patterns characterized by shallow breathing; 0.3 ppm of ozone and vigorous exercise reduce VC slightly but significantly; and 0.3 ppm combined with moderate exercise (45% of maximal oxygen uptake) are associated with wheezing, headache, and other symptoms of discomfort (5). Changes in the lung's mechanical behavior (increased flow resistance, reduced dynamic compliance), and impairment of diffusing capacity are reported at concentrations from 0.45 ppm to 0.75 ppm (21). These effects are generally reversible within hours. Even among normal subjects there may be wide variations in functional response to short-term exposures.

Ozone appears to increase the reactivity of the airways to provocative aerosols such as histamine (7). There is evidence that repeated daily exposure to ozone is attended by diminishing functional effects (tolerance), and that individuals living in Los Angeles, where photochemical smog is commonplace, are less responsive to acute ozone exposure than subjects from regions with little smog (9)(10).

Occupational exposure to concentrations in the range of 2 ppm or higher cause clinical symptoms and signs indicative of pulmonary edema (14). Concentrations of about 10 ppm may be extremely debilitating (13)(15).

Elevated ambient levels of oxidants (of which ozone is considered the most important component) have been associated with increased frequency of headache, cough, eye and chest discomfort among student nurses (11). The threshold for eye irritation, which appeared to be the most sensitive index of response, was estimated at about 0.15-0.19 ppm of ozone, with one-third of the subjects reporting this symptom at 0.5 ppm.

There is epidemiologic evidence to suggest that asthma is aggravated when ambient oxidant concentrations exceed 0.25 ppm (21), and that athletic performance is affected at even lower concentrations (22). The latter is consistent with laboratory findings (5).

Human Effects, Chronic

There is little information on the possible effects of prolonged exposure to low concentrations of ozone, whether among workers or the general population.

One study of shipyard welders exposed to a variety of hazardous pollutants, including ozone, metal fumes, nitrogen oxides, and asbestos, described an increase in residual lung volume suggestive of obstructive airway disease (19). A cohort of pipefitters with little or no exposure to welding fumes or asbestos was used for comparison. The mean ozone concentration to which the welders were exposed was estimated to be 0.10 ppm (range: 0.01-0.36 ppm); the mean nitrogen dioxide concentration was 0.04 ppm (range: 0.01-0.08 ppm). To what extent ozone, among all the pollutants, may have been responsible for the effect is uncertain. An earlier study of seven workers engaged in argon-shielded electric arc welding adduced no evidence of impaired lung function following long-term exposure to 0.2-0.3 ppm of ozone (23). Ventilatory tests of small airway patency and the diffusing capacity, reported to be useful in detecting early emphysematous changes (see Phosgene, (3)) were measured. All subjects smoked cigarettes.

There is no evidence that ozone is mutagenic in humans or that long-term exposure to smog is associated with increased lung cancer mortality (21).

Animal Effects

Considerable research has been done on the effects of ozone on a variety of biochemical systems, cell cultures, and intact animals. The subject is reviewed in two recent monographs (17)(21). Notable among the effects of acute exposure to less than 1 ppm of ozone are changes in the chemistry and function of alveolar macrophages, which imply reduced resistance to infection and impaired clearance of foreign material from alveoli; inflammatory changes, affecting particularly the bronchioles but extending throughout the airways and as far peripherally as the proximal alveoli; and changes in lung function (21). Some of the biochemical toxicity is mitigated by vitamin E (4).

Subacute and chronic exposure may produce changes in the lung akin to aging or emphysema. The primary sites of attack are the bronchioles and alveoli. The bronchioles in rats and monkeys appear to be equally susceptible to mild injury from 0.2 ppm of ozone admin-

istered eight hours daily for seven days (6). Loss of elastic recoil and increased alveolar size have been observed in rats following continuous exposure for 30 days to 0.2 ppm (2). Emphysematous-like changes and thickening of pulmonary arteries have occurred in rabbits exposed 5 days weekly for 10 months to 0.4 ppm (18).

Recommendations

There is need for prospective studies on the possible effects of prolonged, intermittent exposure to ozone on the lungs of workers. This is particularly true of occupations such as welding in which periodic spikes in concentration are likely to occur, since toxicologic evidence suggests that the injurious effects of this gas may be more closely related to peak concentrations than to total dosage (21). (Potentially toxic levels of nitrogen oxides may also be generated during welding.) Such studies should emphasize functional tests that provide information about alveolar elastic recoil and the patency of small airways. Animal experiments suggest that these particular properties as most likely to be affected.

