REGIONAL COPPER-NICKEL STUDY

HUMAN HEALTH LITERATURE REVIEWS

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Note: Reviews on ASBESTOS, COPPER and NICKEL, and PARTICULATES and SULFUR OXIDES appear as separate documents.

ABSTRACTS

ACCIDENTS AND SAFETY HAZARDS IN THE MINERALS INDUSTRY

The minerals industry is one of the most hazardous industries in the United States. Congress, recognizing the hazards inherent to the mining industry, passed the Federal Metal and Nonmetallic Mine Safety Act (PL89-577) in 1966. This law is currently administered by the Mining Enforcement and Safety Administration.

Accident frequency rates for underground mines are close to three times higher than for surface mines and mills. Other stages of mineral development--open pit mining, milling, smelting and refining--tend to be more hazardous when compared to averages of all industries combined, but are much less hazardous than underground mining. Usually the location of the ore deposit dictates whether surface or underground mining methods may be used.

Miners with less than two years of experience are more likely to be involved in accidents than other miners. Machinery, haulage, fires, fall of ground, fall of person, and electricity are the major causes of fatal accidents. Most accidents can be prevented either through adequate attention from supervisors or the elimination of unsafe acts of workers. Strong safety programs, which have reduced accident rates by fifty percent, have been reported.

In 1975, Minnesota had no underground mines. Accident frequency rates for surface mines and mills in the state were one-half and one-fourth, respectively, of the rates for all surface mines and mills in the U.S. The accident record of the copper industry has been similar to that of the minerals industry in general, over the past few years. Data from the nickel industry are not presented because there is only one nickel mine and smelter in the United States.

ALUMINUM AND HUMAN HEALTH

Aluminum is a major constituent in the environment, comprising over eight percent of the earth's crust. It has been detected in Minnesota waters (0.29 $\mu g/ml$), and air concentrations range from 0.01 $\mu g/m^3$ over oceans to 8 $\mu g/m^3$ in urban areas. Typical adult intake of aluminum is 10-100 mg per day.

Respiratory disease associated with aluminum was observed in ammunition workers during World War II; however, it occurred only when aluminum particles were less than 7μ in size.

Nonoccupational diseases associated with aluminum have been limited to side effects of medicinal uses of aluminum. These include encephalopathy in uremic patients on dialysis who had been treated with phosphate binding gels for more than three years and phosphate deficiency causing osteomalacia in patients using aluminum hydroxide as an antacid.

Animal studies have supported the human findings of respiratory effects and adverse effects on uremic patients therapeutically treated with aluminum. Experimental studies have also indicated that dermatitis or growth retardation may occur from excessive aluminum exposure.

The threshold limit values (TLVs) are 10 mg/m^3 for alundum and corundum (both Al_2O_3), and both compounds are classified as nuisance particulates. There are no standards for aluminum in drinking water, air, or food.

AMMONIUM NITRATE BLASTING AGENTS

Ammonium nitrate blasting agents are widely used in the mining industry and account for ninety percent of all blasting done in the United States. Low cost and relative freedom from the hazards of accidental detonation account for the popularity of these blasting agents.

Safety hazards are involved with the use of any explosive. During the years 1970-75, there were 28 deaths related to explosives in metal and nonmetallic mines in the United States. Extensive safety recommendations have been recently published by the Bureau of Mines.

Toxic gases, most notably nitrogen dioxide and carbon monoxide, may be formed as byproducts of explosions. Hazardous levels of these gases may persist following detonation, particularly in poorly ventilated, enclosed areas.

Nonoccupational hazards of explosives may include increased noise and dust production, flying rock, and under extraordinary circumstances, dermatitis from ingestion of ammonium nitrate.

ARSENIC AND HUMAN HEALTH

Arsenic ranks twentieth (2-5ppm) in abundance in the earth's crust, and twelfth (0.2-0.3 ppm) in the human body. It has been used for a wide variety of purposes including medicines, herbicides, insecticides, wood preservatives, and rat poisons. Arsenic has been found in the air near coal burning industries and smelters, and in some public water supplies. Typical adult intake of arsenic is 900 µg per day, although those frequently consuming seafood may ingest up to five times this amount.

The trivalent form of arsenic (arsenic trioxide, arsenites) shows some tendency to accumulate in the kidney and liver, as well as in hair, nails, and skin; and is considered to be much more toxic than pentavalent arsenic (arsenates), which does not accumulate.

Exposure to arsenic has been epidemiologically linked to lung cancer in a number of occupations, including copper smelting. The lowest arsenic exposure associated with increased risk of lung cancer is 3 $\mu g/m^3$ for less than one year. Time between first exposure and onset of cancer is a minimum of fifteen years. Skin cancer has also been observed; and there have been one or two reports associating arsenic with lymphatic cancers and liver cancer. Dermatitis has been ovserved in a number of occupational settings.

A study of children, age 1-5 years, living in eleven towns within four miles of a U.S. copper smelter, found hair arsenic levels significantly higher than controls in all eleven towns and urine arsenic levels significantly higher than controls in eight of the eleven towns. Dermatitis has been observed in a community which was exposed to arsenic emitted from a gold mine-mill site. An epidemiological study has suggested a relationship between lung cancer and industrial air emissions containing inorganic arsenic.

Attempts to produce cancer in animal experiments have been unsuccessful, with two possible exceptions. Because of this, the question of whether arsenic is a carcinogen remains controversial.

The threshold limit values (TLVs) for arsenic are: arsenic trioxide (As_2O_3) production, 0.05 mg/m^3; arsenic trioxide handling and use 0.25 mg/m^3; and arsine (AsH_3), 0.2 mg/m^3. The National Institute of Occupational Safety and Health (NIOSH) has recommended lowering the TLV for inorganic arsenic to 0.002 mg/m^3. The United States Environmental Protection Agency has set the maximum contaminant level (MCL) of arsenic in drinking water at 0.05 mg/l.

ASBESTOS

"Asbestos" is a general term applied to a group of fire-resistant mineral silicates that are similarly fibrous in structure but very different in respect to several other properties. The two main mineral subdivisions are serpentines (chrysotile) and amphiboles (crocidolite, amosite, tremolite, actinolite, anthophyllite). The distinction between fibers of natural commercial asbestos and cleavage fragments involves minor differences in their structural and chemical makeup. The actual fibers existing in Northern Minnesota are cummingtonite-grunerite cleavage fragments most closely resembling commercial amosite.

Workers exposed to varying types, sizes, and concentrations of commerical asbestos fibers have experienced increased rates of asbestosis, respiratory cancers, gastrointestinal cancers, and pleural and peritoneal mesotheliomas. Two studies of occupational exposure to non-commercial asbestos cleavage fragments gave conflicting results concerning carcinogenicity: one study found a three-fold increase in respiratory cancer in workers exposed for at least 60 months, while the other found no increase of respiratory or abdominal cancer in workers with at least 21 years of employment with the mining company.

Persons without occupational exposure may show evidence of exposure to asbestos. Asbestos fibers and asbestos bodies have been found in the lungs of persons with no occupational exposure; radiological changes have been demonstrated in populations living in close proximity to an asbestos mine or factory; and mesothelial tumors have been found in persons with no occupational exposures to asbestos. Two non-occupational studies have reported no excess cancer rates due to ingestion of city water supplies containing high concentrations of non-commercial asbestos minerals in the cummingtonite-grunerite series; however, the time between first exposure and the times of the studies may have been insufficient for the development of cancers.

Several theories about the mechanism of carcinogenicity have been proposed: the fiber theory, the trace metal theory, the organic materials theory, and the multi-factor theory. Smoking appears to increase the risk of lung cancer among asbestos workers. The risk of mesothelioma in man and animals seems to be higher for crocidolite than amosite or chrysotile. Long fibers and thin fibers both seem to be more carcinogenic.

The threshold limit value (TLV) for asbestos is two fibers per cubic centimeter greater than five microns in length.

(This review appears as a separate document.)

CADMIUM AND HUMAN HEALTH

Cadmium has not been determined to be an essential element to man. It has been found in food, water, and air, and has been shown to accumulate in the kidney and liver of man.

Acute effects from exposure to cadmium metal or oxide fumes generally consist of respiratory effects such as pneumonitis and pulmonary edema. In one incident, the lethal dose of cadmium oxide was calculated to be 8.6 mg/m^3 for five hours. Chronic exposure to cadmium most commonly results in emphysema and proteinuria. Onereseacher estimated that10-20 years of exposure to 50 $\mu g/m^3$ of cadmium fume or dust could result in proteinuria.

In the nonoccupational setting cadmium poisoning has most commonly arisen when cadmium has been leached out of food or drink containers. Itai-itai disease, a type of osteomalacia affecting mainly women over 45 years, occurred in Japan when rice, irrigated by water containing cadmium in mine wastes, accumulated cadmium to very high levels. Cadmium levels in the water used for irrigation were below 0.01 ppm. A study of children, age 1-5 years, living in eleven towns within four miles of a U.S. copper smelter, found hair cadmium levels significantly higher than controls in nine of the eleven towns.

Experimental work has substantiated the effects on the kidney, lung, and bone, and has also indicated other possible health effects. Evidence of a relationship between chronic exposure to low levels of cadmium and occurrence of hypertension, heart disease and carcinogenesis has been shown in animals. Calcium and zinc appear to decrease the affects of cadmium.

The threshold limit value (TLV) for cadmium oxide fume is 0.05 mg/m^3. The maximum contaminant level (MCL) set by the Environmental Protection Agency for drinking water is 0.01 mg/liter.

CARBON MONOXIDE AND HUMAN HEALTH

Carbon monoxide is a colorless, ordorless, and tasteless gas. Manmade sources of carbon monoxide arise from incomplete combustion of carbon-containing compounds. Carbon monoxide exerts its effects on humans by competing with oxygen for binding sites on the hemoglobin molecule and thereby reducing the availability of oxygen to body tissues.

In the occupational setting carbon monoxide poisoning has occurred in places with poor ventilation and a source of carbon monoxide. It is a well known hazard in underground mines. Carbon monoxide poisoning may: affect the brain, as manifested by personality changes; aggravate cardiovascular disease in terms of angina pectoris, intermittent claudication, and altered electrocardiogram; and affect vision, with blindness observed in severe cases. The relationships between carbon monoxide concentrations and effects on human health have been well defined.

Studies of rabbits and dogs have suggested that these animals may be able to adapt to increased carbon monoxide concentrations.

The threshold limit value (TLV) for carbon monoxide is 50 ppm. Standards for carbon monoxide in ambient air are 9 ppm as an eight-hour average and 35 ppm as a maximum one-hour average.

COBALT AND HUMAN HEALTH

Cobalt is generally recovered as a byproduct of copper or nickel mining. It is essential to man being physiologically active in Vitamin B_{12}.

Respiratory disease attributed to cobalt has been observed in tungsten carbide workers. Reports of dermatitis from cobalt have also appeared in the literature. Cobalt given therapeutically or added to beer has caused dermatitis and heart disease.

Animal studies have confirmed the respiratory damage which may occur and have shown that injection of cobalt or cobalt oxide may induce tumor growth. Studies using nickel refinery dust have shown that the cobalt oxide present can induce tumors in rats but not in mice.

The carcinogenic properties demonstrated in animals and the respiratory damage from large doses shown in both animals and man, indicate the need for much further study on the toxic effects to man from low level cobalt exposures.

The threshold limit value (TLV) for cobalt is 0.1 mg/m^3.

COPPER

Copper is ubiguitous in man's environment. It is a common constituent of the earth's crust and has found wide use in man's utensils and artifacts since the Stone Age. Because of this lengthy and familiar association, metallic copper has long been accepted as an innocuous substance.

In the occupational setting, there have been occasional reports of metal fume fever caused by copper. Copper miners have been found to experience a greater than expected mortality from heart disease, respiratory neoplasms, tuberculosis, and influenza and pneumonia, and an excess in morbidity from pneumoconiosis and accidents. Workers engaged in copper smelting and refining have experienced an elevated mortality from heart disease, respiratory cancer, tuberculosis, and cirrhosis of the liver, and an increased morbidity from chronic respiratory disease; and arsenical melanosis, dermatosis and perforation of the nasal septum. It is difficult to pin-point the causative agents of the diseases observed in workers involved in copper mining, smelting and refining; arsenic and sulfur dioxide have been the agents most often suspected.

In the nonoccupational setting, an epidemiological study found that persons residing in the 36 counties in the United States with major copper, zinc or lead industries experienced lung cancer rates greater than other U.S. residents. People from mining communities have also often been found to experience excess morbidity from chronic and acute respiratory disease. Copper and its compounds are generally not hazardous; however, poisonings from large exposures have occasionally been reported.

Experimental studies have found large doses of copper sulfate to cause an excess mortality, decreased body weight in survivors, and to accumulate in the liver, kidney, intestines and brain. Copper oxide and copper sulfide were found not to be carcinogenic in rats or mice through the intrafemoral route.

Metallic copper has been found to affect the reproductive system of rats.

The threshold limit values (TLVs) for copper are: 0.1 mg/m^3 for copper fume; and 1.0 mg/m^3 for copper dust.

(This review appears as a separate document.)

IRON AND HUMAN HEALTH

Iron, the metal most widely used by man, comprises five percent of the earth's crust. In the past, iron ore mined in Minnesota was predominantly hematite (ferric oxide), while today taconite, which is predominantly magnetite (ferrous oxide), is mined.

Iron is essential to human life. It is needed primarily for the formation of hemoglobin, but has other roles as well. Underground hematite miners have experienced increased incidences of lung cancer although this may have been due to radiation exposure instead of iron oxide. Similar observations have not been observed for surface miners. Respiratory diseases, including siderosis, siderosilicosis, silicosis, and silicotuberculosis have also been observed; however, dust suppressive measures have greatly reduced these problems.

In the nonoccupational setting, adverse effects on health from iron have been limited to poisonings, particularly ferrous sulfate. Animal studies suggest that iron cannot induce cancer by itself, but may enhance the effects of other carcinogens.

The threshold limit value (TLV) for iron oxide fume is 5 mg/m^3.

LEAD AND HUMAN HEALTH

Lead has been used by man for thousands of years. Major uses of lead today include batteries, battery oxides, and gasoline antiknock additives. Levels of lead in the air vary widely ranging from 5 $\mu g/m^3$ in Los Angeles to less than 0.01 $\mu g/m^3$ in wilderness areas. Dietary sources of lead average 300 µg daily in the United States, of which 5-10 percent is actually absorbed in the body by adults. Less than 10 percent of lead intake comes from air and water.

Health effects of lead poisoning have been known for years and have been studied in detail. These effects vary considerably depending on whether lead is in an organic or inorganic form. Inorganic lead poisoning has occurred in groups such as lead smelters and battery workers, manifesting itself through a wide variety of hematological, neurological, renal, and gastrointestinal effects. Lead has had an adverse effect on reproduction, causing sterility, miscarriages and still-births in women exposed to lead. Organic lead poisoning, which usually occurs in workers exposed to leaded fuels, exhibits itself primarily as a psychotic state with a wide range of neurological effects.

Children living in towns near copper smelters show evidence of external exposure to lead, but not systemic exposure. Families of lead workers have shown evidence of lead poisoning, as have children living in close proximity to lead smelters. Women and children appear to be more susceptible to the effects of lead than males. Experimental studies have helped to better define dose-response relationships and mechanisms of lead poisoning.

The threshold limit value (TLV) for lead fumes and dusts is 0.15 mg/m^3. The maximum contaminant level (MCL) for lead in drinking water set by the Environmental Protection Agency is 0.05 mg/liter.

MANGANESE AND HUMAN HEALTH

Manganese is the twelfth most abundant mineral in the earth's crust and is essential for plant and animal life. In humans, it is essential for normal bone formation and the functioning of several enzymens. Normal daily intake for adults is 3 mg, most of which comes from food. Manganese has been detected in urban air, averaging 0.10 $\mu g/m^3$, and may increase because of the replacement of lead by manganese in gasoline. Manganese cations are more toxic than anions.

Manganism, a disease affecting the central nervous system, has been a recognized occupational hazard for over 100 years. Chronic manganism has been found at manganese dust concentrations as low as 20 $\mu g/m^3$. Manganic pneumonia, caused by manganese oxides, has been observed in occupational settings outside the United States. Manganese poisoning has been observed in communities near ferromanganese industries.

Animal studies have further explored the relationship of manganese to respiratory and neurological diseases. Manganese has also been shown to inhibit reproduction.

The threshold limit value (TLV) of manganese is 5 mg/m^3.

NICKEL

Many studies from several countries, including Great Britain, Canada and Norway, have indicated workers involved in the refining of nickel experience an increased risk of developing cancer of the nasal passages and of the lung. Early investigators emphasized the role of nickel carbonyl ($Ni(CO)_4$), but nickel refining which does not involve nickel carbonyl has been found to be equally hazardous. Nickel hazards have been identified in some plants at least through 1960; the length of time between exposure to nickel and manifestation of disease is such that the existence of a hazard beyond 1960 cannot be identified at this time.

Recent studies have been directed at morbidity from chronic respiratory disease. A thorough study, comparing workers who experienced heavy exposure from sulfur dioxide, metal dusts and fumes to workers with light exposure, found significantly more chronic bronchitis and significantly poorer respiratory function tests in the high exposure group: however, the respiratory function test results were within accepted normal limits for both groups. Dermatitis in the nickel occupational setting is recognized as very common. The rash is generally considered to be aggravated by heat.

In the nonoccupational setting, a study comparing residents of Sudbury, the site of a large nickel refinery, and Ottawa, as the control, found that those residing in Ottawa in general had better respiratory function test results and less chronic bronchitis. Occupational exposure, rather than general exposure, may have accounted for these disparities.

Experimental studies have generally supported the findings of epidemiologic studies. Nickel salts, injected intrafemorally or intramuscularly seem to induce tumors in inverse proportion to their solubility. Thus lowly soluble

nickel subsulfide (Ni_3S_2) is highly carcinogenic, while highly soluble nickel sulfate ($NiSO_4$) is poorly or non-carcinogenic. Nickel carbonyl absorbed through inhalation is highly carcinogenic. Conclusive studies demonstrating the carcinogenicity of metallic nickel absorbed through inhalation have not been reported. Rats fed nickel in their diets and allowed to reproduce freely, produce more runts with premature deaths than do control animals.

The 1977 threshold limit values (TLVs) for nickel are: 1 mg/m^3 for nickel metal; 0.35 mg/m^3 for nickel carbonyl; and 0.1 mg/m^3 for nickel soluble compounds.

(This review appears as a separate document.)

NITROGEN OXIDES AND HUMAN HEALTH

Nitrogen oxides include compounds containing nitrogen and oxygen in gaseous, acid and certain particulate forms. Nitric oxide (NO) and nitrogen dioxide (NO_2), are the most important from the public health point of view. Of these two, nitrogen dioxide is the more common and more toxic. Manmade sources of nitrogen oxides arise chiefly from combustion processes at high temperatures.

Nitrogen dioxide has caused adverse effects on the lower respiratory tract in a number of occupational settings, including underground mines. Acute exposure may have delayed effects which may not occur until three weeks after exposure. Brief exposures to high concentrations of nitrogen dioxide appear to have greater adverse effects than longer exposures to low concentrations.

In the nonoccupational setting, nitrogen dioxide has been linked with decreased ventilatory function in children and increased incidence of acute respiratory disease.

The possibility that suspended nitrates may be converted to nitrosamines (known carcinogens) in air has been discussed, but there is little evidence that this occurs to any significant extent. Some nitrogen oxide compounds have been shown to be mutagenic. Experimental studies have examined the effects of nitrogen oxides on the respiratory system in great detail.

The threshold limit values (TLVs) for nitrogen dioxide and nitric oxide are 9 mg/m^3 and 30 mg/m^3, respectively. The ambient air standard for nitrogen oxides is 0.05 ppm (100 $\mu g/m^3$) as an annual average.

NOISE AND HUMAN HEALTH

Noise is unwanted sound. Sound is measured in decibels, a logarithmic scale based upon the ratio of an observed sound pressure level to a reference sound pressure level. Sources of noise may be natural, such as thunder, rain and birds, or manmade, such as machinery and traffic.

In the occupational setting, noise-induced hearing loss has been and continues to be a widespread problem. Noise less than 80 decibels (dB) is generally considered to be not hazardous. A recent survey in the mining industry found 68 sources of noise to create sound pressures of 90 dB or more. Noise may also cause temporary hearing loss. Quality of work, but not quantity, may be affected by noise above 90 dB.

Nonoccupational problems related to noise include speech interference, sleep interference, and annoyance. Annoyance by noise is controversial because one's attitude toward the noise has a great effect on whether it is annoying. Humans do not have the ability to adapt to higher levels of noise.

PARTICULATES

"Particulates" is an all encompassing term used for all dispersed solid or liquid material in the atmosphere. With this definition, all the various sulfur oxides can be considered also to be particulates. Some particles are emitted directly from chemical or industrial sources while others are formed by chemical reactions in the atmosphere.

Deposition of particles in the lung is dependent on size, shape and density of the particles. The major site of particle deposition is the nose. Clearance of particles from the lung depends on the site of deposition. Clearance from the alveolar surface is the slowest of all areas. Deposition in the alveolae has been found to be maximum with particles between one and two microns.

Respirable particulates may be intrinsically toxic, interfere with clearance of other particles from the lung, or act as carriers of toxic materials. Increased pulmonary flow resistence, the dominant physiological alteration produced by irritant particles, is further augmented by small particles size. Small particles may act synergistically or additively to affect health when mixed with various gases.

Early studies of air pollution indicated that excessively high levels of SO_2 and particulates increased mortality and morbidity, especially among the elderly and those with chronic lung and respiratory disease. Morbidity studies have demonstrated an association between the prevalence and incidence of respiratory illness, and SO_2 and particulates. Exposure to these air pollutants aggravates the symptoms of bronchitis in those already having the disease. Sulfur dioxide and particulates contribute to increased frequency and severity of acute respiratory disease in children. Best estimates of the threshold level for effects on health due to short term exposures to particulates are 70 $\mu g/m^3$ with SO_2 levels of 180-250 $\mu g/m^3$ for aggravation of asthma and 80-100 $\mu g/m^3$ with SO_2 levels above 365 $\mu g/m^3$ for aggravation of cardiopulmonary symptoms in the elderly (based upon the CHESS studies). For long term exposures best estimate thresholds are approximately 100 $\mu g/m^3$ with SO_2 levels of 95 $\mu g/m^3$ for increased prevalence of chronic bronchitis in adults and increased acute lower respiratory disease in children (based upon CHESS studies).

Most occupational studies on particulates have dealt with a specific kind of particulate such as silica, aluminum or barium dust. A recent review article concluded that inhalation of most minerals and vegetable dust could lead to increased prevalence of cough and sputum and that some workers show a slight decrease in lung function after prolonged exposure to these materials.