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PHOSGENE

Introduction

Phosgene ($COCl_2$) is a gas at ambient pressure and temperature; it liquefies at elevated pressure or in cold air (boiling point = 7.5°C at 1 atmosphere). Along with chlorine, phosgene was used as a poisonous gas in World War I. Today, industrially, it has only limited importance despite increasing use in the production of isocyanates.

About 10,000 workers are estimated to be potentially at risk to phosgene (8). A source of accidental exposure is the production of phosgene by decomposition of chlorinated hydrocarbons.

The present federal standard for phosgene is 0.1 ppm (0.4 mg/m³), based on an 8-hour time-weighted average concentration (TWA). NIOSH has recommended establishment of a ceiling limit of 0.2 ppm (0.8 mg/m³), not to be exceeded in any 15-minute sampling period (8).

Acute Effects, Human

Phosgene hydrolyzes in the presence of water and biologic liquids to form hydrochloric acid, which is thought to be the basis for its toxicity (7). Following inhalation, phosgene can be absorbed and cause injury throughout the respiratory system. Liquid phosgene can cause severe internal burns as well as burns of the eyes and skin.

Phosgene imparts an odor said to resemble musty hay. Wells et al. reported that none of a group of military personnel could detect concentrations below 0.4 ppm (1.5 mg/m³), which is in excess of both the federal standard and recommended ceiling limit (10). About 39% of the group detected phosgene at 1.2 ppm (4.7 mg/m³), and half could identify the gas at 1.5 ppm (5.9 mg/m³).

Accidental exposure to phosgene may pass unnoticed since a period of up to several hours can elapse before the onset of symptoms. In addition to respiratory symptoms, there may be evidence of nervous system involvement: dizziness, headache, blurred vision, mental confusion, and muscular twitching. Nausea and vomiting also occur.

The severity of respiratory symptoms varies considerably, depending on the magnitude of exposure. Autopsy reports refer to extensive tissue damage at all levels of the airways and parenchyma (5).

The most detailed examination of the consequences of phosgene exposure is contained in two reports by Galdston and co-workers (2)(3). One was a follow-up study of 6 workers acutely exposed to the gas (2); the second was of chronically exposed workers (3). All 6 workers who were acutely exposed required hospitalization. They complained of cough, shortness of breath on exertion, and chest tightness or pain. Rapid, shallow breathing was a prominent finding. Functional impairment followed no consistent pattern, nor was its magnitude great enough to account for the degree of disability. The authors thought that psychologic factors contributed to the lingering incapacitation. Slight functional defects persisted as long as one year following exposure.

Chronic Effects, Human

The chronic exposures reported by Galdston et al. occurred accidently in 5 workers over periods of 18 to 24 months (3). This group, in contrast to the acutely exposed workers, showed little evidence of psychologically-related disability. However, functional defects consistent with emphysema, which connote irreversible damage,

were found in four of the subjects; the fifth had normal function. Three of the affected subjects were only 24, 31 and 32-years-old. Information on smoking was not provided.

There have been no published epidemiologic surveys in the United States of workers who might be exposed to low concentrations of phosgene. NIOSH cites a personal communication received in 1974 in which the writer concluded that 326 workers at a plant that manufactured phosgene showed no ill effects ("pulmonary function, lung problems, and deaths related to lung problems") compared with 6,288 nonexposed workers (8). The average concentration of phosgene, determined during a two-month period, averaged 0.003 ppm (0.012 mg/m^3) with personal air samplers (20-minute period). With fixed position samples, the majority of concentrations ranged from nondetectable to 0.13 ppm (0.52 mg/m^3); a few were offscale, exceeding 0.14 ppm (0.55 mg/m^3). Sampling periods were either 20 minutes or 2 hours.

Animal Studies

Animals have been exposed one or more times to a wide range of phosgene concentrations to determine both the threshold of effect and the lethal dose. In one study on rats, there were no significant changes in carbon monoxide (and ether) uptake below a dose of 30 ppm-minutes (Concentration × Time) (3). Above this dose, uptake of these gases was depressed in direct proportion to the logarithmic increase in Concentration × Time. The changes in carbon monoxide uptake were interpreted to represent abnormal distribution of air and reduced diffusion capacity within the lung. Death was seen with increasing frequency above 180 ppm-minutes.

In another study on rats, histologic evidence of injury was found in slightly more than half of the animals exposed to from 13 to 30 ppm-min. of phosgene (6). The earliest lesion occurred in the bronchioles and thereafter extended to alveoli. Higher doses (range: 0.5 to 4 ppm for 5 to 480 minutes) produced a pneumonitis that persisted for months before receding.

Dogs exposed several times weekly (for a total of 30 to 40 half-hour periods, to concentrations ranging between 24 and 40 ppm) developed progressive damage to bronchioles and parenchyma (1). The changes were said to resemble those seen in the development of human emphysema and to be consistent with the functional defects reported earlier by Galdston et al. (3).

Recommendations

It is uncertain whether repeated exposure to low concentrations of phosgene at or near the federal standard has a cumulative effect on the lung, particularly in the small airways and parenchyma. Valuable information could be provided by animal studies that used quantitative methods of assessing functional and structural damage. Conventional tests that are appropriate for industrial surveys can be used to assess small airways function in populations-at-risk. The single-breath carbon monoxide method of measuring lung diffusing capacity is reported to be useful in detecting early emphysema (4) and might prove useful in such surveys. Measurement of the recoiling force of the lung at different lung volumes is not readily performed outside of the research laboratory, but may be invaluable in following small groups of subjects suspected of having emphysematous-like changes.

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Table VII-8

OCCUPATIONS WITH POTENTIAL EXPOSURE TO SULFUR DIOXIDE

Beet sugar bleachers	Ore smelter workers
Blast furnace workers	Organic sulfonate makers
Brewery workers	Paper makers
Diesel engine operators	Petroleum refinery workers
Diesel engine repairmen	Preservative makers
Disinfectant makers	Protein makers, food
Disinfectors	Protein makers, industrial
Firemen	Refrigeration workers
Flour bleachers	Straw bleachers
Food bleachers	Sugar refiners
Foundry workers	Sulfite makers
Fruit bleachers	Sulfur dioxide workers
Fumigant makers	Sulfuric acid makers
Fumigators	Sulfuryl chloride makers
Furnace operators	Tannery workers
Gelatin bleachers	Textile bleachers
Glass makers	Thermometer makers, vapor pressure
Glue bleachers	Thionyl chloride makers
Grain bleachers	Wicker ware bleachers
Ice makers	Wine makers
Meat preservers	Wood bleachers
Oil bleachers	Wood pulp bleachers
Oil processors	

NIOSH (1974, Table XI-2)

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SULFUR DIOXIDE

Introduction

Sulfur dioxide (SO_2) is a colorless gas that is highly soluble in aqueous solution and it imparts an identifiable taste and odor. It liquefies at high pressure or low temperature (boiling point = -10°C); liquid sulfur dioxide is highly corrosive to biologic tissue.

Sulfur dioxide is useful industrially, but it is also an unwanted by-product. About 500,000 workers are estimated to be potentially at risk to the gas (16). A partial list of these occupations is shown in Table VII-8.

Permissible levels of sulfur dioxide have been set for both occupational and ambient atmospheres. The present federal standard for sulfur dioxide in occupational settings is 5 ppm based on an eight-hour time-weighted average (TWA) sampling time (1 ppm = about 2.65 mg/m³). NIOSH has recommended a reduction in the standard to 2 ppm (16). There are two Primary National Ambient Air Quality Standards for sulfur dioxide: an annual arithmetic mean of 0.03 ppm (80 μg/m³) and a maximum 24-hour concentration of 0.14 ppm (365 μg/m³) not to be exceeded more than once per year.

Acute Effects

Biochemistry—Mechanisms: All but a small fraction of inhaled sulfur dioxide is absorbed by the liquid lining of the upper airways, particular-

ly during quiet breathing. This fractional uptake may fall significantly—and penetration of the lower airways may therefore increase—during physical activity when ventilatory flow rate is accelerated and mouth-breathing becomes obligatory. Inhaled concentrations of sulfur dioxide in excess of several hundred ppm (toxicological experiments, accidental exposures) may injure the entire length of the respiratory tract and cause peripheral edema.

Following absorption, the gas reacts with water forming a weak acid solution that contains sulfite ($SO_3^{=}$), bisulfite (HSO_3^{-}), and hydrogen (H^+) ions. The relative contribution of these ions to the irritation produced is uncertain. Sulfite oxidase, an enzyme, hastens the conversion of bisulfite to sulfate ions. The latter is nontoxic and is excreted in urine.