The national ambient air standards for particulates are: 75 $\mu g/m^3$ as an annual geometric mean, and 260 $\mu g/m^3$ as the maximum 24 hour-average.

(This review appears as a separate document.)

PROCESSING CHEMICALS AND HUMAN HEALTH

Processing chemicals are used in most mining operations to extract desired metals and nonmetals from the mined ore. These chemicals can be divided into six major categories: collectors, frothers, modifiers, activators, depressants, and flocculants.

In general, potential hazards to human health include: safety hazards from the storage, handling, and disposal of chemicals; accidental spills; toxic vapors from the chemicals and decomposition products; and discharge of used chemicals.

Xanthates, the general class of collectors most commonly used in the copper-nickel industry, may decompose to carbon disulfide, hydrogen sulfide, and sulfur dioxide-compounds, which have adversely affected health in other industrial settings. Acids and bases may act as respiratory irritants and cause tissue damage upon direct contact with the skin. For the most part, the large variety of chemicals, which might be used, precluded all but a cursory examination of processing chemicals.

SILICOSIS

Compounds containing silicon and oxygen comprise most of the earth's crust. Silica (SiO_2), the compound responsible for silicosis, occurs in three forms: quartz, cristobalite and tridymite. Uncombined forms of these minerals are called "free silica", to distinguish them from silicates which contain cations. Silicates and noncrystalline silica are not considered be be associated with health problems.

Silicosis is probably the oldest occupational disease known. It is a respiratory disease; the mechanism by which silica affects lung function is discussed. Complications arising from silicosis include tuberculosis, chronic bronchitis, emphysema, and cor pulmonale.

The minerals industry is one of many industries in which silicosis has been widely observed in workers. The incidence of silicosis has decreased considerably since the mid-1930's, when many dust control systems were begun or improved.

SULFUR OXIDES

Sulfur oxides comprise a vast group of compounds, a few of which are found in the atmosphere as a result of man's industrial processes. Ninety-eight percent of all emitted sulfur oxides consist of sulfur dioxide (SO_2); other compounds include sulfur trioxide (SO_3), sulfuric acid (H_2SO_4) and various sulfates (XSO_4). Chemical reaction studies within copper smelters have indicated that the presence of sulfates and sulfites are important considerations in the study of health effects of sulfur oxides.

Sulfur dioxide is a mild respiratory irritant when administered alone. At levels far in excess of ambient levels, SO_2 has been shown to reduce ciliary activity and thereby decrease lung clearance. Since this leads to increased residence time of foreign particles within the lungs, this has been proposed

as the cause of increased illness during exposure to pollution. Sulfuric acid and certain sulfates also act as respiratory irritants.

Early studies of air pollution indicated that excessively high levels of SO_2 and particulates increased mortality and morbidity, especially among the elderly and those with chronic lung and respiratory disease. Morbidity studies have demonstrated an association between the prevalence and incidence of respiratory illness, and SO_2 and particualtes. Exposure to these air pollutants aggravates the symptoms of bronchitis in those already having the disease. Sulfur dioxide and particulates contribute to increased frequency and severity of acute respiratory disease in children. Levels of SO_2 at 92-95 $\mu g/m^3$ with 15 $\mu g/m^3$ suspended sulfates were found to be associated with excess bronchitis in the CHESS studies.

In workers, elevated levels of sulfur dioxide (20-100 ppm) promote fits of coughing, sneezing and other discomforts. Recent studies have shown that exposure to levels of SO_2 below the standard for occupational settings do produce a reduction in forced expiratory volume in one second, and forced vital capacity, and an increase in respiratory symptoms.

The threshold limit values (TLVs) for sulfur oxides are: 13 mg/m^3 (5 ppm) for sulfur dioxide; and 1 mg/m^3 for sulfuric acid. The current ambient air standards in Minnesota for sulfur oxides are 0.02 ppm (52 $\mu g/m^3$) as an annual arithmetic mean, 0.1 ppm (260 $\mu g/m^3$) as the maximum 24-hour average concentration, and 0.25 ppm (650 $\mu g/m^3$) as the maximum 3-hour average concentration.

(This review appears as a separate document.)

ZINC AND HUMAN HEALTH

Zinc has been widely used for a number of purposes for hundreds of years. It is a constituent of all living cells and essential for human life. Average daily intake is 12.6 mg, with food the major source, and smaller contributions from water and air. Zinc compounds are relatively nontoxic to living organisms.

In the occupational setting, zinc compounds (particularly zinc oxide) have been found to cause metal fume fever. This is a mild respiratory disease with complete recovery almost always occurring within 48 hours. Gastrointestinal effects and dermatitis may also occur.

Several outbreaks of zinc food poisoning, caused by leaching of zinc from galvanized containers, have been reported in the nonoccupational setting. In one case of food poisoning, the average dose of zinc was estimated to be 225 to 450 mg. Recovery usually occurs within 24 hours. Zinc deficiency appears to be of more concern. It may be a limiting factor in the normal growth and development of infants. Low zinc levels have been observed in patients with cirrhosis, lung cancer, myocardial infarction, certain hematological disorders and atherosclerosis.

Experimental studies have shown that animals have a high tolerance for zinc. Zinc has been shown to mitigate the effects of cadmium, but may induce deficiencies of copper, iron and calcium.

The threshold limit value (TLV) for zinc oxide fume is 5 $\mu g/m^3$.

INTRODUCTION

Literature reviews serve as the foundation for any study and are the primary source of information used in the Human Health Studies to evaluate possible impacts on health presented by potential copper-nickel development in northeastern Minnesota.

Reviews have been prepared on twenty different subjects. Abstracts for each subject appear in this document. The literature reviews on copper and nickel, asbestos, sulfur oxides and particulates appear as separate documents; while the remaining fifteen literature reviews are presented in this volume.

Emphasis was placed on collecting recent (within the past 10 years) literature and studies which were directly applicable to copper-nickel development, although supplementary information beyond these boundaries was also collected. Each review contains three major sections: Occupational Experience--studies of occupational groups; Nonoccupational Experience--studies of those exposed outside the occupational environment; and Experimental Evidence--including both animal studies and human studies.

Initally, a review about the environmental health hazards of copper and nickel development was prepared. From this review came recommendations for additional literature reviews on arsenic, sulfur dioxide, particulate air pollution and silica. These four agents, along with asbestos (because of the proximity of Reserve Mining), were placed in a priority group. Other subjects for literature reviews were chosen based on an analysis of the concentrate from a 10,000 ton bulk sample from INCO's Spruce Road Site (Table 1) and recommendations from staff of the Copper-Nickel Study. A list of the literature reviews was reviewed by the Health Studies Advisory Committee and other health professionals in February, 1977. At that time the list contained osmium, but not manganese. Osmium was later dropped from the list because it has not been detected in ore samples from the Duluth Gabbro and the quantities produced as byproducts of other copper or nickel smelters are minimal.

In addition to the original review on copper and nickel, reviews on asbestos, particulate air pollution, and sulfur oxides were contracted out to the Epidemiology Department of the University of Minnesota, Minneapolis. These reviews were contracted out because of the large volume of literature and the high potential for impacts on health each presented. Literature reviews on the other topics were prepared by the Health Studies staff during the summer of 1977.

Table 1.

From: "Description of operating concepts required to establish Preoperational Monitoring for INCO's proposed spruce road project" INCO test

Average analysis of bulk concentrate produced from 10,000-ton bulk sample from Spruce Road Site.

Wet Chemical Analyses		Bulk Concentrate %
Copper	(Cu)	13.6
Nickel	(Ni)	2.98
Cobalt	(Co)	0.14
Iron	(Fe)	31.2
Sulfur	(S)	25.3
Silicon dioxide	(SiO_2)	12.1
Calcium oxide	(CaO)	1.23
Magnesium oxide	(MgO)	4.40
Aluminum oxide	(Al_2O_3)	2.42
Arsenic	(As)	0.0031
Molybdendum	(Mo)	N.D.
Manganese	(Mn)	0.032
Lead	(Pb)	0.008
Zinc	(Zn)	0.38
Cadmium	(Cd)	0.004

ACCIDENTS AND SAFETY HAZARDS IN THE MINERALS INDUSTRY

Peter Ashbrook

INTRODUCTION

Mining has long been recognized as one of the most hazardous occupations. An examination of the industry reveals some of the reasons for this. Unlike many other industries, where potential hazards can be engineered out through careful planning and site selection, mines must be developed where the ore is. There are relatively few fundamental changes in mining methods that can be made to improve safety, although increased mechanization has reduced some hazards, and occasionally has made surface mining feasible in places that were once restricted to underground mining. However, in most cases the location of the ore deposit dictates the method, leaving little choice whether to use surface methods or the more hazardous underground methods. As ore is mined, the natural environment is altered, presenting new hazards requiring constant surveillance. In addition there is often a fundamental conflict between management's desire to increase production and the workers' desire to take adequate precautions against potential hazards. The conflict arises over what constitutes adequate precautions.

Congress, in recognizing these hazards, passed the Federal Metal and Non-metallic Mine Safety Act (PL 89-577) in 1966. Data from the National Safety Council (1960-1963), which showed underground mining, excluding coal, to be one of the three most hazardous industries year after year (Table 1), provided the impetus. In addition, a special study by the Mine Safety Study Board (U.S. Department of Interior, 1963) showed that the National Safety Council data under-represented the actual accident statistics by one-third (Table 2).

In 1975, Minnesota had 33 open pit mines, 21 mills, and over 400 sand, gravel and crushed stone mines (U.S. Department of Interior, 1975). Iron and taconite are the dominant mining industries. Although Minnesota had had an annual average of two mine related deaths over the past five years (U.S. Department of Interior, 1975), the Minnesota mining industry has compiled an

impressive record, relative to other states in the country, is reflected by disabling injury frequency rate statistics. As shown in Table 3, the Minnesota rates for surface mines are approximately half, and the rates for mills are less than one-fourth the U.S. average. According to the National Safety Council (1976), Reserve Mining (Silver Bay plant) currently holds the record in the mining industry for the largest number of continuous man-hours worked without a disabling injury--10,659,100 hours. Prior to Reserve setting this record, its Babbitt operation held the record (National Safety Council, 1968); and before that the record was held by the Pickands Mather Company's Mahoning Mine in Hibbing (National Safety Council, 1963). There are several possible reasons for the safety records of Minnesota mining companies: 1) the companies have strong safety programs beginning with top management; 2) there is strong competition among the companies to have the best safety record, possibly brought about by the competition for workers; 3) the taconite mines and mills are relatively new and utilize newer technology than most mines in the country; and 4) the open-pit taconite mines are fairly shallow compared to the deeper western mines allowing for easier removal of ore (Veith, Regional Copper-Nickel Study, personal communication, 1978).

At the present time two federal agencies have statutory responsibility for enforcing occupational health and safety standards in the minerals industry. The Mining Enforcement and Safety Administration (MESA), located in the Department of Interior, is responsible for all stages of mining through the milling stage. The Occupational Safety and Health Administration (OSHA), located in the Department of Labor, is responsible for everything beyond the milling stage, i.e. smelting and refining.

TYPES OF OPERATIONS

Underground Mining

Several limitations make underground mining generally more dangerous than surface mining. Perhaps the most important factor is the lack of light. While artificial lighting is used, the situation is far different from working in broad daylight. Underground mines are often damp and, coupled with irregular floor surfaces, have many potential hazards for slips and falls. Ventilation systems must be monitored constantly to remove toxic gases and maintain an adequate level of oxygen. Falling ground and fires generally have more severe consequences in underground mines than in surface mines.

These hazards are reflected in statistics compiled by both the National Safety Council (Tables 1 and 3) and by the Mining Enforcement and Safety Administration (MESA; Table 4). Although the National Safety Council data (based on voluntary reporting) showed a 20 percent drop between 1963 and 1972, MESA data (based on mandatory reporting), when compared to the comparable Mine Safety Study Board figures (Table 2), show little change between 1963 and 1974--although 1975 showed a drop of approximately 18 percent. In addition to the high injury frequency rates, statistics also show that the injury severity rates are high (Table 5). Injury frequency rates for underground mining, excluding coal were higher than all other industries except underground coal mining, according to the National Safety Council. The Mine Safety Study Board found that an average of 167 days were lost per disabling injury for underground mining in 1963 (Table 2). Although the data are less reliable, the National Safety Council published similar findings in the early 1970's.

Surface Mining

From the safety point of view, surface mining is usually preferable to underground mining. Unfortunately, there is rarely any choice of which method to use. Surface mining is not free from hazards and has serious potential hazards of its own.

The most recent statistics from the National Safety Council (1969-1972) show that the disabling injury frequency rate for surface mining was generally close to the average for all industries combined (Table 5). These surface mining injury frequency rates were approximately one-third those for underground mining. Statistics from MESA (Table 4) show that the 1:3 relationship has continued through 1975.

While surface mining injury frequency rates were similar to the average for all industries, surface mining injury severity rates, the number of days lost per million man-hours worked, were over three times the average for all industries combined (Table 5)--which means that accidents occurring in surface mines tend to be much more severe than those in other industrial settings. Although the injury severity rates for surface mines were approximately one-half those for underground mining, only two of the 41 industrial categories used by the National Safety Council--underground coal mining, and underground mining excluding coal--had higher injury severity rates in all four years from 1969-1972. In fact, the Mine Safety Study Board (Table 2) found that in 1963, an average of 198 days were lost per surface mining injury--21 more than the average for underground mining.

Mills, Smelting, Refining

Data for mills are approximately comparable to those for surface mining (see Tables 2 and 4). Table 6 shows comparable data for smelting and refining. Compared to the averages for all industries combined, the refining industry had

much higher injury frequency rates (over 60 percent higher) and higher injury severity rates (15-30 percent higher). The smelting industry had injury frequency rates close to the average and much higher injury severity rates (about 60 percent higher) than the averages for all industries combined.

Mining-General

Fatal accidents are investigated by MESA to determine causes, circumstances, and other related information that might help to prevent future deaths. In four of the past five years, machinery and haulage have been the top two categories of deaths in mines and mills together (U.S. Department of Interior, 1975). The one exception, 1972, was due to a fire which caused 90 deaths (40 percent of the total for that year). Other major categories include fall of ground, fall of person and electricity.

The experience of a miner appears to be related to the probability of fatalities. Those with less than two years total mining experience account for far more deaths than any other two-year group. This relationship becomes even stronger when one looks at total experience in the particular mine or experience on the regular job. Within these first two years, employees on the job for less than a year account for far more deaths than those on the job one to two years.

These data suggest that most deaths are caused by controllable factors. A report from the Mine Safety Study Board (U.S. Department of Interior, 1963) supported this contention. Approximately half of all deaths were due to "circumstances over which the workmen had no control, but which were within the scope or range of supervisory responsibility." Three-fourths of the remaining deaths could be attributed to unsafe acts of workers or supervisors. Further evidence that accidents can be prevented are published from time to time. For example, St. Joe Minerals (Stover, 1971) reduced its accident frequency rate by one-half over a two-year period, and U.S. Borax (1976), also over a two-year

period, reduced accidents involving new employees by over one-hald, both by increasing emphasis on accident control programs.

Copper and Nickel Mining--Specifically

Injury frequency and severity rates for copper mines and mills are presented in Table 7. These data indicate that safety conditions in the copper industry are typical of the mining industry as a whole. Comparable data for the nickel industry have not been presented and would be less useful because there is only one nickel mine and smelter in the United States.

Table 1. Disabling Injury Frequency Rate*--National Safety Council

	1960	1961	1962	1963
Mining, underground, excluding coal	23.56 (40)**	NA	27.48 (39)	33.71 (39)
Mining, underground, coal	25.20 (41)	NA	35.86 (41)	33.87 (40)
Mining, surface	8.52 (27)	NA	9.64 (27)	8.47 (26)
All industries	6.04	NA	6.19	6.12

*Number of disabling injuries per million man-hours worked.

**Number in parentheses indicate ranking out of 41 rated industries.

NA= not available

SOURCE: National Safety Council (1961-1964)

Table 2. Mine Safety Study Board Findings (1963)

	Injury Frequency Rate*	Severity Rate**	Average Severity***
All underground	44.11	7,361	167
Metal & Nonmetal open pit	12.91	2,553	198
Mills	14.63	2,120	145

*Number of disabling injuries per million man-hours worked.

**Number of days lost per million man-hours worked.

***Number of days lost per disabling injury.

SOURCE: U.S. Department of Interior (1963).

Table 3. Disabling Injury Frequency Rates* for Metal and Nonmetal Mines, 1975 (preliminary data).

	SURFACE MINES	MILLS
Minnesota	7.73	2.71
U.S. Average	15.20	11.76

*Number of disabling injuries per million man-hours worked.

SOURCE: U.S. Department of Interior (1975)

Table 4. Disabling Injury Frequency Rates*--MESA

Type of Mine	1975	1974	1973
Underground	37.78	44.74	45.40
Open pit	13.13	15.41	14.20
Mills	11.76	10.71	10.61

*Number of disabling injuries per million man-hours worked.

SOURCE: U.S. Department of Interior (1975)

Table 5. Disabling Injury Frequency and Severity Rates--National Safety Council

	1972		1971		1970		1969	
	Frequency*	Severity***	Frequency	Severity	Frequency	Severity	Frequency	Severity
Mining, surface	9.24 (23)**	1832 (38)	11.18 (26)	2614 (39)	9.39 (23)	2146 (38)	10.62 (27)	2589 (39)
Mining, Underground, Excl. Coal	27.01 (39)	4120 (40)	26.39 (40)	4469 (40)	31.47 (40)	4839 (40)	29.42 (40)	4846 (40)
All industries	9.37	611	8.87	667	8.08	640	7.35	665

*Number of disabling injuries per million man-hours worked.
**Number in parentheses refer to ranking out of 41 rated industries.
***Number of days lost per million man-hours worked.

SOURCE: National Safety Council (1969-1972)

Table 6. Disabling Injury Frequency and Severity Rates (3-year averages)--National Safety Council

	1971-1973		1968-1970	
	Frequency**	Severity***	Frequency	Severity
Refining*	16.53	860	16.64	761
Smelting*	8.28	1047	8.67	1032
All Industries	10.01	640	8.09	657

*These subcategories were part of the category entitled Non-Ferrous Metals and Products.

**Number of disabling injuries per million man-hours worked.

***Number of days lost per million man-hours worked.

SOURCE: National Safety Council (1971, 1974)

Table 7. Injury Statistics for the Copper Industry, 1973-1976

Category	1976	1975	1974	1973
FATAL				
Injury frequency rate*				
-underground	0.22	0.41	0.78	0.77
-open pit	0.15	0.29	0.21	0.18
-mills	0.12	0.06	0.05	0.06
-total	0.15	0.25	0.31	0.30
Severity rate**				
-underground	1335	2441	4693	4609
-open pit	873	1756	1254	1079
-mills	701	351	299	331
-total	897	1490	1882	1816
NONFATAL				
Injury frequency rate*				
-underground	44.49	40.81	57.83	65.29
-open pit	10.08	12.96	16.38	13.27
-mills	13.26	14.55	9.41	10.70
-total	19.53	21.08	25.31	26.65
Severity rate**				
-underground	NA	1491	1676	2137
-open pit	NA	677	789	1178
-mills	NA	515	568	388
-total	NA	852	948	1213

*Number of disabling injuries per million man-hours worked.

**Number of days lost per million man-hours worked.

NA = Not available

N.B. Fatal and nonfatal rates are combined in the other tables.

SOURCE: A.P. Nelson, Mining Enforcement and Safety Administration, Arlington, Va. letter dated 5/16/77.

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ALUMINUM AND HUMAN HEALTH

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INTRODUCTION

Aluminum was first isolated in 1825, and was produced commercially as a metal in 1854 (Browning 1969). It is present in all soils and makes up over eight percent of the earth's crust (Sorenson et al. 1974). Aluminum has been found in all human tissues examined and may be an essential element to man. The major source of intake is through the diet, which may contain from less than 10 mg to 100 mg per day (Campbell et al. 1957). Concentrations reported in Minnesota waters ranged from 0 to 2.9 µg/ml. Worldwide atmospheric values reported range from 0.01 $\mu g/m^3$ over the oceans to 8.00 $\mu g/m^3$ in Buffalo, New York. There have been no standards set for aluminum in drinking water, in the diet, or in ambient air, because it has not presented any apparent health problems to date (Sorenson et al. 1974).

Aluminum is widely used in construction, electrical equipment, furnishings, and various appliances. It is also used in paints, fuels, explosives, and chemicals, as well as food additives and pharmaceuticals (Sorenson et al. 1974).

OCCUPATIONAL EXPERIENCE

The major health effects reported from the manufacturing of aluminum compounds are due to components other than aluminum. Fluorides released during the process have been of great concern, as have the coal tars and SO_2 given off. The only effects of aluminum compounds have been several reports of respiratory disease.

Two aluminum oxide (Al_2O_3) compounds, alundum and corundum, have been classified by the American Conference of Governmental Industrial Hygienists (1975) as nuisance particles with threshold limit values (TLVs) of 10 mg/m^3.

The first reports of respiratory disease associated with aluminum came from Germany during World War II. Aluminum powder was used in the manufacture of ammunition, and blackouts often led to poor ventilation. Mitchell et al. (1961) have reviewed some of these studies. One study of 628 workers, from 6 factories, found 26 percent to have uncomplicated cases of pulmonary aluminosis. The main symptom was dyspnea, with occasional cough and sputum. Death often occurred within two years from onset. Other industries using aluminum appeared to have no problems; however, the size of the particles was different. Industries using particle size greater than 7μ had no reported health effects, while those using smaller sizes often reported respiratory problems.

Mitchell et al. (1961) examined 27 workers manufacturing fine aluminum powder for fireworks. They found six cases of pulmonary fibrosis, including two which were fatal. The diagnosis of pulmonary fibrosis was conclusive in the two fatal cases; there was sufficient evidence in three other cases; and the sixth case had minimal radiological changes. Respirators had not been provided prior to these cases, and no attempts had been made to prevent inhalation of the dust. The mean concentration of respirable dust was found to range from 19 to 114 mg/m^3 depending on which workman was on duty and the location where the sample was collected. Fifteen workers in the same factory, but using a coarse powder, showed no symptoms.

Several other individual cases of pulmonary disease have been reported. Jordan (1961) reported on a 26-year-old woman employed in a fireworks factory, working with aluminum powder and potassium perchlorate. After five years exposure she experienced marked dyspnea on exertion, reduction in lung volumes, and impaired diffusing capacity of her lungs. Another

case was that of a ball-mill operator working in an aluminum flake powder factory for 13.5 years (McLaughlin et al. 1962). This 49-year-old worker was diagnosed as having extensive aluminum fibrosis. He died of bronchopneumonia, after suffering severe neurological deterioration which included convulsions and aphasia.