Controlled and Occupational Exposures: Among healthy volunteers acutely exposed to sulfur dioxide, the threshold for changes in respiratory function is roughly 1 ppm. Results from different studies, however, are somewhat divergent. For example, impaired ventilatory function was observed in four subjects exposed to only 0.75 ppm for two hours (6). At 1 ppm, no functional effects were found in one study (21); airway narrowing occurred in 1 out of 11 subjects in a second study (9); evidence of airway narrowing was seen only following 25 maximal breaths in a third study (12). In another study 1 ppm of sulfur dioxide administered during quiet breathing affected the function of both upper and lower airways. Among the effects noted over a six-hour period of exposure were slowing of nasal mucus clearance, narrowing of nasal passages, and progressive reduction in ventilatory performance (4).

More often than not, acute functional responses are short-lived, tending to remit even as exposure continues (15)(17). This applies as well to symptoms of throat irritation and cough produced by higher concentrations of 5 to 15 ppm. Reflex-mediated bronchoconstriction is considered to be the mechanism for narrowing of the lower airways (17). Whether these functional changes are likely to increase or diminish (adaptation) with repeated exposure is uncertain.

In the workplace, concentrations of about 20 ppm may provoke sneezing, coughing, and a choking sensation (16). Fifty ppm may become intolerable after several minutes. A few fatalities have followed exposure to unknown but very high concentrations of the gas. One report describes a case of chemical bronchopneumonia that ended in death after 17 days (10).

It is debatable whether synergism between sulfur dioxide and airborne particulates has been demonstrated convincingly in human subjects (17); the results to date have been inconsistent (19). The question is important because these two classes of pollutants are found together in a variety of occupations. Animal toxicology suggests that synergism may be expected between sulfur dioxide and some aerosols—especially those capable of catalytic oxidation of the gas to sulfuric acid or in the form of droplets that can absorb the gas (3)(14). (The solubility of SO_2 in the droplet is inversely related to its pH.) Evidence has also been adduced that low concentrations of sulfur dioxide and ozone act synergistically to impair ventilatory function in healthy subjects (6). However, this observation has not been confirmed (7)(8).

Chronic Effects

Epidemiologic studies of workers chronically exposed to sulfur dioxide are summarized in a NIOSH criteria document (16). A recent study, conducted in a copper smelter, points to an accelerated decline in ventilatory performance over a period of one year plus increased cough and sputum associated with exposure to 1.0-2.5 ppm of sulfur dioxide (18). The functional decline was reported to be independent of other pollutants despite the presence of "respirable dust" levels ranging up to 5.4 mg/m³ (mean = 0.59 mg/m³), and sulfate levels ranging up to 0.24 mg/m³ (mean = 0.070 mg/m³). Concentrations below 1.0 ppm of sulfur dioxide were unassociated with any apparent functional decline. The investigators suggested that continuing exposure to such concentrations of sulfur dioxide could lead to chronic lung disease.

In addition to this prospective study, a second report on the same copper smelter compared exposed workers, employed from less than one year to over twenty years, with a control group from the mine shop (5). Most of the exposure to sulfur dioxide was judged to have fallen between 0.4 ppm and 3 ppm. In general, values for FVC and $FEV_{1.0}$, expressed as percentages of predicted values, declined with increasing years of exposure to sulfur dioxide. The same trend was seen for cough and sputum. Cigarette smoking appeared to act additively rather than

synergistically with the gas.

Animal Effects

Short-term exposure to sulfur dioxide has been shown to cause airway narrowing in a number of animal species. The narrowing may be of the upper airways (nasal passages), tracheobronchial system, or both, depending on the dose and mode of administration. The effect on the nasal passages is due to swelling of the mucous lining and excessive secretions, while that of the lower airways is due primarily to smooth muscle contraction (bronchoconstriction). One investigator has reported finding a slight but statistically significant increase in pulmonary flow resistance in unanesthetized guinea pigs exposed to a mean concentration of 0.26 ppm (range: 0.03-0.65 ppm) (2). This observation has not been confirmed in lightly anesthetized guinea pigs (14). Generally, concentrations in excess of 5 ppm of SO_2 have been required to alter airway caliber or to depress mucus clearance from the lung in animals (16)(20).

Long-term exposures of guinea pigs and monkeys to 0.1-5 ppm of SO_2 have produced little evidence of changes in airway caliber, distensibility, or histological appearance of the lung (1). No synergistic effects were seen when sulfur dioxide was combined with fly ash or sulfuric acid. Dogs may develop some unevenness in inspired air distribution after prolonged exposure to about 5 ppm of gas (13).

Sulfur dioxide does not appear to be a carcinogen (17). To date, one exploratory study suggests that sulfur dioxide may promote the carcinogenic effect of benzo(a) pyrene in rat lungs (11); this possibility has not yet been tested adequately.