Mitchell et al. (1961) also reported that aluminum as a fume may cause respiratory problems. They cited studies showing that the manufacture of corundum (Al_2O_3) abrasive had led to interstitial lung fibrosis. This was often rapidly progressive and accompanied by severe emphysema. On the other hand, Meiklejohn and Posner (1957) reported that the lungs of workers were unaffected by exposure to corundum. They radiographed 97 workers, and found 10 cases of pneumoconiosis. All ten cases, however, had previous exposure to flint dust which was known to cause silicosis.

The agents of greatest concern to aluminum workers are fluorides and coal tar volatiles (Discher et al. 1976). The production of 1000 kg of aluminum requires an input of 2000 kg of alumina (Al_2O_3), 3 kg of cryolite, and 30 kg of AlF_3 (Midttun 1960). The escaping gas contains fluorine, and the dust given off contains AlF_3 and cryolite. Kaltreider et al. (1972) did a radiological survey of 79 aluminum workers with chronic exposure to fluoride. They found that 96 percent showed varying degrees of skeletal fluorosis with no physical impairment or clinical signs of disease. There appeared to be no deleterious effects on the general health of these workers.

Dinman et al. (1976) surveyed 56 workers with 10 to 43 years exposure to fluoride in an aluminum smelter. They found no evidence of renal alterations in 16,000 urine samples analyzed over a five-year period.

NONOCCUPATIONAL EXPERIENCE

Sorenson et al. (1974) concluded that no community exposures have been reported in the literature. There are, however, many medicinal uses of aluminum and aluminum compounds, some of which may have adverse side effects. Phosphate-binding gels, which contain aluminum, are widely used to control serum phosphorus levels in uremic patients on dialysis (Hegsted 1976). Encephalopathy has been reported in patients who have been on this treatment for more than three years.

Dent and Winter (1974) reported phosphate deficiency causing osteomalacia in patients receiving aluminum hydroxide as an antacid. It is often given in large doses to patients with renal failure.

Other medical uses of $Al(OH)_3$ include treatment of peptic ulcers and symptomatic gastric hyperacidity. This may be given as a continuous treatment using an equivalent of six grams $Al(OH)_3$/day applied through a tube directly into the stomach. Although this procedure may continue for months or years, no ill effects have been observed (Campbell et al. 1957).

Particulate aluminum has been used in the prevention and treatment of silicosis. The most common procedure in the United States involved inhalation of metallic aluminum for ten minutes each day. The concentration was about 3.2 mg/ℓ of dust in air flowing at 10 ℓ/minute. Campbell et al. (1957) reported that 73.3 million individual treatments were known to be administered between 1943 and 1956 with no injurious effects observed.

Crapper et al. (1976) have reported that aluminum may be neurotoxic. They found elevated aluminum in the brain, associated with neurofibrillary degeneration, and increased levels in persons with Alzheimer's disease.

EXPERIMENTAL EVIDENCE

Animal Studies

Respiratory effects

King et al. (1955) injected 100 mg each, of three different aluminum solutions, into the lungs of rats. Aluminum hydrate caused massive fibrosis, aluminum phosphate produced a similar but milder fibrosis and condensed fume from a corundum furnace produced a much less severe fibrosis.

Corrin (1963) injected rats with 100 mg of stamped aluminum dust containing stearine, mineral oil, or aluminum only. All compounds produced fibrosis rapidly, while nothing happened in control rats injected with saline. The fibrous reaction was present as early as 16 days, and well established by four months.

Dermatitis

Although this has not been reported in man, there have been animal studies showing epidermal changes occurring from aluminum exposures. Lansdown (1973) treated the skin of mice, rabbits, and pigs with ten percent solutions of six different aluminum compounds. Epidermal changes including hyperplasia, microabscess formation, dermal inflammatory cell infiltration, and, occasionally, ulceration resulted in all three species following application of $AlCl_3$ and $Al(NO_3)_3$. The other four compounds showed no effects on any of the species tested. A ten percent $AlCl_3$ solution produced erythema, thickening and scaling of the skin after five days; while a 25 percent solution produced these changes after two days.

Other effects

Berlyne et al. (1972) have demonstrated aluminum intoxication in uremic and nonuremic rats given the equivalent of 150 mg of elemental Al/kg/day. This was given orally as $AlCl_3$, $Al_2(SO_4)_3$, or $Al(OH)_3$. Other test groups received subcutaneous or intraperitoneal injection of 90 mg $Al(OH)_3$/kg/day. Clinical symptoms observed included periorbital bleeding, lethargy, anorexia, and death. Plasma levels of aluminum were increased from the normal of 0.2 mg/ℓ to 0.5 to 40 mg/ℓ, depending on which route of administration was used. Tissue levels of aluminum were found raised in the liver, heart, muscle, brain, and bone.

Onreicka et al. (1966) studied the chronic toxicity of $AlCl_3$ given in the diet and drinking water of mice and rats. Doses of 19.3 mg Al/kg/day given for 180 to 390 days showed no differences in number of litters or off-spring between test and control animals. However, there was growth retardation in the second and third generation litters which was attributed to aluminum uptake. Slightly higher doses (355 ppm for 40 days) significantly lowered the phosphorus retention, and reduced the amount of phosphorus incorporated into the tissues.

Sorenson et al. (1974) cited a report which suggested that the most significant toxic reactions to aluminum compounds may be the inhibition of glycolysis and phosphorylation. They also cited a study which showed that doses greater than 150 mg of $AlCl_3$/kg/day given orally to rats brought about a negative phosphorus balance. This resulted from a decreased incorporation of phosphorus into phospholipids and nucleic acids of liver, kidney, and spleen, and a drop in the adenosine triphosphate (ATP) level in the blood.

These disorders were less marked in rats receiving a high calcium diet. Furst (1971) has included aluminum in a list of metals reported as potential carcinogens, but has suggested that it may just act as a solid irritant. He also cited a study which has shown that Al_2O_3 dust enhanced the activity of a known carcinogen, 4-nitroquinoline-N-oxide.

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AMMONIUM NITRATE BLASTING AGENTS

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INTRODUCTION

Ammonium nitrate, NH_4NO_3, is probably best known as a fertilizer. It has long been used in explosives; however, it was not until the mid-1950's that ammonium nitrate-fuel oil (ANFO) mixtures, specifically, became widely used (U.S. Bureau of Mines, 1960). These mixtures usually contain approximately 6 percent fuel oil. Today aluminum powder is often used to increase the strength of the ammonium nitrate fuel oil mixture (Damon et al. 1977). In 1975, ninety percent of all blasting in the United States was done with ammonium nitrate-based blasting agents (Damon et al. 1977). Two factors account for the popularity of ammonium nitrate-based blasting agents: the low cost and the relative freedom from the hazards of accidental detonation.

OCCUPATIONAL HAZARDS

Safety Hazards - Although ANFO is a relatively safe explosive, there are safety hazards involved in its use, just as with any explosive. During the years 1970-1975, there were 28 fatalities attributable to explosives (U.S. Department of the Interior, 1975) in metal and nonmetallic mines and mills. Of these fatalities, 17 were in underground mines and 10 in surface mines. Safety recommendations have recently been published by the U.S. Bureau of Mines (Damon et al., 1977).

Toxic Gases - At high temperatures, ammonium nitrate upon decompositon provides a source of oxygen in enclosed systems (Equation 1). When mixed with hydrocarbons, such as fuel oil, reactions such as Equation 2 result. If there is incomplete combustion, insufficient or poorly distributed fuel, the characteristic brown fumes of nitrogen dioxide (NO_2) will be observed (Equation 3).

1) $2NH_4NO_3 \xrightarrow{>300^oC} 2N_2 + 4H_2O + O_2$ (28 Kcal/mole)

2) $3NH_4NO_3 + CH_2: \longrightarrow 3N_2 + 7H_2O + CO_2$ (72 Kcal/mole)

3) $4NH_4NO_3 \xrightarrow{\Delta} 2NO_2 + 8H_2O + 3N_2$ (27 Kcal/mole)

SOURCE: Stites et al. (1960)

All explosions will produce some toxic gases. Nitrogen oxides and carbon monoxide are the two most common toxic gases produced from ANFO explosions (Chaiken et al., 1974). The oxygen balance has a large impact on the relative concentrations of nitrogen dioxide and carbon monoxide which are produced (Van Dolah, Murphy, and Hanna, 1962). A negative oxygen balance enhances production of carbon monoxide, but limits nitrogen dioxide production, while a positive oxygen balance will increase nitrogen dioxide, but limit carbon monoxide. Any improperly balanced composition, or any factors causing detonation at less than optimum velocity will increase the production of toxic fumes (Van Dolah et al., 1962).

Adequate ventilation in underground mines is especially important when ammonium nitrate explosives are being used. Tiffany et al. (1950) found nitrogen dioxide concentrations of more than 100 ppm 15 minutes after firing in an underground test mine. This level is 20 times the threshold limit value of 5 ppm for nitrogen dioxide (American Conference of Governmental Industrial Hygienists, 1975). Carbon monoxide was considered more hazardous than nitrogen dioxide by Tiffany et al. (1950); however, the relatively greater toxicity of nitrogen dioxide has been increasingly realized (Chaiken et al. 1974). The effects of nitrogen oxides and carbon monoxide on health have been discussed in more detail elsewhere (Regional Copper-Nickel Study, 1978 a,b).

POTENTIAL NONOCCUPATIONAL HAZARDS

Potential nonoccupational hazards include increased production of noise, dust and the potential for flying rock. Factors affecting the potential severity of these hazards include proximity of homes and places of community activity and the explosives usage practices of the mining companies.

Jablonska (1975) reported the case of a 13-year old boy who accidently licked a piece of ammonium nitrate, apparently from a fertilizer storehouse, and developed some pigmentary spots. Discovering that he could evade school attendance because of frequent visits to physicians, he licked the fertilizer at irregular intervals in amounts which caused no gastrointestinal disturbances. Cutaneous lesions appeared over most of his body. His brother, an identical twin, had no symptoms, nor did the rest of his family. The author cautioned that ammonium nitrate is a potential food contaminant.

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ARSENIC AND HUMAN HEALTH

Peter Ashbrook

INTRODUCTION

Arsenic (As) has a long history characterized by a variety of uses. Writings of the ancient Greeks refer to sulfides, which are now known as arsenic minerals; and medicinal uses have been known for centuries (Greenspoon, 1975). Mountaineers in the Styrian Alps reportedly consumed arsenic to improve physical stamina (Schroeder and Balassa, 1966; United States Environmental Protection Agency (USEPA), 1976). Fowler's solution, which contains arsenic trioxide was used extensively in the late 19th century to treat acute infections, epilepsy, asthma, psoriasis, and eczema.

Although arsenic ranks 20th (2-5 ppm) in abundance among elements in the earth's crust, it ranks 12th (0.2-0.3 ppm) in the human body. It has been found in public water supplies and in the air near coal burning industries and smelters (Schroeder and Balassa, 1966). Also found in vegetables and forest soils, arsenic is present at high concentrations in seafood, with reports as high as 174 ppm (Schroeder and Balassa, 1966). The two most common valence states of arsenic are the trivalent (arsenic trioxide, As_2O_3; arsenous acid, H_3AsO_3; and its salts, arsenites) and the pentavalent (arsenic pentoxide, As_2O_5; arsenic acid, H_3AsO_4; and its salts, arsenates) forms, the latter generally considered to be far less toxic.

Commercially, arsenic is recovered as a by-product of copper, gold, and silver production (Greenspoon, 1975). Levels of arsenic in the ore can vary considerably depending on location (Table 1). Arsenic is presently used in the manufacture of various chemicals which are important in the agriculture, lumber, and glass industries. Agriculture accounts for 82 percent of the total use of arsenic, including such materials as herbicides, insecticides, and for parasite control (Greenspoon, 1975). Arsenic is also used to preserve wood, and in the

manufacturing of sheep dips, fly paper, arsenical soaps, germicides and rat poisons (Schroeder and Balassa, 1966).

Arsenic is distributed throughout the body. Arsenate is readily excreted and shows no tendency to accumulate; arsenite, however, has been shown to accumulate, showing a strong affinity for the kidney and liver, as well as for hair, nails, and skin (Schroeder and Balassa, 1966). Schroeder and Balassa (1966) calculated the normal intake of arsenic to be 900 µg As/day, of which 1.5 µg would be retained. They also reported that attempts to demonstrate arsenate to be an essential element have been unsuccessful, largely because of its ubiquity in the environment. Arsenic is antagonistic to iodine and selenium.

OCCUPATIONAL EXPERIENCE

Arsenic trioxide is being increasingly accepted as an occupational carcinogen to the skin, lung, and with less certain evidence, the liver (Utidjian, 1976). Arsenic exposure appears to cause an excess risk of lympathic cancers (Kraybill, 1976; Blejer and Wagner, 1976). Controversy concerning the carcinogenicity of arsenic may in part be attributed to the past incrimination of arsenic as responsible for some occupational cancers now known to be caused by other agents. For example, lung cancer observed in the Schneeberg and Joachismal cobalt miners and nickel refinery workers in Swansea, South Wales was once attributed to arsenic. However, the etiologic agents were later identified as ionizing radiation and nickel, respectively (National Institute of Occupational Safety and Health (NIOSH), 1975).

Currently, the threshold limit value for handling and use of arsenic trioxide is 0.25 mg/m^3; for arsenic trioxide production, 0.05 mg/m^3; and for arsine

0.2 mg/m^3 (American Conference of Governmental Industrial Hygienists, 1975). NIOSH (1975) has recommended the standard for inorganic arsenic be reduced to 2 $\mu g/m^3$.

Cancer

Respiratory Cancer

Blejer and Wagner (1976) recently reviewed the eleven epidemiologic studies concerning arsenic exposure. Nine of these showed excess mortality due to lung cancer either initially or upon reanalysis of the data, while the other two were inconclusive. Some of these studies are presented below.

Pinto and Bennett (1963) examined the mortality experience of workers employed at the Tacoma copper smelter during the years 1946-1960. During this time period 229 deaths among active workers and pensioners occurred out of an annual average of 904 workers. Washington State males, aged 15-94, served as the control population. Expected numbers of deaths in the smelter workers were calculated by using the proportion of all deaths observed in each category of the control group (i.e. if 10 percent of the deaths were due to a specific cause in Washington males, then 22.9 (10 percent of 229) deaths would be expected in the smelter group). An excess was found for all cancers (36.7 expected, 43 observed), however, this difference was judged not significant by the authors. In spite of the authors' conclusion that there was no evidence of chronic arsenic trioxide exposure causing systemic cancer in humans, the opposite appears to be true.

This study has recently been criticized and reevaluated by a number of sources (e.g. NIOSH, 1975). Probably the most significant criticism is found in the respiratory cancer data which showed that 41.9 percent of the cancer

deaths in smelter workers were due to respiratory cancer compared to 23.7 percent in Washington males. Pinto and Bennett split the smelter deaths into arsenic exposed and nonarsenic exposed. Because the proportion of excess deaths in each group was about the same, twice as many observed as expected, the authors concluded the apparent excess of respiratory cancers must be caused by a factor other than arsenic trioxide exposure. However, the authors' data suggest that the nonarsenic exposed group actually was exposed to higher levels of arsenic than the control males.

Milham and Strong (1974) examined the respiratory cancer mortality experience of the Tacoma smelter workers for the years 1950-1971. Forty respiratory cancer deaths were observed compared to 18 expected based on U.S. mortality rates. This excess was statistically significant ($p<0.001$).

Lee and Fraumeni (1969) examined the mortality experience of 8,047 smelter workers exposed to arsenic trioxide during 1938-1963, using the mortality experience of the white male population of the same states for comparison. Age and cause specific mortality rates were used to calculate the expected numbers of deaths. Over 90 percent of these workers were known to be living or deceased at the end of 1963. Persons lost to follow-up were included in the analysis through the time they were last known to be living. The study population was divided into five cohorts (Table 2) depending on length of employment and specific years employed. Additionally, they were classified on the basis of three levels of exposure to arsenic. These environmental levels were not presented. Similar divisions were made to study sulfur dioxide, silica, lead fumes, and ferromanganese.

Overall there were 1877 deaths, a significant excess compared with 1634 expected deaths. Several causes of death showed significant elevations

above the expected; however, only respiratory cancer was significantly elevated in each of the five cohorts and tended to increase with the length of employment (Table 3). In the heavy, medium, and low arsenic exposure groups, the observed-to-expected ratio was 6.7, 4.8, and 2.4, respectively for respiratory cancer. A similar gradient was observed within each cohort (Table 3). The excess mortality was greater for foreign-born workers than for native workers (however, the excess for each group was significant). This excess was attributed in part to the greater exposure experienced by foreign-born workers.

Cigarette smoking alone was judged unlikely to be responsible for the observed respiratory mortality experience. Likewise, radiation exposure was dismissed as a cause. Sulfur dioxide showed the same relationships as arsenic. The authors were unable to distinguish between the influence of arsenic and sulfur dioxide or any unknown agents correltated with arsenic levels. It was noted that while sulfur dioxide has not been considered carcinogenic it may enhance the effects of other carcinogens.

Kuratsune, et al. (1974) performed a case control study comparing 19 males who died of lung cancer with 19 controls randomly selected from deaths attributed to diseases other than cancer of the lung, skin, and urinary bladder. The study was initiated because the 19 lung cancer cases occurred in a small village over a 3-year period. Eleven of the cases worked at a copper smelter compared to three in the control group ($p=0.01$). The cases also had higher rates of smoking and drinking, however, these differences were not significant. In the eleven cases who had worked at the smelter, the period of exposure ranged from 2 to 39 years, with a median of 31 years. The latent period between first exposure until onset of lung cancer was 26-48 years. All the cases had retired before developing lung cancer.

Ferguson (1976) discussed an unpublished study of workers at an Allied Chemicals plant which manufactured arsenic acid, arsenical pesticides and herbicides, and a variety of agricultural chemicals. Significant excesses of total cancer, pulmonary cancer, and lymphatic cancer were observed. These cancer cases were found in three categories of workers: operators in the old arsenic acid plant, warehouse laborers who charged the old arsenic acid reaction kettles, and operators and packers in the insecticide plant. Exposure period from first arsenic exposure until death from cancer ranged from 10 to 56 years with a median of 33 years.

Ott, et al. (1974) studied the proportionate mortality experience of workers at a Dow Chemical plant. Arsenic was primarily in the form of lead arsenate and calcium arsenate. A comparison was made between 173 deaths of those working with arsenic and 1809 deaths of nonexposed workers. Of the 173 deaths, 138 had worked in the arsenic exposure area for less than one year. Malignant neoplasms, cancer of the respiratory system, and cancer of the lymphatic and hematopoietic tissues, except leukemia, accounted for a larger proportion of the deaths in the exposed group than in the controls (Table 4).

Significantly greater numbers of excess deaths were observed with increasing arsenic exposure (Table 5). Time between first arsenic exposure and death was at least 15 years. Sixteen of those who died from respiratory cancer worked in the exposure area for less than one year (Blejer and Wagner, 1976). Although tests of statistical significance were not performed, excess respiratory deaths were observed at arsenic concentrations as low as 3 $\mu g/m^3$.

Osburn (1969) described the occurrence of lung cancer near a Rhodesian gold mine, which was known to contain arsenic. Of the 37 male patients with lung cancer admitted to the district hospital during the years 1957-1962, all but one were miners or had previous mining experience. Six of the patients were nonsmokers

and had worked in underground mines. Only one-third of the miners had palmar hyperkeratoses.

Other Cancers

Evidence implicating inorganic arsenic as a skin carcinogen has recently been reviewed by the USEPA (1976). The skin undergoes a progression of responses to chronic arsenic exposure, beginning with hyperpigmentation, followed by hyperkeratosis, and finally, skin cancer. These responses have been observed under a variety of arsenic exposures including: medicinal use of Fowler's solution (potassium arsenite); vineyard workers using arsenic sprays and dusting powders, and drinking arsenic-contaminated wine; workers manufacturing sodium arsenite for use as a sheepdip; and residents of a localized area of Taiwan whose drinking water was contaminated by naturally occurring arsenic for over 45 years. Approximately 15-30 grams spread over a long time period, appears to be the average dose required to produce an appreciable incidence of skin cancer.

Two studies have found an excess of deaths due to lymphatic cancers among workers exposed to inorganic arsenic (Blejer and Wagner, 1976; Table 4); and an increased incidence of liver cancer was observed in another study (cited by USEPA, 1976).

Dermatitis

Holmqvist (1951) extensively described the arsenical dermatitis experience of workers at a Swedish smelting works. The incidence of arsenical dermatitis was higher in the summer than winter, suggesting a relationship with perspiration. Perforation of the nasal septum was more common in the winter, possibly due to the greater prevalence of rhinitis in those months. One specifically mentioned

method of controlling exposure was the removal of sensitive individuals from high exposure jobs. Apparently, a number of workers adapted to arsenic exposure somewhat, as evidenced by the fact that they developed skin lesions during their first few years of employment, but were subsequently able to continue work with no discomfort. The author could not tell if this observation was due to "hardening", desensitization, or an increasing ability to avoid risks.

Arsenic Poisoning

Reeves (1976) has compiled an extensive table of signs and symptoms of arsenic poisoning (Table 6).

Acute Inorganic Arsenic Poisoning

Acute arsenic poisoning shows a characteristic delay of one-half to several hours in the onset of symptoms even after comparatively large doses (Buchanan, 1962). Throat constriction, followed by difficulty in swallowing and epigastric discomfort are frequently the first symptoms. Violent abdominal pain, accompanied by vomiting and diarrhea are experienced next. Other gastrointestinal symptoms may also be present.

Arsine poisoning is an acute disease caused by exposure to arsine gas. Symptoms of moderate to severe arsine poisoning include: migratory abdominal cramps and tenderness, nausea, vomiting, and painless hemoglobinuria (Pinto, 1976). Laboratory analysis will show leucocytosis, elevated plasma hemoglobin, and hemoglobinuria without cellular debris. Pinto (1976) has suggested a complete exchange transfusion if plasma hemoglobin is greater than 1.5 gm/100 ml. Kidney function must be closely monitored because renal failure is a distinct possibility.

Chronic Inorganic Arsenic Poisoning

Chronic arsenic poisoning may follow an acute case of arsenic poisoning, but is more commonly chronic in nature of the outset (Buchanan, 1962). Symptoms of chronic poisoning can be divided into three phases.

In phase one, symptoms include weakness, loss of appetite, some nausea, and occasional vomiting. There may be a sense of heaviness in the stomach and some diarrhea; however, the latter is not typical.

In phase two, common symptoms include conjunctivitis and a catarrhal state of the exposed mucous membranes of the nose, larynx, and respiratory passages. Symptoms of coryza, hoarseness, and mild tracheitis or bronchitis may also be present. Also common are skin manifestations consisting chiefly of eczematoid features, predominantly vesicular lesions. Hepatitis and jaundice are occasionally observed at this stage.

At phase three, onset of manifestations of peripheral neuritis occurs. Initially the hands and feet are the main areas affected. When sensory perception begins to be impaired, the victim may suffer from ataxia. Other sensory perceptions may be variously affected, either increased or deadened. Motor paralyses can occur in severe cases.

Biological Levels in Response to Industrial Exposure

Pinto et al. (1976) studied arsenic trioxide absorption and excretion in 24 occupationally exposed workers. Airborne arsenic, as measured by personal air samplers, was found to be significantly ($p < 0.01$) correlated with urinary arsenic. Urinary arsenic levels decreased over weekends

and vacation periods. Consumption of seafood had a profound effect on urinary arsenic. In 204 samples collected in preemployment physicals without regard to seafood consumption, urinary arsenic averaged 52.6 µg/l.

Other Effects

Pinto and Bennett (1963) observed an 11 percent excess of cardiovascular deaths compared with the State of Washington mortality experience in their study of the Tacoma copper smelter workers. However, the authors concluded this excess was not significant.

Lee and Fraumeni (1969) observed significant excess mortality for tuberculosis, diseases of the heart, and cirrhosis of the liver, in their study of smelter workers exposed to arsenic trioxide. However, unlike the case of respiratory cancer, a dose-response relationship between arsenic exposure and mortality from these causes could not be demonstrated. The authors suggested that factors other than environmental exposures in the smelter were responsible for these observations.

NONOCCUPATIONAL EXPERIENCE

The maximum contaminant level for arsenic in drinking water is 0.05 mg/l as given in the National Interim Primary Drinking Water Regulations (USEPA, 1975).

Respiratory Cancer

Blot and Fraumeni (1975) examined the mortality experience of the 36 U.S. counties with manfacturing units engaged in primary smelting and refining of copper, lead, or zinc ores and in which at least 0.1 percent of the county population worked in the industry. These industries were chosen because the ores of copper, lead or zinc may contain "substantial amounts of inorganic

arsenic" (this assumption was not verified by ore analyses). Thirty-five counties with aluminum and other nonferrous metal industries were also studied; and the remaining 2985 counties in the 48 contiguous states served as controls. Mortality due to lung cancer was significantly higher for both males ($p < 0.001$) and females ($p < 0.05$) in the copper, lead, and zinc counties compared to the controls for the years 1950-1969. Rates for both sexes were elevated in each 5-year interval of the study period. Counties processing other nonferrous ores showed no elevation of lung cancer mortality.

Occupational exposure alone did not account for the magnitude of excess deaths observed. Smoking habits were judged an unlikely factor. Confounding variables such as urbanization, regional differences, socio-economic factors, or exposure to other manufacturing processes were not responsible for the observed correlations. The authors concluded that neighborhood air pollution from industrial sources of inorganic arsenic was the most likely explanation for increased lung cancer. They noted that other industrial agents may be contributing factors. The conclusions of this study have been criticized by the industry (Nelson, 1977).

Dermatitis

Birmingham et al. (1965) described an outbreak of arsenical dermatoses in a community near a gold mine. Arsenical dermatoses, including eczematous contact dermatitis, folliculitis, furunculosis, pyodermas, and ulcerations, were observed in elementary and pre-school children, and housewives, but not in high school children who were bused to a distant school. Apparently the domestic animal population had been virtually eliminated by illness.

June grass, also dead, near the school ground contained 925 ppm of arsenic. Dust samples collected at the mine-mill site were above one percent arsenic in several instances, the highest being 44 percent arsenic. Within several weeks after the closing of the mill the dermatoses improved markedly. Arsenic trioxide was considered the primary irritant, although a contribution from sulfur dioxide was possible.

Biologic Levels in Response to Industrial Pollution

Milham and Strong (1974) described community exposure to inorganic arsenic (As_2O_3) as a result of emissions from a copper smelter in Tacoma. Urinary and hair arsenic levels of third and fourth grade children were measured at two schools, one 300 yards from the smelter complex and the other (the control) eight miles away. Children living closer to the smelter had a median urinary arsenic level of 0.08 ppm compared to 0.02 ppm for the control group. Similarly, hair arsenic levels averaged 50 ppm in children near the smelter compared to 3 ppm in the controls. Additional studies showed that urinary arsenic levels decreased with distance downwind from the smelter. Vacuum cleaner dust in homes showed a similar gradient in arsenic levels. An attic dust sample collected near the smelter contained 2100 ppm of arsenic. Weekly urine samples, collected for six consecutive weeks from six children living near the smelter, showed arsenic levels to fluctuate in a synchronous fashion consistent with shifting wind patterns and suggesting inhalation as the primary route of arsenic intake.

Other Effects

Datta (1976) suggested that arsenic contaminated water may have a role in

the pathogenesis of noncirrhotic portal hypertension in India. The arsenic content of one village's water was above 50 µg/l in 19 of 48 wells. High levels of arsenic were found in patients with noncirrhotic portal hypertension. He noted that cirrhosis, noncirrhotic portal fibrosis, and extrahepatic vein obstruction in adults are "very very common" in India. Buchanan (1962) described several other instances of portal cirrhosis apparently related to ingestion of arsenic compounds over a long time period.

EXPERIMENTAL EVIDENCE

Arsenic is the only environmental and occupational carcinogen for man that does not have a counterpart in an animal model (Kraybill, 1976). Fraumeni (1975) noted that largely because of its failure to produce tumors in animals, arsenic has not been accepted universally as a carcinogen.

Human Studies

Detailed investigations into occupational arsenical dermatitis were described by Holmqvist (1951), who studied employees at a copper ore smelting works. Three groups were examined: arsenic workers (heavy exposure to arsenic), other employees at the smelting works (little exposure), and new employees (no exposure).

Arsenic Trioxide

Epicutaneous testing produced positive reactions in 80.4 percent of arsenic workers, 35.2 percent in other workers, and 30.3 percent of new employees. Holmqvist noted that these experiments demonstrated that arsenic trioxide exposure caused sensitization. The progressive stages were described grossly as: erythema, erythema and swelling, papules, vesicles, nonfollicular pustules,

and folliculitis. Age appeared to have no effect on reactivity of the skin to arsenic trioxide.

Sodium Arsenite

Nonsensitive persons showed no reaction until the concentration exceeded 1 percent in solution. The reactions were characterized by erythema, erythema and swelling, pustules, or folliculitis. Individuals sensitive to arsenic trioxide showed reactions to a 1 percent solution of sodium arsenite.

Arsenic Pentoxide

A threshold for toxic reaction on the skin was observed at a 2.5 percent solution in water. Concentrations above 5 percent produced toxic skin lesions; at 40 percent the lesions were very severe with necrosis of the epidermis and outer layers of the corium. Reactions at 2.5 percent were morphological similar to those produced by arsenic trioxide.

Sodium Arsenate

Highly variable responses were observed. Reactions were observed at concentrations as low as 0.01 percent solution, yet in other cases, there was no response to solution concentrations up to 40% sodium arsenate. Generally, a 10% sodium arsenate solution produced reactions similar to those caused by arsenic trioxide and arsenic pentoxide in 1.5% solution.

Calcium and Lead Arsenates

These substances caused responses much less often than the arsenic compounds mentioned above. Holmqvist attributed this to the fact that calcium and lead arsenates are relatively insoluble in water.

Animal Studies

Cancer

With two possible exceptions, attempts to demonstrate the carcinogenicity of arsenic in experimental studies have been unsuccessful. Halver (cited by USEPA, 1976) reported that trout fed a synthetic diet containing Carbarsone developed hepatomas (malignant tumors of the liver). A possible confounding factor was the presence of aflatoxin contamination of the diet. Osswald and Goertller (cited by USEPA, 1976) produced leukemia in both the mothers and their offspring by subcutaneous injections of sodium arsenate in pregnant Swiss mice. Injections of 0.5 mg/kg were given daily for 20 days. Leukemia was observed in 46 percent (11/24) of the mothers, 21 percent (7/34) of the male offspring and 16 percent (6/37) of the female offspring. Only three (all male) of the 55 control offspring developed leukemia. Test offspring given weekly injections of 0.5 mg/kg arsenic for 20 weeks showed an even higher incidence of leukemia: 41 percent of males and 48 percent of the females. Lymphoma was observed in 58 percent (11/19) of mice given weekly injections of 0.5 mg sodium arsenate for 20 weeks.

The International Agency for Research on Cancer (1973) commented that adequate oral studies using arsenic trioxide on mice gave negative results. Also, studies designed to test the cocarcinogenicity to mouse skin among potassium arsenite, sodium arsenate and arsenic trioxide gave negative results. This group further concluded that the studies of Osswald and Goerttler cited above are difficult to interpret and the results await confirmation.

Toxicity

Schroeder and Mitchener (1971) studied the toxicity of arsenic to breeding mice. Five ppm arsenic as an arsenite salt were added to the doubly deionized

drinking water used for the experiments. Mice were inbred and followed through three generations. Arsenic-fed mice survived well through the third generation. Two abnormalities were observed: the ratio of males to females increased from 0.93 in the first generation to 1.71 in the third generation and litter sizes were significantly smaller compared to a control group of mice. These effects were considered minor by the authors.

Dermatitis

Ulcerative lesions were produced in albino rabbits by applying arsenic trioxide-containing material between the shaved neck folds (Birmingham, er al. 1965). These lesions could not be produced by application to open skin. The authors noted that these results were consistent with human experience, in that arsenic trioxide powder does not readily irritate dry skin, but can cause lesions if a certain amount of trauma, such as warmth or moisture, is present.

ADDENDUM

Baker et al. (1977) studied arsenic absorption in children living in towns near eleven U.S. copper smelters. These children were one to five years old and were compared to children in three control towns. All children in the copper smelter towns lived within four miles of the smelter. In all eleven smelter towns, the mean hair arsenic levels were significantly elevated over that of the controls, indicating increased external exposure to arsenic. Similarly, mean arsenic levels in the urine were significantly higher than the controls in eight of the eleven towns, reflecting increased systemic exposure. Arsenic levels in the hair appeared to be correlated with arsenic levels in the urine.

Authors believed that the major routes of uptake were inhalation and ingestion of arsenic particulates deposited by smelters in air, dust, and soil. One town also had arsenic present in its drinking water at a level above the standard set by the Environmental Protection Agency. Emission characteristics and proximity of residences to the smelter were judged to be the most important factors relating to arsenic absorption in children. The authors found the significance of these findings to be difficult to assess, but did suggest follow-up studies to see if there is any relationship between these exposures and effects on health.

Baker, E.L. and C.G. Hayes, P.J. Landrigan, R.T. Leger, J.L. Handke and J.M. Harrington 1977. A nationwide survey of heavy metal absorption in children living near primary copper, lead, and zinc smelters. American Journal of Epidemiology 106:261-273.

Table 1: Arsenic content in feed of some U.S. smelters.

SMELTER	AVERAGE PERCENT ARSENIC IN FEED
Tacoma, Washington (Asarco)	5.2
Anaconda, Montana (Anaconda)	0.96
El Paso, Texas (Asarco)	0.80
Garfield, Utah (Kennecott)	0.135
Hayden, Arizona (Asarco)	0.040
Hayden, Arizona (Kennecott)	0.015
San Manuel, Arizona (Magma)	0.007
Hurley, New Mexico (Kennecott)	0.005
White Pine, Michigan (Copper Range)	0.002

SOURCE: Nelson (1977).

Table 2: Cohorts in Lee and Fraumeni (1969) study.

COHORT	LENGTH OF EMPLOYMENT
1	15 or more years, with 15th year completed before 1938.
2	15 or more years, with 15th year completed between 1938 and 1963.
3	10-14 years
4	5-9 years
5	1-4 years

Table 3: Respiratory cancer SMR's in smelter workers according to arsenic exposure.

Cohort	Respiratory Cancer Mortality	All Members of cohort	Maximum exposure to arsenic (12 or more months)* Heavy	Medium	Light
1	Observed	61	8	22	14
	Expected	13.0	1.0	3.3	5.6
	SMR**	469+	800+	667+	250+
2	Observed	37	6	12	9
	Expected	10.0	0.9	2.2	2.9
	SMR	370+	667+	545+	310+
3	Observed	10			
	Expected	4.3			
	SMR	233++			
4	Observed	15	4	10	22
	Expected	5.6	0.9	3.8	10.3
	SMR	268+	444++	263++	214+
5	Observed	24			
	Expected	11.8			
	SMR	203+			

*This does not include 2,862 men who worked less than 12 months in their category of maximum arsenic exposure and who had an SMR of 286+

**SMR = Standard Mortality Rate or: (Observed/Expected) x 100.
+significant at 1% level
++significant at 5% level

SOURCE: Lee and Fraumeni (1969).

Table 4 Percent of deaths due to selected causes at a chemical plant.

	EXPOSED TO ARSENIC	CONTROL
Malignant neoplasms	32.9%	20.7%
-Respiratory system	16.2%	5.7%
-Lymphatic and hematopoietic tissues, except leukemia	3.5%	1.4%

SOURCE: Ott et al. (1974).

Table 5: Observed and expected deaths due to respiratory malignancies, by exposure category.

TIME-WEIGHTED AVERAGE CONCENTRATION TIMES MONTHS OF EXPOSURE	DAILY TWA DOSE, $\mu g/M^3$*	OBSERVED DEATHS	EXPECTED DEATHS	OBSERVED/ EXPECTED
<1	1	1	1.77	0.6
1-1.9	3	2	1.01	2.0
2-3.9	6	4	1.38	2.9
4-5.9	10	3	1.36	2.2
6-11.9	20	3	1.70	1.8
12-23.9	40	2	0.97	2.1
24-59.9	90	3	0.77	3.9
60-95.9	160	5	0.79	6.3
96+	740	5	0.72	7.0

*Calculated by Blejer and Wagner (1976).

SOURCE: Ott, et al. (1974).

Table 6: Symptoms and signs of arsenic poisoning.

Symptom Group	Symptoms
Gastro-intestinal	metallic taste in mouth garlic odor of breath dryness of mouth and throat burning pain in stomach profuse diarrhea blood "rice water" stool
Dermatologic	skin eruption skin ulceration perforation of nasal septum
Musculoskeletal	muscular cramps
Circulatory	rapid, feeble pulse cold, clammy extremities increased capillary permeability sighing respiration cyanosis
Neurologic	frontal headache vertigo depression stupor convulsions

SOURCE: Reeves (1976).

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CADMIUM AND HUMAN HEALTH

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INTRODUCTION

Cadmium was first isolated from pharmaceutical zinc carbonate by Strohmeyer of Gottingen in 1817 (Browning, 1969). He observed it as the yellow tinge in a sample of iron-free zinc carbonate. Before this time, there was no distinction made between zinc and cadmium, although the name "cadmia" had been given to the earth-like substance used in the manufacture of bronze in the first century A.D. by Dioscorides and Pliny (Prodan, 1932a). The first use of cadmium was as a pigment, but in 1906, cadmium metal was commercially extracted from a by-product of zinc ore smelting and by 1917 domestic cadmium production reached 100 tons (DeFilippo, 1975). Production continued to rise and by 1974 world production was 18,800 short tons.

Some of the uses of cadmium include: protective coating for iron, steel, and copper; alloy with copper for coating telephone cables, trolley wires, and welding electrodes; alloy with lead, bismuth, silver or nickel; pigments resistant to high temperatures in manufacture of glass and paints; nuclear reactor neutron absorbers; and insecticides for fruit (Browning, 1969). Cadmium is also used in the manufacture of electrical conductors, bearings, ceramics, vapor lamps, dental prosthetics, and storage batteries, as well as rust-proofing of tools and other steel articles (Louria, 1972). During times of metal shortages, such as World War II, its uses increased and have included cooking utensils and parts for automobiles.

Cadmium is present in the earth's crust at concentrations of about 150 parts per billion (ppb), and is usually closely associated with zinc in a zinc to cadmium ratio of about 100. Fresh water generally has less than 1.0 ppb of cadmium (Fassett, 1975).

Schroeder and Balassa (1961) reported that the cadmium intake in man may vary from 4 to 60 micrograms per day, depending on the foods chosen. Friberg et al. (1975) reported that the average diet in the United Kingdom probably contains 0.01 to 0.02 µg/g. This results in an average daily intake of 15 to 30 µg.

A study by Thomas et al. (1973) found concentrations of cadmium in canned food ranging from 0.01 to 0.18 ppm, with a mean of 0.02 ppm. They determined that canned food in the average English diet resulted in two percent of the suggested weekly intake of 350 micrograms of cadmium.

Schroeder and Balassa (1961) indicated that cadmium was found in appreciable but small amounts (up to 1 µg/l) in some water samples in contact with galvanized iron pipes overnight. In a review by Flick et al. (1971), it is reported that cadmium was sufficiently high in many water samples to constitute grounds for rejection according to the U.S. Public Health Service drinking water standard of 0.01 mg/l. Although the cadmium content of our waters may have little influence on our total daily intake of cadmium, it does accumulate over time (Schroeder and Balassa, 1961), and may be taken up by food products, resulting in disease (Tsuchiya, 1969).

Cadmium in the air may also contribute small amounts to total daily intake. Schroeder (1970) indicated that cadmium in urban air ranges from 0.002 to 0.37 $\mu g/m^3$, while in nonurban areas, the range is from 0.0004 to 0.026 $\mu g/m^3$. He concluded, "There is little question that cadmium in air is a real and present hazard to human health."

A significant portion of the daily intake may be attributed to smoking cigarettes. Lewis et al. (1972) have shown that cigarettes contain appreciable

amounts of cadmium, and that smokers accumulate more cadmium in their tissues than nonsmokers. This was also shown to be directly related to the number of pack-years smoked.

The total body burden for the "American Standard Man" has been reported by Schroeder and Balassa (1961) as 30 mg; however, there appears to be much variation within a country as well as among countries, in this value. Kubota (1968) reported concentrations of cadmium in human blood from 19 locactions within the U.S. and found no consistent geographic pattern. The median value was 0.7 µg/100 ml; 83 percent were below one µg cadmium/ 100 ml; and the highest mean, occurring in North Dakota, was 7.99 µg/100ml. Schroeder and Balassa (1961) have shown that cadmium is nearly absent in the newborn, accumulates in the kidney for the next fifty years, and then declines.

OCCUPATIONAL EXPERIENCE

Prodan (1932a) reported that the first toxic effects of cadmium on man were recorded by Sovet in 1858. He reported pneumonia occurring in those polishing silverware with cadmium carbonate. Prodan also mentioned that in 1920, Stephens reported chronic exposure to cadmium by zinc smelter workers led to nausea, loss of appetite, thirst, and diarrhea or constipation. Since these early reports, there have been many cases reported, indicating the toxicity of cadmium to workers with both acute and chronic exposure. Acute occupational exposures result primarily in respiratory problems, while chronic exposures may have kidney and metabolic involvement as well as respiratory.

The American Conference of Governmental Industrial Hygienists (1975) has set the Threshold Limit Value (TLV) for occupational exposure to cadmium metal

dust and soluble salts at 0.2 mg/m^3 (recommended change to 0.05 mg/m^3). The TLV for cadmium fume is presently 0.05 mg/m^3.

Acute Effects

Acute industrial cadmium poisoning occurs from inhalation of cadmium metal fume in concentrations of several milligrams/m^3 (Louria, 1972) and generally results in pneumonitis and pulmonary edema (Kazantzis, 1976) with a mortality rate of 15-20 percent (Bonnell, 1965; Flick et al., 1971; and Louria, 1972). During the exposure, there are no clinically apparent symptoms (Louria, 1972), and, therefore, the worker is unaware that he is being poisoned. The first symptoms generally appear 4 to 20 hours after exposure and are characterized by dyspnea, cough, and a feeling of chest constriction (Louria, 1972). Other symptoms reported are shown in Table 1. Paterson (1947) studied the lungs of two cases of accidental death due to cadmium oxide exposure. In both cases, the lesions were confined to the lungs. He determined that acute pulmonary edema begins within a few hours of exposure, and lasts for several days. After this stage, proliferation of the lung parenchyma begins, which lasts until about the tenth day after exposure. These two cases, however, died on the fifth and eighth days after exposure. Barrett et al. (1974) also reported that the lung is the primary target of acute exposures. They analyzed the lung tissue from the above two cases of cadmium oxide exposure, and found 1.7 and 1.8 mg cadmium per 100 grams dry tissue.

Beton et al. (1966) described the accidental poisoning of five workers cutting cadmium-plated bolts with an oxyacetylene burner. They were in an enclosed work space for five hours with no ventilation, and were unaware that the cadmium oxide fumes produced were harmful. One man died on the fifth day after exposure,

having experienced breathlessness, irritating cough, and cyanosis. The necropsy showed respiratory tract involvement, and necrosis of kidney tissue, with the other organs being normal. The four patients surviving the incident experienced a variety of symptoms including cough, malaise, shivering, sweating, headaches, and myalgia. The resporatory involvement lasted about a week, showing signs of pulmonary edema and possibly bronchopneumonia. Using a respiratory rate of 20 liters/minute, and a lung retention of 11 percent of the cadmium oxide, Beton calculated the lethal dose in this instance to be 8.6 mg/m^3 for five hours.

Chronic Effects

The long-term exposure to low levels of cadmium appears to be much more widespread, and also more difficult to diagnose. Hardy and Skinner (1947) suggested the possibility of chronic cadmium poisoning in five men working in a plant which manufactured cadmium faced bearings. The symptoms reported included fatigue, dental trouble, reduced hemoglobin, gastrointestinal problems and respiratory troubles on damp days. These workers had exposures from 4 to 8 years, and all had detectable cadmium in their urine. The most common symptoms in chronic exposures are shortness of breath due to emphysema, and excretion in the urine of a characteristic low molecular weight protein (Bonnell, 1965). Other effects reported in the literature include: total or partial loss of smell, coughing, depressed appetite, weight loss, and generalized irritability (Flick et al., 1971). Many of these chronic exposures as well as the acute poisonings were due to improper ventilation, before the toxic nature of cadmium fumes was realized (Smith et al., 1960).

Respiratory Effects

Friberg (1948) studied workers exposed to cadmium oxide dust at an alkaline battery plant. Of 17 workers with more than eight years of exposure, 15 were suffering from emphysema.

The clinical impression of an industrial medical officer (Holden, 1965) working with 23 men in a cadmium-copper factory, was: "there is no doubt, that inhalation of cadmium oxide fume causes emphysema." According to lung function tests he performed, 8 of the 23 workers had som degree of emphysema.

Bonnell (1955) described the exposure of 100 men to cadmium fume from several factories manufacturing an alloy of copper-cadmium. During his initial examination, he found nine men with emphysema and proteinuria, three men with emphysema only, and four others who had been forced to give up work due to severe dyspnea. Kazantzis (1956) using this same group of men, performed ventilatory function tests, and found a significant difference between them and a control group from the same plant. A follow-up of these men (Bonnell et al., 1959) five years later showed that respiratory function tests indicated greater deterioration in performance in those suffering from emphysema, even though most of them had no further cadmium exposure.