Recommendations

The results of one prospective study suggest that repeated exposure of workers to concentrations of sulfur dioxide below the present occupational standard may be injurious to the lung (18). Additional studies of this type which combine air monitoring of other pollutants as well as sulfur dioxide are needed to confirm the observation. The question is important because of the large industrial population potentially at risk.

Whether or not sulfur dioxide is a co-carcinogen is unresolved and should be examined in toxicological experiments (11). The effect of prolonged exposure to a mixture of sulfur dioxide and an aerosol that either absorbs (droplet) or oxidizes (catalyst-containing) the gas is also recommended. Such a study should include functional tests that are sensitive to changes in both small and large airways, as well as lung morphometry at the conclusion of the exposure.

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Table VII-9

OCCUPATIONS WITH POTENTIAL EXPOSURE TO VANADIUM

Alloy makers	Petroleum refinery workers
Boiler cleaners	Photographic chemical workers
Ceramic makers	Textile dye workers
Dye makers	Uranium millers
Ferrovanadium workers	Vanadium alloy makers
Glass makers	Vanadium millers
Ink makers	Vanadium miners
Organic chemical synthesizers	Vanadium workers

NIOSH (1977, Table XII-2)

VANADIUM PENTOXIDE

"Vanadium " is a general term that includes the pure metal, chemically combined forms such as the oxides, alloys such as ferro- and aluminum-vanadium, and vanadium carbine. Of these, vanadium pentroxide is probably the most hazardous to health.

The bulk of vanadium extracted from ore is used in metal alloys to harden steel. The pentoxides serve as catalysts for a variety of industrial processes. Approximately 174,000 workers are estimated to be potentially at risk from exposure to vanadium. These occupations are listed in Table VII-9.

Federal standards exist for three forms of vanadium. These standards refer to time-weighted-average (TWA) concentrations for an 8-hour work shift. The standards were originally proposed by the American Conference of Governmental Industrial Hygienists as threshold limit values (TLV) and are as follows:

1. Vanadium pentoxide fume: 0.1 mg/m^3
2. Vanadium pentoxide dust: 0.5 mg/m^3
3. Ferro-vanadium: 1 mg/m^3

The NIOSH criteria document of 1977 recommended the following changes in these standards (4):

1. Substitution of a ceiling limit of 0.05 mg/m^3, based on 15-minute sampling periods for vanadium pentoxide, vanadates, sulfates, halides, and other unspecified salts of vanadium. This ceiling is to apply to pentoxide fumes and dusts and is to supersede the present 8-hour standards.
2. The standard for ferro-vanadium is to be maintained as a TWA concentration for up to 10 hours/day, not to exceed 40 work-hour/week.

Acute Exposure, Human

As a trace element, vanadium is an essential component of enzymatic and other biologic systems (2). It usually enters the body in food (7), and in humans is stored mostly in fat and serum lipids. When inhaled in sufficient concentrations, vanadium acts as a direct irritant to the respiratory system. The skin and conjunctiva of the eyes are also affected. The irritant action has been attributed to the acidity of vanadium (pentoxide) in aqueous solution (6). There is evidence that vanadium pentoxide may also be sensitizing or allergenic (8)(16).

The clinical picture resulting from short-term exposure to vanadium is described in a number of reports (1)(9)(14)(16). Many of these exposures have been accidental, occurring in a variety of activities associated with manufacturing and processing; boiler cleaning has been implicated in several reports. Symptoms may appear within 24 hours of exposure onset.

Irritation of the upper airways is reflected in sneezing, nasal discharge or bleeding, and throat soreness. A green-black discoloration of the tongue has been described (9).

Irritation of the lower airways is reflected in coughing—with or without sputum, wheezing, shortness of breath, chest tightness, and pain. Rhonchi and rales may be heard. In some instances, sulfur dioxide and sulfuric acid may also be inhaled and contribute to the clinical picture. (The irritant effects of the latter agents are not readily distinguishable from those of vanadium; perhaps the best means of weighing their individual effects is through precise air monitoring.)

Conjunctivitis is common. Skin irritation is typified by itching, rash, and eczema. Identification of vanadium in urine has been tried as a means of assessing exposure, but the results have not proven to be a useful correlate of clinical effects.