Another study (Kazantzis et al., 1963) investigated workers at a small plant manufacturing cadmium pigments, and found that of six workers exposed for more than 25 years, three had mild respiratory symptoms, and one died at the age of 46 from respiratory insufficiency and emphysema.

A study on the pathological effects of cadmium fume (Smith et al., 1960) examined five cases of death from emphysema, without evidence of chronic

bronchitis. Because of the lack of preliminary bronchitis, they concluded there must be a direct effect on the alveolar walls. The fumes appeared to be highly reactive, very small in size, and with no color or immediate irritant effect. This would allow them to be inhaled in fatal concentrations producing severe damage to alveolar walls. Prolonged, milder inhalation could lead to the emphysema observed. Smith et al. (1960) also indicated that the initial site of deposition is the lung; but after long term exposure, cadmium is distributed to other parts of the body with little remaining in the lung.

Lauwerys et al. (1974) observed a significant reduction in ventilatory function in 22 men exposed for more than 20 years to cadmium dust below the American TLV of 0.2 mg/m^3. They also indicated that workers exposed from 1 to 20 years showed a decrease in all pulmonary indices; however, the differences were not significant. They recommended the TLV be reduced to 0.05 mg/m^3.

Kazantzis (1976) reported that respiratory impairment and increased breathlessness during exertion have developed after exposure to cadmium fume or dust. He explained that in most cases, this was slowly progressive, although more rapid in a few, ultimately leading to death from respiratory insufficiency.

Proteinuria

Friberg (1948) reported on workmen exposed to 0.002 to 0.9 mg of cadmium oxide per liter of air in an alkaline battery plant. The workers had complained of fatigue, nervousness and irritability; increased thirst and parched mouth; cough and shortness of breath. Proteinuria was found in 18 of the 19 workers with more than eight years exposure, and in none of the 19

workers with one or two years exposure. In 14 of the proteinuria cases, impaired kidney funciton was observed, while all eight blood samples examined showed biochemical changes indicating the possible occurrence of a low molecular weight protein which is not found in healthy persons.

Potts (1965) reported on the health effects of 70 men exposed for more than six years to cadmium oxide dust during the manufacturing of alkaline batteries. Proteinuria was present in 31 (44 percent) of these men. In the 11 men with more than 30 years exposure, 9 (82 percent) had proteinuria. Another study (Tsuchiya, 1967) found that workers smelting alloys of silver and cadmium had urinary protein levels significantly higher than controls after exposures from 9 months to 12 years. It was determined that concentrations a little over the TLV would cause workers to excrete higher amounts of protein than a nonexposed group. Studies of copper-cadmium alloy workers (Bonnell 1955; Bonnell et al. 1959, and Kazantzis 1956) indicated that the first signs of chronic cadmium poisoning can occur after a long latent period, and the renal lesions may be the most important part of the disease. Forty-three of the original 100 men they examined experienced some form of cadmium poisoning, most including proteinuria.

In the study of the pigment workers by Kazantzis et al.(1963), all six men exposed for more than 25 years showed proteinuria and evidence of renal tubular malfunction. Three of the 4 workers with 12 to 14 years exposure were excreting above normal levels of protein, although no clinical proteinuria was present in this group.

Lauwerys et al. (1974) found proteinuria in 15 percent of the workers they studied with less than 20 years of cadmium exposure. The average total cadmium dust concentration was 134 $\mu g/m^3$, and the highest average respirable dust in this group was 88 $\mu g/m^3$. Proteinuria was present in 70 percent of

the men with more than 20 years exposure and still working. The average total and respirable dust in this group was 66 $\mu g/m^3$ and 21 $\mu g/m^3$, respectively.

Kjellstrom (1976) reviewed the epidemiological studies of proteinuria due to chronic cadmium exposure. He concluded that 10 to 20 years of exposure to cadmium fume or dust concentrations of about 50 $\mu g/m^3$ can result in proteinuria. Kjellstrom (1976) calculated that it would require 10 to 15 µg of cadmium dust/m^3 of air for 25 years to reach the critical concentration in the human kidney cortex of 200 µg/g, which has been reported by others (Nordberg, 1976). Some of this data is shown in Table 2.

Other Effects

Although the major effects of chronic cadmium poisoning are emphysema and proteinuria, many other deleterious effects have been reported in literature.

Several studies have indicated there may be a relationship between cadmium exposure and cancer. Potts (1965) reported that five of eight observed deaths among battery workers were due to cancer, three of them being cancer of the prostate. Lemen et al. (1976) studied the causes of death in a cadmium smelter from 1940 to 1974. They compared the mortality of 292 workers to the U.S. population and found excess deaths from total malignant neoplasms (27 observed vs 17.51 expected), respiratory system tumors (12 vs 5.11) and prostate tumors (4 vs 1.15 for the entire cohort and 4 vs 0.88 for those who had lived for at least 20 years after their first exposure to cadmium). The National Institute for Occupational Safety and Health (1976) reported that these workers were also exposed to many other compounds including arsenic, however, the amounts were considered "insignificant".

Olfactory damage, or anosmia, is an often cited effect of chronic cadmium

exposures (Flick et al., 1971; and Louria et al., 1972). The initial study by Friberg (1948) indicated that 12 of the 19 men with more than 8 years exposure suffered from a loss of smell, while none of those in the control group had this impairment. In Pott's (1965) study of the 70 battery workers, he found that 65 percent of those with 10 to 19 years exposure had anosmia, compared with 53 percent of those with 20 to 29 years, and 91 percent of those with 30 to 40 years exposure. Anosmia was also found in the pigment workers studied by Kazantzis et al. (1963).

Other indications of renal damage in workers with cadmium exposure include glycosuria and aminoaciduria. These symptoms have been mentioned by Potts (1965); Kazantzis et al. (1963); Kazantzis (1976); Bonnell (1965); and Nordberg (1976).

Among the other symptoms reported are reduced hemoglobin and anemia (Flick et al., 1971; Hardy and Skinner, 1947; Nordberg, 1976; and Tsuchiya, 1967), dental troubles, including yellowing of the teeth (Bonnell, 1965; Flick et al., 1971; Hardy and Skinner, 1947; and Kazantzis, 1976), rhinitis (Bonnell, 1965,; Holden, 1965; and Kazantzis, 1976), epistaxis (Holden, 1965, and Kazantzis, 1976), skeletal changes (Bonnell, 1965, and Kazantzis, 1976), and generalized tiredness and irritability (Flick et al., 1971,; Holden, 1965; and Kazantzis, 1976).

NONOCCUPATIONAL EXPERIENCE

Acute Effects

Acute poisoning is generally a result of inadvertent ingestion of a food or drink containing high concentrations of cadmium. Flick et al. (1971)

reported that prior to 1941 only 20 cases of cadmium poisoning via the oral route had been reported, while in the next 5-year period (1941-1946), there were at least 689 cases documented. The symptoms reported included: severe nausea, salivation, vomiting, diarrhea, abdominal pains, and myalgia. Frant and Kleeman (1941) reviewed the history of cadmium food poisoning and reported on four outbreaks they had investigated. The first reported cases were by Wheeler in 1876, when two patients were given cadmium bromide from a mislabled bottle. In 1928, an outbreak was reported in Los Angeles from fruit juice served in cans coated with cadmium. Other outbreaks reported included: a dessert made in an ice cube pan which had been cadmium coated; coffee made in a kettle which had been treated with hydrochloric acid containing cadmium salt; and food made in a cast iron roasting pan which had been electrolytically plated with cadmium. The four outbreaks investigated by Frant and Kleeman (1941) involved a food or drink prepared in a cadmium plated ice cube tray or pitcher. The symptoms experienced were nausea, abdominal pains, vomiting, and diarrhea. The cadmium concentration in the food ranged from 67 ppm to 530 ppm. A more recent episode resulted from persons eating candy beads containing large amounts of cadmium (Louria et al., 1972). The gastrointestinal symptoms occurring in all these outbreaks generally appeared within 0.5 to 5 hours after intake (Louria et al., 1972).

Itai-itai Disease

Most of the chronic cadmium poisoning reported from occupational exposures are in men. Itai-itai, however, occurs in women over the age of 45 who have had multiple pregnancies (Louria et al., 1972). The disease was observed in a small farming community near the city of Toyama in Japan (Tsuchiya, 1969). The name, which means ouch-ouch disease, was first used by Kono in 1955.

Studies by Hagino, Kobayashi, and Yoshioka in the late 1950's indicated that cadmium was the most probable etiological agent (Kjellstrom, 1976). The clinical symptoms usually begin with lumbago, followed by pain in the groin and joints, waddling gait, and eventually confinement to bed. X-ray films show bone deformity, decalcification, thinning of the cortex, and thickening of the bones (Tsuchiya, 1969). These bone fractures often resulted in shortening of height. Proteinuria and glycosuria were present in all cases.

Pathological findings indicated that the disease was a type of osteomalacia, and that death in some of the cases was due to disturbed nutrition (Tsuchiya, 1969). Tsuchiya (1969) indicated that 56 deaths had been attributed to itai-itai up to that time.

The cadmium contamination resulted from a mining operation nearby which began production in 1874. The mine was located upstream from the community, on the river used for irrigation of their rice crop. While the water contained less than 0.01 ppm cadmium, the levels found in rice ranged from 0.37 ppm to 3.36 ppm, depending on where in the irrigation system it was grown. Rice crops irrigated by other river systems nearby showed values from 0.05 to 0.07 ppm cadmium. The hypothesis of the interactions occurring in the causation of itai-itai disease deduced by the investigating group is given in Figure 1.

The group found that this disease was not a result of the cadmium acting alone, but instead resulted from an interaction between the cadmium, the zinc or lead present, and a vitamin D deficiency (Tsuchiya, 1969). Recent epidemiological investigations by Kjellstrom (1976) have indicated that an average cadmium concentration in rice of 0.4-0.6 μg/g may be coupled with an increase in proteinuria, in the exposed population over 40-50 years of age.

Other Reported Health Effects

It has been suggested that cadmium may have a role in hypertension, bronchitis, and lung carcinoma (Louria et al., 1972). In a review of cadmium, Fassett (1975) concluded that the relationship between cadmium and hypertension or cardiovascular disease is unlikely, and that there is no good evidence indicating its role in carcinogenesis. Nordberg (1976), however, has stated that effects other than renal and pulmonary, include hypertension, liver disturbance, effects on bone tissue, and endocrine functions, as well as genetic, carcinogenic, and teratogenic effects. The only effects which appear to have any human data are those related to hypertension, and heart disease. Other effects will be considered with the animal studies.

Hypertension

Schroeder (1965) studied 187 adults from 10 United States cities and 171 adults from 22 other cities throughout the world. He found that the concentrations of renal cadmium, and the cadmium to zinc ratios were markedly higher in those patients dying of hypertensive causes. In this study, hypertension included hypertensive cardiovascular disease, cerebral hemorrhage, toxemia of pregnancy, and left ventricular hypertrophy.

Because of the variation between countries in levels of cadmium and zinc, it was more meaningful to compare the ratios. The cadmium/zinc ratio in the U.S. was 0.79 for patients dying of hypertension, and 0.60 for those dying in accidents, while in foreign countries it was 0.94 for hypertensive deaths, and 0.66 for accidents. Comparing various countries, Schroeder has shown that, in Japan, where renal cadmium averages 6030 ppm ash, hypertension accounts for 22.6 percent of all deaths, while in the U.S., with a mean renal cadmium value of 3200, 15.9 percent of the deaths are hypertensive related. In Cairo, where the mean renal cadmium is 1300 ppm, 2.5 percent of deaths are related to

hypertension. Schroeder concluded that there is a suggestive relationship between renal cadmium and hypertension, although no cause and effect has been established yet. Further studies (Schroeder, 1970) found that urine of hypertensive patients contained 40 times as much cadmium as normotensive patients.

Heart Disease

Carroll (1966) found a correlation between the average concentration of cadmium in the air, and the death rates from hypertension and arteriosclerotic heart disease. For air cadmium levels, he used the geometric mean of 26 samples reported by the National Air Sampling Network in 1960 or 1961. These data were available for 28 cities in the U.S. Death rates were determined for the county which each city was in, and they were standardized for age, sex and race. The mortality ratios for diseases of the heart (except rheumatic diseases) correlated significantly with the cadmium levels in the air. The coefficient of correlation was 0.76. Other possible explanations, such as a correlation between air pollution level and heart diseases, or an inverse relationship between hardness of drinking water and heart disease were ruled out. This study, like those of Schroeder (1965, 1970) did not establish a cause and effect, but does indicate there may be some relationship.

EXPERIMENTAL EVIDENCE

Prodan (1932a) reported that the earliest experiments to determine the toxicity of cadmium were done by Marme in 1867. Some of the lethal doses he determined for cadmium salts include: intravenous injection of 30 mg for dogs, 16 mg for cats, and 10 to 20 mg for rabbits; subcutaneous injections 2 to 3 times these amounts, and 15 mg for pigeons; and oral adminstration of

300 to 600 mg for rabbits. Symptoms produced by the cadmium, regardless of method of introduction were: vomiting, diarrhea, loss of energy, loss of appetite, and finally death.

After a review of the literature, Prodan (1932a) concluded that cadmium in small doses is lethal to experimental animals. He also indicated that cadmium causes a direct paralyzing effect on the central nervous system, and ingestion of cadmium induces vomiting. In his own studies, Prodan (1932b) found that cadmium poisoning could be produced in cats by inhalation. Large doses resulted in development of edema in the lungs, while smaller doses led to pneumonia and emphysema. Cadmium excretion was found to be very slow, and accumulation occurred in the kidney, liver, and bone.

Acute Intoxication

Barrett et al. (1947) reported that cadmium oxide inhalation resulted in 11 percent retention in the lungs in all animals studied. Pathological examinations of rats after inhalation of cadmium oxide and cadmium chloride indicated that the lung is the primary organ affected (Paterson, 1947). The stages observed were: 1) acute pulmonary edema within 24 hours of exposure; 2) proliferative interstitial pneumonitis from the third until the tenth day after exposure; and 3) permanent lung damage. About 25 percent of the animals surviving an exposure large enough to produce symptoms, showed residual pulmonary fibrosis. The safe dosage of cadmium oxide for rats was determined to be 125 min.-mg/m^3. Extrapolations from this indicated that a safe concentration for industrial exposed workers would be 50 min.-mg/m^3 for an 8-hour day, or 0.1 mg/m^3 in the factory air.

Studies by Kawai et al. (1976) indicated that many organs may be affected by acute intoxication. The kidney, pancreas, and testes all developed necrotic

lesions while the gastrointestinal tract, salivary glands, spleen, and prostatic glands were also found to be sensitive.

Chronic

Izmerov (21) has reported on studies determining the toxicity of 0.01 mg/l to 100 mg/l cadmium sulfate in drinking water. This water was fed to rabbits for 255 or 122 days. Although no external symptoms were observed, histological examination indicated marked degeneration in the internal organs of the rabbit given water with 100 mg/l, and slight changes in the kidneys of the rabbit given 0.1 mg/l. In rabbits given 300 µg/g $CdCl_2$ in their food for 54 weeks, a relationship was found between dose, cadmium level in renal cortex, urinary excretion of cadmium, and signs of renal dysfunction (Nomiyama et al., 1976). Observations included aminoaciduria and enzymuria at levels of 200 µg/g in the renal cortex, and proteinuria and glycosuria at 300 µg/g. They also found that the same cadmium dose does not always result in the same cadmium level in the renal cortex, and the same level does not always result in the same response.

Studies on rats given 10 to 200 ppm cadmium in drinking water showed effects on bone, spleen, salivary glands, pancreas, gastrointestinal tract, and kidney after 37 weeks (Kawai et al., 1976). At levels of 50 ppm, lesions were found in the kidney and interstitial edema was evident. After administration of 200 ppm for 18 months, renal lesions had progressed to interstitial fibrosis and moderate anemia was present in all groups receiving over 100 ppm. The latent period in this investigation was estimated to be three to four months for higher doses, and 6 to 12 months for moderate doses. However, there was not a good correlation between the level of cadmium in the kidney, and the toxic responses.

Friberg et al. (1975) concluded that histological changes in bone may be the earliest signs of chronic cadmium exposure, although the renal tubules are still the critical organs. They also indicated that experimentally induced osteomalacia has been reported in rats.

Hypertension

Schroeder (1967) found that rats given 5 µg/ml of cadmium in their drinking water would develop hypertension after one year. This was shown to be very similar to the hypertension occurring in humans. Females had a greater incidence, males had a greater mortality, and both sexes had a decreased life-span when compared to control rats. This study also showed that the rats given soft water with cadmium had an 80 percent chance of developing hypertension, while those given hard water had only a 17.7 percent chance. It was found that the ratio of cadmium to zinc was more influential than the absolute amounts of cadmium in the kidney in determining which rats would become hypertensive. The kidneys of the rats which were hypertensive had an average Cd/Zn ratio of 1.02, while the normotensive rats averaged 0.35. When the hypertensive rats were treated with zinc to replace the cadmium in the kidney, they become normotensive. A good correlation was established between Cd/Zn ratio of kidneys and hypertension. A ratio of 0.64 or greater sometimes resulted in hypertension, while a ratio of 0.80 always resulted in hypertensive rats.

Perry and Erlanger (1974) showed that rats given concentrations from 1.0 to 5.0 ppm cadmium in drinking water had an average increase in systolic blood pressure of 13 to 19 mm Hg. This was significantly different from the controls. Rats given 10 to 25 ppm cadmium, however, showed less of an increase, while those given 50 ppm were sick and showed a decrease in systolic blood pressure.

Fischer and Thind (1971) indicated that cadmium in blood vessels at a concentration of 1.0 µg/gm tissue may play a role in the pathophysiology of hypertension. They determined the cadmium levels in the kidneys of normotensive rabbits to be 0.290 µg/gm, and the liver 0.077 µg/gm, while hypertensive rabbits showed kidney levels of 35.64 µg/gm, and liver values of 33.36 µg/gm of tissue. The growth and development of these rabbits was unaffected throughout the experiments.

Other Reported Effects

Parizek (1960) found that within a few hours of injection of $CdCl_2$ into rats, testicular changes occurred. The testes increased considerably in size, edema occurred, and they changed to a blue or violet color. Within a few days, they decreased in size and became small, firm, dirty-yellow scars. He determined that complete necrosis of rat testes could be produced with a subcutaneous injection of 0.02 mmole/kg body weight. Histological changes occurred within the first hour after injection. The rats survived in good condition for more than two years following the experiments. Necrotic testicular changes were also observed in mice, rabbits, guinea pigs, and hamsters. Although this has not been demonstrated in man, human sperm cells have been affected by cadmium in vitro (Parizek, 1960). It appears that a certain threshold must be exceeded for this effect to occur in animals, and this is probably determined by the relationship between cadmium and zinc. Parizek indicated that protection by zinc occurred at levels 80 to 200 times the molar equivalent of cadmium.

Further studies indicated that the cadmium cations cause selective circulatory damage in the tests and other estrogen-producing organs (Parizek, 1964). An injection of 0.02 M solution of cadmium salt subcutaneously into 70 pregnant rats between the 17th and 21st days of gestation, caused complete destruction

of the placenta within 24 hours. Changes in the gonads of the male mice included edema, hyperemia, hemorrhage, and vascular thrombosis, resulting in testicular necrosis.

Lucis et al. (1972) reported that interstitial cells within the testes of rats can undergo proliferation, when damaged by cadmium, and form tumors. They also indicated that fibrosarcomas occasionally formed at the site of injection.

Studies by Ferm and Carpenter (1967) showed that cadmium sulphate can be teratogenic in hamsters and that this effect can be inhibited by zinc. An intravenous injection of 2 mg/kg $CdSO_4$ into pregnant hamsters caused malformations, mostly in the jaw and face, in 66 percent of the offspring. Simultaneous injection of 2 mg/kg $ZnSO_4$ almost completely inhibited the teratogenic effect. The maternal animals in these studies survived well, and no pathological changes were observed after death.

Barr (1973) reported that $CdCl_2$ is teratogenic in rats. Intraperitoneal injections of 7 to 18 μM/kg were given to pregnant rats on the 9th, 10th, or 11th day of gestation. The animals lost weight for several days, but did not differ from the controls by day 21. Malformations occurred in the abdominal wall, the forelimb, the diaphragm, and the anus, and differed between the strains of rats used. Subcutaneous cadmium was shown to be nonteratogenic in these studies.

Friberg et al. (1975) concluded that it is difficult to make any correlation between the teratogenic effects in animals, and possible effects in man. The number of species studied has been small, and all teratogenic effects have been produced by injection.

Physiological Mechanisms and Interactions

There is a great deal of information in the literature in regards to possible mechanisms of cadmium metabolism and interactions with other substances. Some of these ideas are discussed below.

Webb (1972) indicated that preinjection of zinc into male rats, before administration of cadmium, partially protects against changes in the testes. Zinc apparently induces synthesis of a cadmium binding protein, and the cadmium ions accumulate and are immobilized. It was found that when the cadmium was injected, it did not replace the zinc or the protein, but stimulated synthesis of more protein.

Nordberg (1972) studied cadmium metabolism in mice using autoradiography. He found that cadmium is rapidly transported from the blood to the tissues, and very slow changes occur in organ distribution after this. In the blood, cadmium is eliminated quickly from the plasma and accumulated in the blood cells. Shortly after injection, cadmium in the blood cells was found to be bound to large proteins, but later became bound to a small protein called metallothionein.

Nordberg (1972) found that mice accumulate cadmium until renal tubular damage occurs, and then increase the amount excreted in the urine. He found that fecal excretion was dependent on the daily dose, while urinary excretion was dependent on the total body burden. Although this has not been established in man, it does indicate some possibility for monitoring urine samples to indicate early kidney damage. It was also indicated that pretreatment of the mice with small doses of cadmium would stimulate

metallothionein formation, and this was capable of preventing necrosis of the testes from acute exposures.

In addition to these interactions with zinc and metallothionein, it has been reported that cadmium has an effect on calcium and vitamin D metabolism. Friberg et al. (1975) indicated that calcium-deficient rats have a higher cadmium uptake, and there is a high prevalence of renal stones among cadmium workers. This suggests a disturbance of the calcium and phosphorus metabolism. Friberg et al. (1975) also reported that cadmium in vitro and in vivo may inhibit enzyme activities which affect the formation of vitamin D in the kidney tubular cells, but that the data are insufficient to explain the role of cadmium in bone mineral metabolism.

ADDENDUM

Baker et al. (1977) studied cadmium absorption in children living in towns near eleven U.S. copper smelters. These children were one to five years old and were compared to children in three control towns. All children in the copper smelter towns lived within four miles of the smelter. In nine of the eleven smelter towns, the mean hair cadmium levels in these children were significantly higher than that of the controls, indicating increased external exposure to cadmium.

The authors believed that the most important factors relating to cadmium absorption were the smelter emission characteristics and proximity of residences to the smelter. The biologic significance of these findings were characterized as difficult to assess. Follow-up studies were recommended to help determine if there are any effects on health from the low level cadmium exposures observed in this study.

Baker, E.L. and C.G. Hayes, P.J. Landrigan, R.T. Leger, J.L. Handke and J.M. Harrington 1977. A nationwide survey of heavy metal absorption in children living near primary copper, lead, and zinc smelters. American Journal of Epidemiology 106:261-273.

Table 1. Clinical features of acute cadmium poisoning.

During Exposure (latent period 0-4 hours)
few symptoms; cough
slight irritation of throat and mucosae
Stage of Irritation (4-10 hours)
irritation of throat with feeling of constriction
cough
tight chest
pain in chest on coughing
dyspnea
malaise, ague, chill
sweating
shivering
aching pains in back and limbs
headaches and dizziness
metallic taste in mouth
irritation and soreness after smoking
Stage of Pulmonary Reaction (8 hours to 7 days)
severe dyspnea and wheezing
chest pain and precordial constriction
persistant cough
weakness and malaise
anorexia, nausea, and perhaps diarrhea and nocturia
abdominal pain after meals
hemoptysis
prostration

SOURCE: Beton et al. (1966)

Table 2. Epidemiological data from industrial exposures resulting in Proteinuria

Estimated Air Concentration	Exposure Time	Number with Proteinuria/ Number Studied
40-50 $\mu g/m^3$ CdO fume	Controls	1/60
	<9 years	6/22
	9-13 years	7/15
	14-18 years	9/19
	19-23 years	8/14
	>23 years	7/30
Average for worker with longest exposure time 114 $\mu g/m^3$ (range among air samples 24-1220 $\mu g/m^3$)	<10 years	0/14
	>10 years	3/5
Total dust 130-1170 $\mu g/m^3$	1-12 years	7/16
Total CdO dust 400-15,000 $\mu g/m^3$	1-5 years	0/26
	6-10 years	1/4
	11-15 years	3/9
	16-20 years	6/12
	21-25 years	3/9
	>26 years	6/9
Total dust 500 $\mu g/m^3$	>5 years	20%

SOURCE: Nordberg (1976)

Figure 1. Interaction of agent, host and environment in the causation of Itai-itai disease.

Mine	→→	Waste piles water	→→	River contamination	→→	cadmium lead zinc	→→
Contamination of drinking water	→→	contamination of rice paddy	→→	contamination of food and drinking water	→→		
absorption from GI tract	→→	accumulation in body (kidney)	→→	tubular changes in kidney (proteinuria)	→→		
glycosuria and loss of calcium	→→	nutrition or hormonal disturbances (age and delivered pregnancies)	→→	Osteomalacia			

SOURCE: Tsuchiya (1969)

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CARBON MONOXIDE AND HUMAN HEALTH

Peter Ashbrook

INTRODUCTION

Carbon monoxide (CO) is a colorless, odorless, and tasteless gas, and is slightly lighter than air (National Air Pollution Control Administration (NAPCA), 1970). It is flammable, but does not support combustion. Normally, 530 million tons of carbon monoxide are present in the troposphere, causing background levels estimated at 0.1 ppm.

Natural sources of carbon monoxide have not been very well defined until relatively recently. These studies suggest that 3.5×10^9 tons of carbon monoxide per year are produced naturally in North America (Maugh, 1972). Oxidation of methane in the troposphere is the predominant source, but growth of plants in the summer and death of plants in the fall also make significant contributions. The average residence time of carbon monoxide in the atmosphere was estimated to be 0.3 years. Natural sinks are even less well-defined. Micro-organisms in soil can remove carbon monoxide from the atmosphere. In the U.S., this could account for removal of 600×10^6 tons of carbon monoxide per year (Maugh, 1972).

Anthropogenic sources of carbon monoxide, estimated to be 270 million tons per year (Maugh, 1972), arise from the use of organic materials in combustion processes. Incomplete combustion of carbon-containing compounds will produce carbon monoxide in varying amounts depending on four factors. These factors are (NAPCA, 1970): a) oxygen concentration; b) flame temperature; c) gas residence time at high temperature; and d) combustion chamber turbulence. Increased oxygen concentration and residence time at high temperatures will both decrease the amount of carbon monoxide produced. Higher flame temperatures and combustion chamber turbulence increase reaction rates. Internal combustion

engines are by far the largest manmade source of carbon monoxide; less important sources include stationary heat-generating facilities, industrial processes, and solid-waste combustion (NAPCA, 1970). Although no data are available on total carbon monoxide production from cigarette smoking and other uses of tobacco, exposures from these sources often are the most important to humans.

Humans produce small amounts of carbon monoxide. Healthy males at rest produce 0.4 ml carbon monoxide per hour (Stewart, 1976). This source of carbon monoxide causes normal blood carboxyhemoglobin (COHb) levels of 0.4-0.7 percent of total hemoglobin, a level considered neither harmful nor beneficial.

Oxygen is required by body tissues to support and maintain aerobic metabolism (Hackney, 1976). Delivery of oxygen to the tissues is accomplished by the reversible binding of oxygen to hemoglobin in the blood. Carbon monoxide competes with oxygen for binding sites on the hemoglobin molecule, reducing the number of sites available for oxygen. The affinity of carbon monoxide for hemoglobin (to form carboxyhemoglobin) is 200-250 times that of oxygen. In addition, carbon monoxide appears to bind to the more labile sites, creating a situation whereby the remaining available oxygen is more tightly bound to hemoglobin. Hence, the oxygen-carrying capacity of the blood is reduced even more than expected. The relationship of inhaled carbon monoxide concentration to carboxyhemoglobin levels at equilibrium is shown in Table 1.

Under conditions of continuous exposure to carbon monoxide, carboxyhemoglobin levels will reach equilibrium in 8-12 hours (NAPCA, 1970). If the individual is engaged in vigorous activity, this time will be reduced.

Other heme proteins (myoglobin, for example) capable of reversibly binding carbon monoxide account for 10-15 percent of the CO normally present in the body.

Potential sources of carbon monoxide from mining activities include explosives (particularly if used underground), combustion from machinery, combustion from increased traffic, and combustion due to the production of additional energy. The potential for accidental fires, which are an important possible cause of carbon monoxide in underground mines, has prompted the Mining Enforcement and Safety Administration to require underground miners to carry a "one-hour self rescue device" which converts carbon monoxide to the less hazardous carbon dioxide.

OCCUPATION EXPERIENCE

The threshold limit value(TLV) for carbon monoxide is 50 ppm (55 mg/m^3) as a time weighted average (American Conference of Governmental Industrial Hygienists, 1975).

Acute Effects

The effects of various levels of carboxyhemoglobin on humans are illustrated in Table 2.

Carbon monoxide poisoning symptoms have recently been discussed by Ginsburg and Romano (1976). Patients in the emergency room often have nausea and, depending on the degree of cardiovascular competence, may also have hypotension, metabolic acidosis, and angina pectoris. Frontal headache is often a delayed phenomenon. Symptoms of carbon monoxide poisoning can mimic those of psychotic depression or hysteria and may lead to false diagnosis. Pathological effects of fatal carbon monoxide poisoning are present in all organs of the body, the most important changes occurring in the brain where edema, capillary and venous dilation, and hemorrhagic necrosis are acute.

Chronic Effects

Occupations in which carbon monoxide poisoning presents a potential hazard include traffic tunnel employees, steel mill workers, parking garage attendants, and other occupations which might have poor ventilation and sources of carbon monoxide. Most studies concerning occupationally exposed groups appear to be concerned with measuring carboxyhemoglobin levels in the workers.

Studies which found significant increases in carboxyhemoglobin levels in workers as compared to control groups have been reviewed by the National Air Pollution Control Administration (1970). These workers were exposed to an average carbon monoxide concentrations of 17 to 70 ppm. Altered electrocardiograms of workers have been observed in occupations with high exposure to carbon monoxide, such as fire fighters (Goldsmith and Aronow, 1975). Carbon monoxide poisoning is not uncommon to miners. For example, Smith and Brandon (1973) reported that two of 74 patients in their morbidity study of survivors of carbon monoxide poisoning were miners, one of whom experienced severe personality changes including instability characterized by aggressiveness and irritability.

NONOCCUPATIONAL EXPERIENCE

Ambient Air Standards and Baseline Carboxyhemoglobin Levels

Currently, the federal standards for carbon monoxide in ambient air are an eight-hour average of 9 ppm with a maximum one-hour average of 35 ppm. A normal, resting, nonsmoking man, when exposed to 9 ppm carbon monoxide for eight hours, will have a carboxyhemoglobin level of about 1.5 percent (Hackney, 1976; compare with Table 1).

As mentioned above, nonsmokers have a normal carboxyhemoglobin level of approximately 0.4 percent. Smokers have higher carboxyhemoglobin levels

than nonsmokers. Studies have shown that cigarette smokers of one pack/day have carbosyhemoglobin levels of 5-6 percent; 2-3 packs/day will cause levels of 7-9 percent during waking hours (Stewart, 1976). Heavy cigar smoking may raise carboxyhemoglobin levels to 20 percent. Carboxyhemoglobin from smoking appears to be at least partially additive to that from other sources. The biological half-life of carbon monoxide in the body is 4-5 hours in healthy, sedentary adults.

Neurological Effects

Ginsburg and Romano (1976) recently discussed carbon monoxide encephalopathy. Reviewing the literature, they concluded that 60-75 percent of patients with carbon monoxide poisoning survive the initial trauma. Approximately 10-30 percent of the survivors develop neuropsychiatric signs one to three weeks after exposure. These patients often recover to resume full activities relatively quickly, only to relapse 2-21 days later.

Smith and Brandon (1973) investigated the morbidity experience of 74 patients surviving suicidal or accidental carbon monoxide poisoning. These patients were followed over a three-year period. About 15 percent of these patients died during the study period. Gross neuropsychiatric sequelae in the form of cognitive change, personality change, or frank neurological abnormality were observed in 10 percent of the patients and were attributed directly to carbon monoxide poisoning. In addition to the 10 percent with gross neuropsychiatric sequelae, a large number of the patients suffered milder forms of brain damage in the form of personality change of an irritable, aggressive, and violent type with associated cognitive impairment.

Cardiovascular Effects

Primary effects of exposure to low level carbon monoxide result from hypoxic stress secondary to the reduction in oxygen-carrying capacity of the blood (Stewart, 1976). Increased cardiac output and flow to critical organs normally occurs; however, those with advanced cardiovascular disease are less able to compensate for these changes and are at risk of injury from carbon monoxide-induced hypoxic stress.

Goldsmith and Aronow (1975), in a review of cardiovascular effects of carbon monoxide, state there is convincing evidence that: 50 ppm carbon monoxide for 90 minutes aggravates angina pectoris; 50 ppm carbon monoxide for 120 minutes aggravates intermittent claudication; and 100 ppm carbon monoxide for four hours alters the electrocardiogram of normal subjects.

Effects on the Eye

Retinal findings following carbon monoxide poisoning may include venous congestion, papilledema, and optic atrophy (Dempsey, O'Donnell, and Hoff, 1976). Sequelae of carbon monoxide poisoning may include temporary or permanent blindness. Although blindness, if it occurs, usually develops after recovery from coma, it has been reported to occur in cases of carbon monoxide poisoning in which coma was not present.

Other Reported Effects

Goldsmith and Aronow (1975), in a review of carbon monoxide and coronary heart disease, concluded there is suggestive evidence that carbon monoxide impairs survival of patients with acute myocardial infarction, and there is probably a role for carbon monoxide in the development of stroke and cerebral atherosclerosis. This conclusion is based largely upon the work of Cohen, Deane, and Goldsmith (1969) who studied 3080 admissions for myocardial

infraction in Los Angeles County over a one-year period. Admission case fatality rate, (defined as: cases admitted during the week and who subsequently died, divided by the cases admitted during the week) was significantly higher in the high carbon monoxide area (annual carbon monoxide above 8 ppm) than in the low carbon monoxide area (annual carbon monoxide below 8 ppm) 35 of the 52 weeks.

However, Kuller et al. (1975) were unable to find a relationship between ambient carbon monoxide level and the incidence of sudden cardiac death, transmural myocardial infarction, or total arteriosclerotic heart disease deaths, in a geographically defined area of Baltimore (population of 500,000).

Wald et al. (1973) examined 950 people, aged 30-69, to investigate the relationship between atherosclerotic diseases and carboxyhemoglobin levels. The presence of myocardial infarction, angina pectoris, and intermittent claudication were confirmed from past records. Blood was drawn after lunch and within one hour of smoking. Within those groups with similar smoking habits, the relative risk of atherosclerosis for those with carboxyhemoglobin above 5 percent was 21.2 times greater than for those with carboxyhemoglobin below 3 percent. The 95 percent confidence interval for this relative risk of 21.2 ranged from 3.3-734.3. Whether this excess risk was due to carbon monoxide or some other agent in cigarette smoke which is correlated with carboxyhemoglobin was not determined.

Some investigators have suggested that the carbon monoxide in cigarette smoke may be the underlying cause of the known relationship between smoking and cardiovascular disease. However, the large number of other toxic components in cigarette smoke make it very difficult to single out one agent.

Carbon monoxide may be related to motor vehicle accidents (reviewed in NAPCA, 1970). Drivers in heavy traffic have been found to have higher carboxyhemoglobin levels than normal.

EXPERIMENTAL EVIDENCE

Human Studies

Aronow has used double-blind studies to investigate the effect of carbon monoxide on treadmill exercise performance in several different groups. Normal middle-aged subjects (Aronow and CAssidy, 1975), who had normal hematocrit, normal hemoglobin, blood pressure below 140/90, and were taking no medication, were exposed to 100 ppm carbon monoxide or compressed purified air for one hour. When exposed to carbon monoxide, the carboxyhemoglobin levels rose significantly ($p<0.001$) from 1.67 to 3.95 percent. Compressed purified air had the opposite effect, significant reducing ($p< 0.001$) carboxyhemoglobin from 1.63 to 1.30 percent. On the treadmill test, carbon monoxide significantly lowered ($p <0.001$) time until exhaustion from 697.7 to 662.7 seconds. Controls showed no significant change in time until exhaustion.

Patients with angina pectoris due to documented coronary artery disease (Aronow, 1976) were exposed to 50 ppm carbon monoxide or compressed purified air for two hours. Carboxyhemoglobin levels again increased after carbon monoxide exposure (to an average of 2.68 percent carboxyhemoglobin) and dropped after compressed purified air. Mean exercise time until onset of angina pectoris decreased from 224.3 seconds in the control period to 187.6 seconds after carbon monoxide exposure ($p< 0.001$). Controls showed no significant change in time until onset of angina pectoris. At onset of angina pectoris, both mean systolic blood pressure and mean heart rate significantly decreased

after carbon monoxide exposure (153.5 to 149.4 mm Hg and 129.2 to 120 beats/minute, respectively). Thus, carbon monoxide caused the patients with angina to develop angina pectoris sooner and after less work.

Similar findings were found in patients with intermittent claudication of the calf or thigh due to angiographically documented occlusive ilio-femoral arterial disease with patent distal vessels. After exposure to 50 ppm carbon monoxide for two hours, the average venous carboxyhemoglobin level rose significantly to 2.77 percent. Mean exercise time until onset of intermittent claudication decreased from 174.3 seconds in the control period to 144.0 seconds after carbon monoxide exposure. Compressed purified air had no significant effect on carboxyhemoglobin levels or mean exercise time until onset of intermittent claudication.

Impairment of mental performance has been found after exposure to low levels of carbon monoxide (National Research Council, 1969). At five percent carboxyhemoglobin, ability to carry out arithmetic is impaired and at 2.5 percent carboxyhemoglobin (10 ppm carbon monoxide exposure), ability to judge slight differences in successive time intervals is reduced. Changes in visual acuity and relative brightness threshold have been observed when carboxyhemoglobin reaches 3 percent (NAPCA, 1970). Stewart (1975), however, cautioned that findings concerning the effects of carboxyhemoglobin levels of 2-5 percent have been difficult to duplicate or confirm.

Animal Studies

Experimental animal studies have further investigated the effects of carbon monoxide-induced impairment of oxygen transport. In one study (cited in NAPCA, 1970), dogs exposed to 50 ppm carbon monoxide, intermittently or continuously, for six weeks developed abnormal EKG's after three weeks.

Morphological changes were found in the brains of these dogs at autopsy. However, another study on dogs exposed to 50 ppm carbon monoxide continuously for three months showed no such changes, but rather found increased hemoglobin, hematocrit, and red blood cell counts (cited in NAPCA, 1970), suggesting adaptation to the higher carbon monoxide levels. Rabbits have also appeared to have the ability to adapt to higher levels of carbon monoxide.

Table 1. Carboxyhemoglobin (COHb) equilibrium at one atmosphere pressure and O_2 concentration of 18 percent.

ppm CO Inhaled	COHb (percent of total hemoglobin)
1	0.46
3	0.83
5	1.19
7	1.55
8.7	1.85
10	2.08
25	4.68
30	5.51
35	6.33
50	8.71
70	11.69
90	14.49
100	15.83
300	35.84
500	48.17
700	56.53
900	62.58
1000	65.01
3000	84.82
5000	90.33

SOURCE: Stewart (1975)

Table 2: Effects of carboxyhemoglobin on humans.

Blood Saturation COHb (%)	Response of Healthy Adult	Response of Patient Ill with Severe Heart Disease
0.3-0.7	Normal range	
1-5	Selective increase in blood flow to certain vital organs to compensate for reduction in oxygen-carrying capacity of the blood	Patient with advanced cardiovascular disease may lack sufficient cardiac reserve to compensate
5-9	Visual light threshold increased	Less exertion required to induce chest pain in patients with angina pectoris
16-20	Headache; visual-evoked response abnormal	May be lethal for patients with severely compromised cardiac function
20-30	Throbbing headache; nausea; fine manual dexterity abnormal	
30-40	Severe headache; nausea and vomiting; syncope	
50-60	Coma; convulsions	
67-70	Lethal if not treated	

SOURCE: Stewart (1976)

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COBALT AND HUMAN HEALTH

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INTRODUCTION

Cobalt has been in use since 1450 B.C. when the Babylonians and Egyptians used it to color pottery and glass (Schroeder et al. 1967). It was isolated as a metal in 1742, established as an element in 1780, and was first used as an alloy in 1907. Cobalt is presently used in heat- and corrosion-resistant materials, high-strength materials, and permanent magnets (Sibley, 1975). It is generally recovered as a byproduct or coproduct of copper or nickel mining, with the major producers being Zaire and Zambia.

Cobalt is physiologically active in Vitamin B_{12}, and is an essential element to man (Pier, 1975). It has been detected in 150 foods and beverages, in wild animals, water, soils, and human tissues (Schroeder, et al. 1967). Cobalt shows no tendency to accumulate with age, and the average daily intake has been reported to be about 300 µg. The major source of intake is the diet, contributing 140 to 580 µg/day, with the only good sources being fish, cocoa, bran and molasses (Schroeder et al. 1967). A deficiency of cobalt may lead to anemia, while an excess may lead to respiratory problems, dermatitis, heart problems or polycythemia. Schroeder et al. (1967) however, reported that no common chronic disease has been associated with either a low or a high level of cobalt in the tissues.

OCCUPATIONAL EXPERIENCE

The major industrial health effect of cobalt is due to inhalation during the manufacture of tungsten carbide. In some cases this may lead to bronchial asthma, while in others, disabling fibrosis may occur. There have also been reports in the literature, indicating there may be dermatological or gastric effects from occupational exposures. The threshold

limit value (TLV) for occupational exposure to cobalt metal fume and dust is 0.1 mg/m^3 (American Conference of Governmental Industrial Hygienists, 1975).

Respiratory Effects

Bech et al. (1962) reviewed the literature on hard metal disease occurring in tungsten carbide workers. Eight of 27 workers in a German factory which had been in production for two years showed reticular shadowing in the lungs, which was suggestive of pneumoconiosis. An examination of 696 workers in 1948 and 1949 found a high incidence of bronchitis with bronchospasm, and 23 of 40 workers in another study complained of respiratory difficulties. A 1955 study mentioned by Bech et al. (1962) investigated 331 hard metal workers and found respiratory disorders and radiographic changes in 59 of them. An earlier Swedish study reported three cases suffering from cough and marked dyspnea. Two of these cases showed nonspecific interstitial pneumonia at autopsy. In other studies cited by Bech et al. (1962) pulmonary lesions were found. These were characterized by proliferation of interstitial tissue. Disorders of the upper respiratory tract including bronchitis, and an early pneumoconiosis were also common. The study carried out by Bech et al. (1962) included six cases of pulmonary disease, and a radiological survey of 255 hard metal workers. The survey identified one worker with metal disease and several others with indications of early fibrosis. The symptoms most often present in the studies reviewed (Bech et al. 1962) were cough, expectoration, shortness of breath, and tightness of the chest. The agent suspected in all of these cases was cobalt, although it was not definitely known.

Bruckner (1967) reported on a tungsten carbide worker who developed asthma. He was exposed to dust from grinding tungsten carbide tools, and experienced shortness of breath, chest tightness, audible wheezing and a productive cough. Bruckner (1967) suspected a hypersensitivity mechanism was involved because the symptoms appeared within one to three minutes after starting work.

Coates and Watson (1971) reported on 12 tungsten carbide workers with progressive diffuse interstitial pneumonia. Symptoms present included cough with little sputum, dyspnea and weight loss. They later experienced basilar rales and three patients showed clubbing of the fingers. Eight of these patients had died at the time of the report. Coates and Watson (1971) also observed a sensitization in five other workers. The symptoms they experienced were coughing, wheezing and shortness of breath, all of which were alleviated immediately upon removal from exposure. The authors felt this would not lead to interstitial lung disease.

The symptoms present in respiratory illnesses caused by inhalation of cobalt compounds are shown in Table 1.

Dermatitis

Browning (1969) cited a study which showed tungsten carbide workers may develop dermatitis. The eruptions were localized to points of friction such as ankles, elbows and side of the neck, and patch tests were positive for metallic cobalt. Further patch tests showed the loose powder produced in the factory was positive, while all the separate ingredients except cobalt were negative.

Bech et al. (1962) mentioned a study which supported the findings that cobalt is a cutaneous sensitizer, and a recent study by Spruit and Malten

(1975) indicated the occurrence of a dermatitis in an offset printing factory. Three workers in the latter study were exposed daily to high concentrations of cobalt and chromium in the dyes and printing substances.

Gastric Effects

Browning (1969) reported that inhalation of dry powdered cobalt acetate has produced gastric disturbance. The symptoms, which appeared shortly after leaving work, included vomiting, severe pain and tenderness in the epigastrium, pain in the limbs with marked weakness, and some hematemesis with blood in the stools. Complete recovery occurred within three weeks with no residual injury.