A single laboratory study involving healthy volunteers is the underpinning for the proposed ceiling of 0.05 mg/m^3 (17). Exposure was to vanadium pentoxide particles (98% under 5 μm in diameter) for up to 8 hours at rest. Two volunteers exposed for 8 hours to 0.1 mg/m^3 (0.04 mg vanadium/m^3) experienced cough with sputum starting 24 hours later and lasting 4 days. Five subjects who inhaled 0.2 mg/m^3 (0.08 mg vanadium/m^3) developed cough that persisted 7-10 days. In the same study, inadvertent exposure of two subjects to 1 mg/m^3 (0.3 vanadium/m^3) caused frequent coughing commencing within 7 hours. There were no changes in pulmonary function as measured by spirometry in any subjects. Possible effects on small airway caliber and lung clearance were not tested. (The viability and phagocytic function of alveolar macrophages may be affected by soluble vanadium oxides (12).)

Chronic Exposure, Human

The question of whether long-term exposure to vanadium-containing dust causes or contri-

butes to irreversible lung disease is unresolved. Three epidemiologic studies have been carried out in which the size-distribution and mass concentration of the dusts were assessed.

In the first of these reported studies, which covered a two-year period, workers were exposed principally to vanadium pentoxide at concentrations estimated to range from 0.03 mg/m³ to 5.58 mg/m³ (8). Only 22% of the particles were less than 8 μm diameter. (Particles this large would be expected to deposit principally in the upper airways, trachea, and central bronchi (5).) During this period, symptoms and signs of bronchitis were common. Five of the 36 workers had evidence of pneumonitis. (A clear distinction between infectious and chemical pneumonitis was not made.) Neurasthenia was observed but was considered secondary to the respiratory symptoms and possibly to undesirable features of the workshift. A follow-up report on six of the workers with the most marked respiratory symptoms was made 6 years later (9), when complaints associated with bronchitis were still present. Chest x-rays and spirometric tests provided no evidence of lung fibrosis or emphysema.

The vanadium dusts in the two later studies appear to have been smaller in size range than in the Swedish study (8)(9); hence, these small particles would be expected to have a different, perhaps more peripheral pattern of deposition. Lewis studied workers (average employment 2.5 years) who were exposed, almost without exception, to concentrations of vanadium-containing dust ranging from 0.018 mg/m³ to 0.38 mg/m³; 97% of the particles were under 5 μm diameter (3). About half of the 24 subjects developed productive cough. Lewis described "bronchospasm" in these subjects, which persisted 2 to 3 days beyond the occupational exposure. He concluded that there was no evidence of chronic injury to the lung but performed no functional testing.

Tebrock and Machle studied workers exposed to a vanadium-bearing phosphor that is used to make color television picture tubes (11). Vanadium pentoxide concentrations ranged from 0.02 mg/m³ to 3.2 mg/m³ (mean: 0.844 mg/m³); 90% of the particles collected were under 1.5 μm diameter. Clinical evidence for tracheobronchitis was common. These authors, like Lewis, observed "bronchospasm," which was aggravated with repeated exposure. They also concluded there was no evidence of permanent damage to the lungs, but did recommend follow-up studies of the workers (3).

In the absence of functional testing in these studies, it would seem prudent to reserve final judgment about the occurrence of permanent lung damage from exposure to vanadium. Sjoberg's study provided findings consistent with central nervous system toxicity; otherwise there was no evidence of systemic effects (8). Earlier, Wyers had reported findings, in workers exposed to vanadium, that he interpreted as evidence of systemic toxicity: elevated blood pressure, palpitation on exertion, and coarse tremors of the fingers and arms, apparently reflecting involvement of the nervous system (15). The manifestations of neurobehavioral toxicity from vanadium are summarized in Weiss (13).

Animal Studies

Studies on a variety of laboratory species confirm the irritant potential of vanadium for the respiratory system. Stokinger found no histologic evidence of lung injury attributable to vanadium pentoxide dust in guinea pigs, rats, rabbits, or dogs after 6 months' exposure to 0.5 mg/m³ (10). There have been no studies of the effects of prolonged exposure to vanadium on lung function, lung clearance, or resistance to infection.

Recommendations

Several questions remain unanswered about the possible hazards posed by soluble vanadium compounds. Whether they may induce immunologic or allergic changes should be defined more clearly. (Are atopic individuals at increased risk?) There is also a need for more precise monitoring data (size distribution as well as mass concentration) and more incisive pulmonary function testing in clinical and epidemiologic studies.

Vanadium's potential for inducing neural and behavioral toxicity should be examined in animal studies. Mechanistic and descriptive types of information are needed. Greater attention should be given to possible neural and behavioral abnormalities in clinical and epidemiological research.

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