NONOCCUPATIONAL EXPERIENCE

The literature on nonoccupational exposures to cobalt consists primarily of reports on the side effects from therapeutic administration, and theories on the cobalt-beer cardiomyopathy of the 1960's. There has been very little work done on epidemiological investigations of chronic exposure to small doses. One study (Berg and Burbank, 1972), looked at metal concentrations in water supplies and cancer mortality in 16 basins in the U.S. No significant correlation between cobalt and any of the 34 cancers studied was found.

Therapeutic Side-Effects

In a review, Louria et al. (1972) reported that cobalt given orally had produced anorexia, nausea, vomiting, diarrhea, tinnitus and neurogenic deafness. They indicated it has also increased red cell production, and caused goiters by blocking the uptake of iodine. Browning (1969) reported that toxic effects may follow a single oral dose of 500 mg of $CoCl_2$ or intravenous injection of 5-10 mg.

Schirrmacher (1967) reported the case of a 35 year-old woman being treated for anemia with $CoCl_2$. A six-month treatment, with a total of 18 grams, resulted in nausea, vomiting and unsteady walking. Temporary glycosuria and amino-aciduria indicated that renal damage was taking place. All symptoms disappeared when treatment iwth the $CoCl_2$ stopped.

Smith et al. (1975) reported that when $CoCl_2$ was applied to the skin in a 10 percent solution for a sweating test, a stinging sensation occurred immediately. They indicated that this had been reported by others also, but the mechanism was unknown. The review by Louria et al. (1972) mentioned that $CoCl_2$ had resulted in hyperlipemia and secondary skin xanthomatosis.

Schroeder et al. (1967) reported that cobalt salts in excess have caused polycythemia (increase in red cells), with hyperplasia of the bone marrow. They also observed vasodilation, with flushing, after injection of cobalt salts.

Myocardiopathy

In the late 1960's, there were outbreaks of cardiomyopathy in heavy beer drinkers in Quebec, Omaha and Minneapolis. The cause of this was attributed to cobalt. Apparently, the synthetic detergents used for washing the glassware left a thin film on the glass, which caused the beer not to foam. A process was then patented to add 1.0 to 1.5 mg/l of cobalt chloride to the beer to prevent this from happening. Local breweries in the three cities mentioned above used this process and cardiomyopathy resulted. The mortality varied from 18 to 47 percent, while the estimated intake was 5 to 10 mg/day (Alexander, 1972). Sullivan et al. (1969) reported that 20 of the 34 surviving patients from Omaha regained normal cardiac status, even though half of them continued to

consume beer once the cobalt additions were discontinued. The amount of cobalt causing the cardiomyopathy is considerably less than that used therapeutically, however the patients with cardiomyopathy appeared to have sensitive hearts. Factors important in making the heart more sensitive to cobalt included inadequate protein and vitamin intake, zinc depletion, and prior heart damage from alcohol (Alexander, 1972).

ANIMAL STUDIES

Cancer

Heath (1956) produced tumors in rats by injection of cobalt metal powder. There was little or no immediate reaction and no systemic effect from the injection of 0.028 g cobalt. Tumors appeared 5 to 12 months later at the site of injection in 17 of 30 rats. There was only one tumor occurring in the control rats, and this was not at the site of injeciton. The tumors arose from striated muscle and connective tissue.

Gilman and Ruckerbauer (1962) studied the carcinogenic properties of the flue dust from a nickel refinery and cobalt oxide, which was one percent of the dust. The refinery dust induced sarcomas at 45 percent of the injection sites in two strains of rats, after an average latent period of 6 months. Most of the tumors were of striated muscle origin and metastases were common. When cobalt oxide was used, rhabdomyosarcomas occured in 50 percent of the rats. The refinery dust was capable of inducing fibrosarcomas in mice after a long latent period, while none could be induced using cobalt oxide. The authors concluded that there must be something in the refinery dust, other than cobalt oxide, capable of producing tumors.

Later work by Gilman (1962) showed that nickel sulfide was probably responsible for the carcinogenic activity of the refinery dust. Further studies on cobalt showed that cobalt oxide induced tumors in 13 of 29 rats injected and metastases

in 55 percent of those autopsied. Again, no tumors were induced in the mice they studied.

Respiratory Diseases

Schepers (1955b) investigated the effects of cobalt oxide dust injected into the lungs of guinea pigs. Three injections of 50 mg each produced a subacute, peribronchial inflammatory reaction within 1 month. These effects were completely reversed in 12 months, and he concluded that the toxicity of cobalt oxide was doubtful. Schepers (1955a) also studied the effects of intratracheal injection of particulate cobalt metal in the guinea pig. The immediate response was pulmonary edema, but with doses of 10 and 25 mg, the animals were back to normal in 12 months. A dose of 50 mg, however, still showed diffuse fibrosis 12 months after the injection.

Kerfoot et al. (1975) performed a semichronic inhalation study, using pure cobalt metal powder on miniature swine. They used concentrations of 0.1 mg/m^3 (which is the present TLV) and 1.0 mg/m^3. Animals were exposed six hours/day, five days/week, for three months. The animals appeared normal until the fourth week, and then became lethargic, and some began wheezing. A functional impairment was demonstrated in the lungs of the test animals, but not in the controls. Animals which were put in clean air for one to two months following exposure showed improvements. This indicated that lung damage may be reversible in the early stages. None of the animals in this study showed any evidence of diffuse pulmonary disease or fibrosis.

TABLE 1: Symptoms of respiratory disease from cobalt exposures.

cough
expectoration
shortness of breath (dyspnea)
tightness of chest
audible wheezing
basilar rales
clubbing of fingers

SOURCES: Bech et al. (1962), Bruckner (1967) and Coates and Watson (1971).

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IRON AND HUMAN HEALTH

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INTRODUCTION

Iron is the fourth most abundant rock-forming element and comprises five percent of the earth's crust. The mineral substance is iron ore, which when heated in the presence of a reductant, will yield iron, the metal most widely used by man (Klinger, 1975).

Minnesota has been one of the leading producers of iron ore for many years, and in 1974 accounted for 69 percent of the total U.S. production (Klinger, 1975). The taconite being mined in northeastern Minnesota is magnetite, while the iron ore which has been mined in the past occurred as hematite. Iron oxide dusts produced from copper-nickel development in Minnesota are expected to be primarily magnetite.

Waldbott (1973) reported that the National Air Sampling Network in 1964 found an average iron concentration of 1.58 $\mu g/m^3$ with a maximum of 22 $\mu g/m^3$. Almost all iron ore mined (98 percent) is smelted in blast furnaces (Klinger, 1975) which are the major source of iron in the atmosphere (Waldbott, 1973). Atmospheric sources of iron in a mining operation other than the dust, may include welding, incineration, and burning of fuel oil.

Iron is essential to human life. It is needed for the formation of hemoglobin, which is responsible for transporting oxygen from the lungs to tissue cells of the body. Iron also plays a role in oxidation mechanisms, and any excess appears to be stored in the liver and spleen as ferritin (Waldbott, 1973).

Health effects of iron, as with any of the metals, will depend on the chemical form in which it is present. It can be found as elemental iron, iron oxides, as a salt, and as iron carbonate (Plamenac et al., 1974). The iron ore which

is mined usually contains an iron oxide. The three forms which occur are hematite (ferric oxide), magnetite (ferrous oxide), and geothite. The ore may also contain siderite (iron carbonate), pyrite (iron sulfide), or iron silicates (Klinger, 1975).

OCCUPATIONAL EXPERIENCE

The present threshold limit value (TLV) established by the American Conference of Governmental Industrial Hygienists (1975) for occupational exposure to iron oxide fume is 5 mg/m^3.

Cancer

Doll (1958) reported that Turner and Grace found foundry workers, smiths, and metal grinders to have a high mortality from lung cancer as early as 1938. He also cited a study by Kennaway showing metal grinders had a high lung cancer mortality.

Faulds and Stewart (1956) reported on the incidence of lung cancer among hematite miners in the Cumberland district of England. They analyzed post-mortem records between 1932 and 1953 of 180 miners, and found 9.4 percent to have carcinoma of the lung. Nonminers in the same area had an incidence of 2.0 percent. Another 89 miners examined between 1950 and 1956 showed an incidence of 15 percent. The location of the tumor was usually in an area of fibrosis caused from previous siderosilicosis. They concluded that the siderosilicosis predisposes to carcinoma of the lung.

Boyd et al. (1970) reported on another study of miners in the same mining district. Death certificates of 5811 men who died between 1948 and 1967 were examined. Iron ore miners were compared with other local men and with the national rates. During those 20 years, there were 36 deaths in underground

miners attributed to lung cancer. Based upon the experience of local nonmining males, 20.6 deaths would have been expected; using the national experience, 21.5 lung cancer deaths would have been expected in the underground miners. The number of deaths observed was significantly different from both controls. There was no evidence of excess mortality from lung cancer among surface workers, and the mortality from other cancers was close to the national rates for all iron miners. The authors calculated that the underground miners had a 70 percent higher than normal mortality from lung cancer. Environmental sampling showed that the mines had an average radon concentration of 100 pCi/litre. This led the authors to suspect that the excess deaths may have been from radiation exposure. They concluded that if iron oxide were the risk factor, then the cancer rate would be expected to decline with silicosis; while if radon was responsible, the risk would be more likely to persist.

A study cited by Hueper and Payne (1962) reported that pulmonary carcinomas and pleural and peritoneal mesotheliomas appeared frequently in persons with asbestosis after exposure to asbestos dust containing about 44 percent iron. Asbestos bodies found in the asbestotic lungs were coated with a sheath composed of an iron-protein complex. They speculated that iron in the coating or protein complex may be involved in cancers in asbestotic lungs.

Respiratory Disease

Siderosis develops from the inhalation of pure iron oxide and is considered an innocuous lung disease which does not result in disability (Doll, 1958). Siderosilicosis is a mixed-dust pneumoconiosis produced by the inhalation of iron oxide and silica. It is speculated that under certain conditions, this may lead to carcinoma of the lung (Faulds and Stewart, 1956). Iron oxide occurs

as a dust in iron-ore mining, silver polishing, electric welding, boiler scaling, metal grinding, and blast furnace working (Faulds, 1957).

Boyd et al. (1970) reported that iron ore mining was considered to be a healthy occupation until 1913. At that time, pneumatic drilling was introduced, and an increase in the frequency of bronchitis and emphysema was subsequently observed. This was followed by descriptions of pulmonary lesions along with many cases of silicosis and silico-tuberculosis. Dust levels present were much higher than the present TLV's. The dust suppressive measures introduced in the 1930's have greatly reduced these problems (Boyd et al., 1970).

Boyd et al. (1970) reported that deaths from respiratory diseases other than cancer were 166 percent higher in iron ore miners than expected from the national experience. Of the 174 respiratory deaths observed among Cumberland hematite miners, 56 percent were certified to pneumoconiosis.

Faulds and Stewart (1956) reported that extensive areas of the lung may be replaced by dense, hard, fibrous tissue of a brick-red color. Although the color was from hematite, they concluded that the resulting pneumoconiosis was from the silica present.

A review of the causes of death among iron and steel workers other than foundry workers (McLaughlin and Harding, 1961) showed that conditions were much improved over 50 to 100 years ago. They examined the clinical, occupational and pathological findings in 10 grinders and 16 other nonfoundry workers. Although silicosis and mixed dust fibrosis still affected the grinders, the authors concluded that improved conditions had greatly reduced the disease rates. These improvements included better grindstones, exhaust ventilation, and raising the standard of housekeeping. In only one of the 16 other deaths was pneumoconiosis considered a factor.

Jones and Warner (1972) reported that welders' siderosis is also a mixed-dust pneumoconiosis. They examined 14 steelworkers exposed for five hours per day for up to 16 years. Four men had radiological evidence of pneumoconiosis, two had normal pulmonary function, and two had a measurable loss of pulmonary function. The concentrations of the fumes they were exposed to ranged from 1.3 to 294.1 mg/m^3. The fumes consisted mostly of iron oxide with varying amounts of chromium oxide and nickel oxide. They concluded that iron oxide alone probably never leads to fibrotic pulmonary changes, whereas iron oxide combined with certain other substances obviously does.

A study by Plamenac et al. (1974) showed that long-term exposure to dust compounds containing iron oxide produced extensive alterations of the bronchial epithelium. They examined 47 non-smokers with normal chest roentgenograms and no indications of acute or chronic respiratory disease. The workers had been exposed to three different concentrations of dust containing 40 to 65 percent iron (usually Fe_2O_3), 17.5 percent SiO_2, 6.1 percent Al_2O_3, 3.24 percent MgO, and a variety of other compounds. The temperature of the exposures also varied and may be a factor in the occurrence of disease. Cytologic examination of the workers sputum showed iron-containing macrophages in 93.3 percent.

Levy and Margolis (1974) examined a gas torch cutter with siderosilicosis of the lung, diffuse interstitial fibrosis, and highly atypical alveolar epithelium. Iron oxide was found in the lung tissue. They concluded that inhalation of relatively pure iron oxide even in high concentrations for many years does not produce pulmonary fibrosis, however, diffuse interstitial fibrosis may develop if welding is carried out in an atmosphere containing other inorganic dusts, such as silica or asbestos.

NONOCCUPATIONAL EXPERIENCE

No community health effects from low level industrial exposures have been reported; however, iron has been used medically for several centuries and poisonings have resulted from this. Crotty (1971) reviewed the history of acute iron poisoning and pointed out its present prevalence.

Accidental and homicidal poisoning from iron salts was widespread in the mid-nineteenth century, but then diminished until the 1930's and 1940's. The reported oral toxicities ranged from 40 to 1600 mg/kg of elemental iron. There are thousands of over-the-counter iron preparations marketed for therapeutic use, and at least 42 iron products have been indicated in poisoning reports (Crotty, 1971).

Ferrous sulfate, one of the most widely-used iron compounds, is sixth among medicines causing hospitalization in children under five (Crotty, 1971). It has also been reported to enhance the irritating effect of SO_2. Ferrous sulfate catalyzes the oxidation of SO_2 to SO_3 which then forms the irritating sulfuric acid (Waldbott, 1973).

EXPERIMENTAL EVIDENCE

Cancer

Heuper and Payne (1962) implanted metallic iron in the pleural cavity and muscle tissue of rats and found no cancer produced at those sites. Pellets containing 25 mg of iron were suspended in 50 mg of wool fat and surgically implanted.

Although elemental iron does not appear to be associated with cancer production, the role of iron oxide as a cancer-inciting agent has been well established (Waldbott, 1973). A variety of malignant tumors have been produced in hamster lungs by administering iron oxide with benzo(a) pyrene.

Benzo(a) pyrene is a proven carcinogen which is present in tars used for roofing and roads, and is found in tobacco smoke (Waldbott, 1973). Harris et al. (1971) found that intratracheal administration of benzo(a) pyrene carried by ferric oxide caused acute cellular changes in the tracheobronchial epithelium of hamsters. Ferric oxide alone produced basal cell hyperplasia which was reversible. Stenback et al. (1976) also reported no tumors were produced from ferric oxide alone, whereas when applied with benzo(a) pyrene, a variety of tumors were observed. In their study, the hamsters with benzo(a) pyrene were found to have tracheal papillomas, while those with both ferric oxide and benzo(a) pyrene had papillomas, squamous cell carcinomas, a few adenomas, and adenocarcinomas of the larynx, trachea and lungs.

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LEAD AND HUMAN HEALTH

Peter Ashbrook

INTRODUCTION

Lead has been used by man for thousands of years. Evidence of its use by the Egyptians goes back as far as 1500 B.C. (Waldron and Stöfen 1974). Uses of lead at that time included: decorative ornaments, sinkers for fishing nets, dishes, and as pigments in eyepaints. Other cultures used lead in building work and for wartime purposes. The Romans made extensive use of lead in their aqueducts and water mains, as well as in cooking utensils. In fact, it has been postulated that lead poisoning contributed to the fall of the Roman culture (Gilfillan 1965). Today, over one and a half million tons of lead are used annually in the U.S. (Table 1). About one-third of this lead comes from recycling. The three major uses of lead, batteries, battery oxides, and gasoline anitknock additives, are closely related to the motor vehicle industry. Other uses include ammunition, ceramic glazes, the printing industry, radiation shielding, electrical, and paints. It should be noted that use of lead-based pigments in paints has declined considerably in recent years.

There have been numerous studies of airborne lead concentrations. Levels of lead have been found to vary by more than a factor of one hundred between the remote areas of the world and large cities. Los Angeles, for example, had lead concentrations of approximately 5 $\mu g/m^3$, while the White and Laguna Mountains of California had 0.008 $\mu g/m^3$ (Waldron and Stöfen 1974). Major sources of lead emission in the U.S. are shown in Table 2. (Note that 98 percent of this lead came from gasoline combustion.)

Dietary sources are probably the most important in terms of human lead intake. Lead content of food generally varies between 0.01 and 2.5 ppm, with an average of about 0.2 ppm. In the U.S., the average daily lead intake is

thus about 300 µg, an amount which probably has not changed much over the past 30 years (National Research Council 1974). Concentrations of lead in water are usually lower than 50 µg/ℓ, the maximum contaminant level permitted by the United States Environmental Protection Agency (1976). Average daily intake of lead through water is about 20 µg/ℓ. Of the total lead ingested, only 5-10 percent, or 30 µg/day, is actually absorbed into the body. Inhaled lead, though less well understood, may contribute to the daily intake. Existing data indicate air levels need to be greater than 2-3 µg/m^3 to increase blood lead levels (National Research Council 1972).

OCCUPATIONAL EXPERIENCE

Lead was recognized to cause disease as early as the second century B.C. (National Research Council 1972). Studies clearly demonstrating dose-response relationships between lead exposure and severity of disease were first performed in the early 1900's. In 1912, Legge and Goadby (cited in National Research Council, 1972) wrote that lead concentrations in the air of 0.5 mg/m^3 rarely caused symptoms of lead-poisoning, and that 2 mg of lead inhaled as fume or dust was the lowest daily dose which could cause chronic plumbism. Symptoms of lead poisoning vary depending upon whether the lead is in an organic or inorganic form. The threshold limit value (TLV) for inorganic lead fumes and dust is 0.15 mg/m^3 (American Conference of Governmental Industrial Hygienists 1975). This level has also been recommended by NIOSH (Wagner, 1975). Blejer (1976) noted, however, that this concentration does not prevent all workers from having impaired health or functional capacity. An industry-wide survey of U.S. copper smelters (Wagner 1975) showed that lead concentrations in the air were well below this recommended standard. Lead concentrations in the urine of these workers (n=278) averaged 35 µg/ℓ with a maximum of 120 µg/ℓ. These levels are within the normal range (see Table 3).

Inorganic Lead

Inorganic Lead Poisoning

Lead poisoning, as an industrial disease, has been markedly reduced since the turn of the century. Lane (1964) has presented English data which illustrate this reduction. Over 1000 cases and 40 deaths were attributed to lead poisoning of industrial origin in 1900, while less than 100 cases and no deaths occurred in 1960. Waldron and Stöfen (1974) reported that one fatal case of industrial lead poisoning has occurred in Great Britain since 1950. Reasons for these declines, which occurred in spite of rising lead consumption, include improved engineering control, closer medical surveillance, and stricter legislative controls.

Cooper and Gaffey (1975) examined the mortality experience of 7032 men employed for at least one year in lead production facilities (smelters) and battery plants. Standardized mortality ratios (SMRs) were calculated using the total population of U.S. males as a base. Overall, smelter workers had an SMR of 107 and battery workers had an SMR of 99. Although these data suggest that the mortality experience of lead workers is not different from that of U.S. males (SMR = 100 by definition), the authors noted that one might have expected that SMRs of the lead workers to be lower because working populations tend to be healthier than the general population as a whole. Excess deaths were found for malignant neoplasms, due predominantly to the two categories of 1) digestive organs, peritoneum; and 2) respiratory system. Although the numbers were small, excesses were found also for other hypertensive disease and chronic and unspecified nephritis. The authors noted that the data support the view that high lead levels may be associated with chronic renal disease.

Diagnosis of Lead Poisoning

Lane et al. (1968) presented guidelines for diagnosis of inorganic lead poisoning. Mild symptoms include: tiredness, lassitude, constipation, slight abdominal discomfort or pain, anorexia, altered sleep, irritability, anemia, pallor, and less frequently, diarrhea and nausea. Occasionally, the patient will have a blue line in the gums and a metallic taste in his mouth. Severe symptoms include: colic, reduction of muscle power (such as wrist drop), muscle tenderness, paresthesia, and other symptoms of neuropathy or encephalopathy. Even in a lead worker with severe symptoms, supporting laboratory evidence should be obtained. The most commonly used tests and suggested interpretations of results are given in Table 3.

In addition to the tests given in Table 3, a reduced hemoglobin measurement may be associated with excessive and dangerous levels. Basophilic stippling of red blood cells, although a common occurrence with lead poisoning, is not a reliable indicator and its use is not advised (Johnstone, 1964). If chelating agents have been used, the numbers in Table 3 may not be applicable. Excessive levels mean that there is an unacceptable risk of potential long-term effects or sequelae, even if signs and symptoms of lead poisoning are lacking (Blejer 1976).

Hematological Effects

Lead inhibits several steps in the synthesis of heme. Hernberg (1976) reports that the inhibition of δ-aminolevulinic acid (ALA) dehydratase is the earliest observable effect of lead to occur. He noted that other researchers had found inhibition of ALA dehydratase at blood lead levels of 10-20 µg/100 ml, which is within the generally accepted normal range (see Table 3). Roels et al. (1976) determined that if a threshold for inhibition of ALA hydratase exists, it must be below 8-10 µg/100 ml. Inhibition of ALA dehydratase is apparently

not harmful as long as the activity of ALA dehydratase is at least 20-30 percent of normal. At blood lead levels of 70-90 µg/100 ml, ALA dehydratase is almost totally inhibited.

Of more significance than inhibition of ALA dehydratase is an increase in free erythrocyte porphyrins (FEP). Inhibition of ferrochelatase, the step in which iron is bound to protoporphyrin, appears to be the rate limiting step in heme synthesis (Hernberg 1976), and causes an accumulation of free erythrocyte porphyrins. Because free erythrocyte porphyrins are direct precursors of heme, an increase should be treated with caution. At higher blood-lead levels, ALA synthetase and coproporphyrinogen decarboxylase may be inhibited as well. The normal pathways for heme synthesis and steps inhibited by lead are shown in Figure 1.

Shortened life span of circulating erythrocytes occurs in lead poisoning, although the mechanism by which this occurs is not well understood (Hernberg 1976). Inhibition of heme synthesis and shortened life span of erythrocytes leads to anemia.

Neurological Effects

Peripheral neuropathy in humans is associated with high-level chronic and uncontrolled lead exposure (National Research Council 1972). Electrophysiologic abnormalities in peripheral nerve conduction have been reported in some occupationally exposed workmen considered clinically asymptomatic and who had blood lead concentrations of 70-80 µg/100 g whole blood (acceptable levels according to the British statement-Table 3). Higher blood lead levels are usually observed when effects on the peripheral nervous system are found. In the past, lead palsy (wrist drop) was commonly found in occupational lead poisoning. To a less frequent extent, other upper limb muscles, the extraocular eye muscles, and extensors of the lower limbs were

sometimes affected as well.

Lead encephalopathy usually occurs only when blood lead levels are well above 150 µg/100 ml. It may be either chronic or acute, and is observed most often in children. Factors which influence the severity include age and general health of the patient, amount of lead absorbed, length of exposure, and chronic alcoholism.

Renal Effects

According to Hernberg (1976), "lead nephropathy develops only after heavy, persistent lead exposure, lasting for ten years or more, or after short or repeated episodes of severe acute poisoning." In severe cases, the Fanconi syndrome of aminoaciduria, glycosuria, and phosphaturia is observed. Fructose and citrate occur in urine, which helps distinguish lead poisoning from other diseases characterized by the Fanconi syndrome (Waldron and Stöfen 1974). The characteristic pathological finding is the presence of intra-nuclear inclusion bodies, composed of a lead-protein complex, in the cells of the proximal tubule (Hernberg 1976).

Gastrointestinal Effects

Gastrointestinal effects such as anorexia, digestive disturbances, and either constipation or diarrhea, begin to appear when blood lead levels reach 80 µg/100 ml. These symptoms become more severe when blood lead levels exceed 100 µg/100 ml, and lead colic develops at greater than 150 µg/100 ml (Hernberg 1976).

Effects on Reproduction

A review of this subject by Rom (1976) recently appeared in the literature. Around the turn of the century, a large number of reports appeared showing high rates of sterility, miscarriage, neonatal mortality, and stillbirths in

women occupationally exposed to lead. Similar findings were found in women without occupational lead exposure, but who were married to men working in the lead industry. Although lead exposures at that time were not known, Rom noted that they "were uncontrolled, and may have been very high." More recent studies have demonstrated abnormal spermatogenesis in lead workers (cited in Rom, 1976).

Organic Lead

Organic lead has received increased attention in recent years. Lead alkyls, particularly tetraethyl and tetramethyl lead, are used as antiknock agents in gasoline. Although lead alkyls are readily broken down by light and heat in the atmosphere (National Research Council 1972), consumption of gasoline and the ready absorption of lead alkyls through the skin (Green et al. 1976) have caused concern about organic lead.

Diagnosis

Symptoms of organic lead poisoning are considerably different from those of inorganic lead poisoning. Some of these symptoms include: nervous irritability; excessive dreaming, which is often wild and terrifying; emotional instability; inability to remain calm and composed; heightened and erratic physical activity; anorexia; and vomiting (Sanders 1964). If these early symptoms are not controlled and the intoxication worsens, the subject will develop an irrational, delusional and hallucinated state (Sanders 1964). Urine lead levels are higher than those found in inorganic lead poisoning, but there is no lowering of hemoglobin levels, no effect on porphyrin metabolism (Sanders 1964), rarely abdominal colic (National Research Council 1972), and blood lead levels are usually not as high. It can be seen, then, that organic lead intoxication, in contrast to the inorganic case, exhibits itself as a psychotic state (Sanders 1964).

Morbidity

Sanders (1964) reported that most cases of organic lead poisoning occur from cleaning out storage tanks of gasoline. One such incident, reported by Beattie, et al., (1972) consisted of four men who had cleaned out a tank of aviation fuel, which had contained 1.4 grams of lead per liter. These men had encephalopathy, ranging in severity from mild anxiety to toxic psychosis. The most severe case had a blood lead concentration of 65.7 µg/100 g of blood (compare with Table 3).

Concern has been raised about workers involved in production of lead alkyls and those handling lead containing fuel, such as gasoline vendors. Robinson (1974) examined the mortality experience of 592 workers occupationally exposed to tetraethyl lead and compared that to 660 men at the same plant with no occupational exposure. Mortality differences were not significant. It should be noted that urine lead levels were prevented from exceeding 0.18 mg/ℓ by a medical surveillance program and the mean level for the exposed group was estimated at 0.07-0.10 mg/ℓ.

An Australian study (Moore et al. 1976) of 48 petrol vendors found significantly elevated blood lead levels (mean of 32.9 µg/100 ml) as compared with 47 controls (mean of 14.3 µg/100 ml). The authors, however, did not comment on the significance of these observations.

NONOCCUPATIONAL EXPERIENCE

Some of the more common occurrences of nonoccupational exposures to lead (National Research Council 1972) include: lead paint poisoning in children; leaching of lead by acid foods in improperly lead-glazed earthenware vessels; use of discarded battery casings made of wood as fuel in stoves and fireplaces by the poor; and consumption of illicitly distilled whiskey, due to the lead in automobile radiators used as condensors. This section will concentrate on

nonoccupational exposures most applicable to potential mining and smelting activities.

Children Living Near Copper Smelters

Baker et al. (1977b) studied children age 1-5 years living in towns near 11 copper smelters in the United States. All children studied lived within four miles of the smelter. Control children were chosen from three communities without smelters, but in states with smelters. The mean blood lead level for the children in the combind study group was not statistically different from that of the controls. Children in two of the towns had significantly higher mean blood lead levels than the controls, while four of the towns had significantly lower mean levels. When blood free erythrocyte porphyrins (FEP) were examined, there was no significant difference between the combined study group and the controls. Children in three of the towns had significantly higher blood FEP levels than the controls, while two had significantly lower levels. Hair lead levels in the combined study group were significantly higher than controls. Mean hair lead levels were higher than the control group in all eleven copper smelter towns, of which eight were significantly higher than the controls.

These findings indicate that increased external exposure to lead, as evidenced by hair lead levels, occurred near most of the copper smelters. Systemic absorption as determined from blood tests occurred only in sporadic cases. Emission characteristics and proximity of residences to the smelter were judged to be the most important factors in determining lead absorption by children. The authors noted that blood lead levels in the study children were rarely high enough to be associated with hematological or neurological toxicity. They also stated that the biological significance of the increased hair lead levels was difficult to assess.

Lead Poisoning

Baker et al. (1977a) studied 91 children and 12 wives of current and recently terminated workers of a secondary lead smelter. The concentration of lead in the dust of workers' homes averaged four times that of controls. Blood lead levels in the children were found to correlate with the lead concentration in the dust. The father of every child with a blood lead level $\geq$ 80 µg/100 ml also had a blood lead level $\geq$ 80 µg/100 ml. High dust lead concentrations in workers' homes were attributed to the accumulation of lead dust on workers' clothes and bodies. Control measures consisted of leaving work clothes at work and showering each day after work before coming home.

High levels of lead have been found in the environment around smelters. Roberts et al. (1974) studied two secondary lead smelters in Toronto which emitted 15,000 and 30,000 kg of lead/year, respectively. Lead levels in the soil were well over 10,000 µg/g of soil near the smelters compared to an urban background of 100-500 µg/g of soil. Of the children (0-14 years) living within 300 meters of the two smelters, 28 and 13 percent, respectively, had blood lead levels over 40 µg/100 ml compared to less than one percent of the children in the control group with such levels. These differences were found to be significant. Blood lead levels for children increased as distance from the smelter decreased. Adults, however, showed no significant trends. Other potential sources of lead (such as water, homegrown vegetables, and paint) were examined, but were judged to have had little effect on the observed findings. The authors concluded that poor personal hygiene and play habits of children in areas of high lead content resulted in excessive lead absorption. Although clear-cut symptoms of lead poisoning were not observed, metabolic and subtle neurological changes did occur in some cases.

Landrigan et al. (1975) reported about a smelter in El Paso which extracted lead, copper, and zinc. Over a three-year period, 1012 metric tons of lead were emitted. Lead levels in the soil were highest near the smelter (mean of 3457 ppm within 200 meters of the smelter) but remained above the background level of <50 ppm as far out as 10 km. Blood lead levels over 40 µg/100 ml were found in 43 percent of those living within 1.6 km, in eight percent of those living 1.6-3.2 km, and one percent of those living more than 3.2 km from the smelter. Four children had blood lead levels of 80-90 µg/100 ml, but none had symptoms of acute lead poisoning in preliminary studies. Prevalence studies using random samples showed that 69 percent of children one to four years old, living within 1.6 km of the smelter had blood lead levels above 40 µg/100 ml. Older children and adults showed lower prevalence rates of elevated blood lead levels and these tended to decrease as age increased. The prevalence of elevated blood lead levels within 1.6 km of the smelter was significantly higher in all age groups than in those living more than 1.6 km from the smelter. Other potential lead sources (paint, water, food and pottery) were considered, but were found to have little, if any, effects on blood lead levels. Blood lead levels were highly correlated with environmental lead concentrations, particularly those in air and dust.

Roels et al. (1976) examined blood lead levels in children near a smelter. Average blood lead levels ranged from 30.1 µg/100 ml blood in children living less than one km away, to 21.1 µg/100 ml in children 2.5 km, and 9.4 µg/100 ml in children in rural areas.

In what is probably the most severe case of excess community lead exposure, Landrigan et al. (1976) found 98.9 percent of the children, aged 1-9 years and living within 1.6 km of an Idaho lead smelter, had blood lead levels $\geq$ 40 µg/100 ml. Of these, 22 percent were over 80 µg/100 ml and the highest was 164 µg/100 ml. As in other studies, the prevalence of elevated blood lead

decreased with age of child and distance from the smelter. L .d levels in the air were found to be the principal source of lead, but soil and dust were also important sources.

Smoking and Lead

Lead has been found in cigarettes at 19-80 ppm (Schroeder and Blassa 1961). Concentrations in cigarette smoke range from 1.0-3.3 µg/cigarette, or 20-66 µg/pack. McLaughlin and Stopps (1973) conducted a study based on over 4000 responses to a questionnaire (69 percent response rate) mailed to DuPont employees. Urine levels of lead were found to be significantly elevated in smokers, but the elevation was only 1.5 µg/l, an increase which was judged to have little, if any, biological significance. Blood lead levels showed no differences between smokers and non-smokers.

Increased Susceptibility of Women and Children

There is considerable evidence suggesting that women and children are more susceptible to lead poisoning than men. In the early part of this century, several reports of increased incidence of lead poisoning in women appeared in the literature. Although these results were questioned by some as due to a combination of other environmental factors, the evidence was strong enough that laws were passed in many countries banning women from working in lead industries. For this reason, recent epidemiological studies concerning increased susceptibility of women have not been possible.

Boulos (1976), in a review of this subject, cited evidence that at comparable lead exposures, women had lower lead levels in their blood and urine than men. These data suggest there is a greater accumulation of lead in target organs of women.

In addition to possible increased susceptibility, there are a number of reports showing the increased incidence of miscarriages and higher infant mortality rates in women with high lead exposure. Fahim (cited by Rom, 1976) compared 253 pregnancies in Rolla, Missouri, a city in the lead belt, with 249 pregnancies in Columbia, Missouri, a control city. Pregnancies were categorized as: normal delivery at term; preterm--less than 37 weeks and weighing less than 2500 gm; and premature membrane--those with premature rupture of the membrane. In Columbia, over 96 percent were normal deliveries at term, three percent were preterm and less than one percent were premature membrane. Comparable figures for Rolla were: 70 percent normal, 13 percent preterm and 17 percent premature membrane. Concentrations of lead in fetal blood in Rolla were three to four times higher in the premature and premature membrane groups than in the normal deliveries.

Children are believed to be more susceptible to lead for several reasons. Studies have shown children with acute lead poisoning to develop permanent neurological damage and chronic renal disease (Waldron and Stöfen 1974). More controversial, however, is whether low lead exposure can impair mental development. This possibility was suggested by studies showing elevated blood lead levels in mentally retarded children. For example, Beattie et al. (1975) studied 77 children who were mentally retarded of unknown etiology and 77 matched controls. Blood lead levels in 30 of the mentally retarded children were significantly higher than in 20 of the controls (25.4 and 17.8 µg/100 ml, respectively). Apparently, the other children did not have their blood lead levels determined. More suggestive, however, was the finding that 11 of the 77 mentally retarded children had over 800 µg Pb/ℓ in their drinking water, while none of the controls did. (Note: maximum permissable concentration in the U.S. is 50 µg/ℓ). They estimated that a child exposed to drinking water containing lead in concentrations over 800 µg/ℓ "is at least 1.7 times (and probably a much greater factor) more likely to be defective than a child whose

exposure to water lead is completely unknown." These authors suggested that lead exposure was one element of a multifactorial etiology of mental retardation.

However, evidence to the contrary is found in other studies. For example, Hebel et al. (1976) examined children living near a lead factory, children living in an industrial area without a lead factory, and children living in heavily residential areas. No evidence of any effect on mental aptitude was found as judged by a standard test administered to 11-year-olds. Confounding variables (social class, birth rank, and maternal age) were taken into account in this study. Similar results were found by Lansdown et al. (1974). In this study, over 200 children living within 500 meters of a smelter works were examined. Although blood lead levels were related to the distance from the smelter and 21 children had blood lead levels over 40 µg/100 ml, no relationship was found between blood lead level and: 1) intellectual development; 2) generally deviant behavior; or 3) overactivity in school.

Several factors cause young children to be less resistant than adults to low levels of lead exposure. At young ages, the brain undergoes a period of rapid growth, at which time vulnerability to environmental insults is greatly increased (National Research Council 1976). Age and diet have the effect of producing a high intestinal absorption rate for lead in young children (50 percent for children compared with 10 percent for adults).

The National Safety Council (cited in National Research Council 1976) concluded that since metabolic effects in children first become evident when blood lead levels exceed 30 µg/100 ml, children in the one to five year age group should not have lead exposures causing an increase beyond this figure. In addition, they recommend that groups of children should not exceed a mean of 20 µg lead/100 ml.

Because of the elevated levels of free erythrocyte porphyrins even at "normal" blood lead levels, and the potential toxic effects of these agents in children, a number of sources have recommended a maximum acceptable concentration of 25 µg lead/100 ml blood in children (Roels et al. 1976).

Multiple Sclerosis and Cancer

Evidence in humans that lead may be related to these two diseases is generally based on the geographic distribution of these diseases and the correlation with lead in the environment (National Research Council 1972; Berg and Fairbank 1972). Considering how thoroughly lead has been studied and the lack of findings relating lead and cancer (with the exception of Cooper and Gaffey 1975), one is inclined to look for other causes to explain the statistical relationships.

EXPERIMENTAL EVIDENCE

Human Studies

Kehoe has performed a number of studies examining the effects of lead on humans. Dose-response studies (Kehoe 1964) indicated that the severity of lead intoxication increases as the lead levels in the soft tissues increase. Lead levels in the soft tissues reflect how fast the dose has accumulated. Therefore, the most severe intoxications occur with a fast rate of lead absorption even if the body burden is low. One experiment showed that a daily intake of 1.27 mg Pb/day, an excess of one mg over normal, would be dangerous in eight years. Greater excesses of lead intake would be dangerous in a short period of time. Another experiment in which a male was exposed to 0.15 mg/m^3 lead in the air for 7.5 hour/day for five days/week, for 102 weeks showed only marginally raised blood lead levels. Kehoe (1964) stated that in fatal lead encephalopathy the lead concentration in the brain should be at least 0.2-0.6 mg/100 g, otherwise the diagnosis is doubtful.

Cools et al. (1976), using lead supplements of 30 µg/kg/day, increased blood lead levels in males to 400 ppb (the boundary between normal and acceptable). After a lag period of 0-21 days, free erythrocyte porphyrins increased. It was suggested that free erythrocyte porphyrins be used along with blood-lead levels in biological monitoring programs. These authors mentioned similar experiments with women, who appeared more susceptible to lead-induced effects than men, as evidenced by a doubling of free erythrocyte porphyrins after 21 days of receiving 20 µg lead/kg/day. These females showed smaller rises in blood-lead than males.

Animal Studies

Although there have been numerous studies clarifying the biochemical mechanisms of lead poisoning, there have been so many studies of human exposures that the animal evidence will not be reviewed here. A comprehensive summary has been published (National Research Council 1972). The evidence presented in this section will instead look at the more controversial effects of lead.

Schroeder and Mitchener (1971) examined the innate toxicity of lead in breeding mice and rats by including 25 ppm lead in the drinking water and 0.20 ppm wet weight lead in food. This was done for several generations of the laboratory animals. In mice, the strain died out so rapidly that the experiment could not be continued past the F_2 generation. Over 95 percent of the live offspring in the F_1 generation averaged 48 days compared to 30 days in controls. In rats, the experiments were carried through three generations. There was a significant number of runts in all generations ranging from 8-20 percent of live births. Approximately 10 percent of the young were still-born. At this level of lead in the diet, the life span was shortened without interfering with growth.

Furst and Haro (1969) reviewed attempts to induce tumors in laboratory animals. Results have been mixed: some investigators have found nothing, while others have been able to induce tumors with lead salts. One report was given of lead phosphate producing renal tumors in rats; however, repetition of the study at a later time found only benign tumors.

Table 1. Lead consumption--1974.

Where it comes from*		Where it goes*	
U.S. Supply		U.S. Demand Pattern	
Domestic smelters		Gasoline additives	250
domestic ore	586	Transportation (mainly batteries & battery oxides)	785
foreign ore	97	Construction	78
secondary	601	Paints	116
Government stockpile sales	266	Ammunition	87
Imports, metal	118	Electrical	133
Industry stocks (Jan. 1)	214	Other	83
Total U.S. Supply	1,882	Total Industry Demand	1,532
Distribution of U.S. Supply			
Industry stocks (Dec. 31)	288		
Exports, metal	62		
Industry demand	1,532		

*Numbers represent 1000 short tons.

SOURCE: U.S. Bureau of Mines (1975).

Table 2. Lead emission in the U.S., 1968.

Source	Lead emitted (tons/year)
Gasoline combustion	181,000
Coal combustion	920
Fuel oil combustion	24
Lead alkyl manufacturing	810
Primary lead smelting	174
Secondary lead smelting	811
Brass manufacturing	521
Lead oxide manufacturing	20
Gasoline transfer	36
TOTAL	184,316

SOURCE: National Research Council (1972).

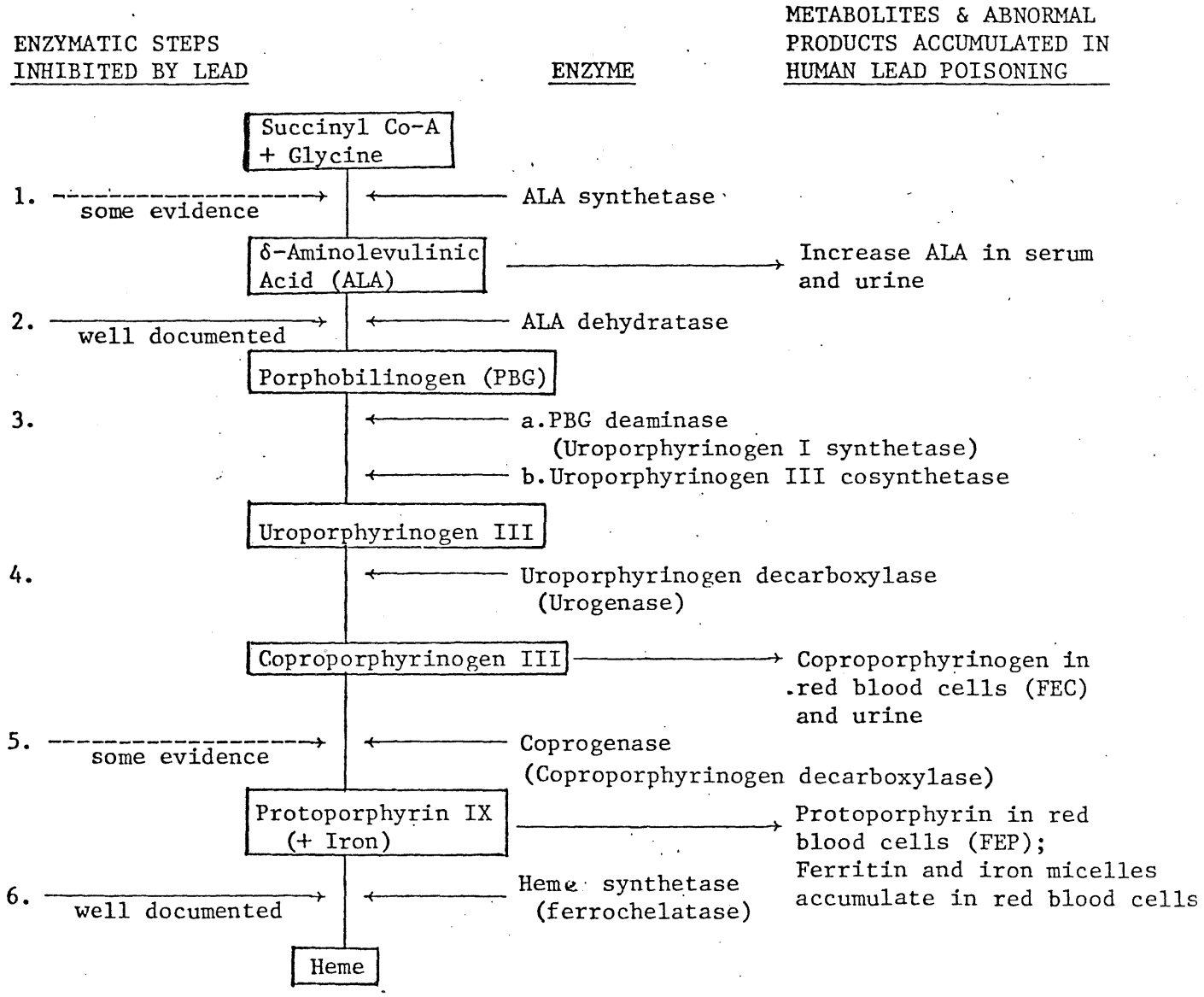
Table 3. Categories of lead absorption.

	Normal		Acceptable		Excessive		Dangerous	
Test	Brit.	Amer.	British	Amer.	British	Amer.	Brit.	Amer.
Blood Lead*	<40	<40	40-80	40-60	80-120	60-100	>120	>100
Urinary Lead*	<8	<8	8-15	8-12	15-25	12-20	>25	>20
Urinary Copro-porphyrin*	<15	<15	15-50	15-30	50-150	30-100	>150	>100
Urinary δ-amino-levolinic acid**	<0.6	<0.6	0.6-2	0.6-1.5	2-4	1.5-3.5	>4	>3.5

* µg/100 ml
** mg/100 ml

SOURCE: Lane et al. (1968)-British; Blejer (1976)-American.

Figure 1. Heme synthesis and inhibition by lead.



SOURCES: Waldron and Stöfen (1974); National Research Council (1972).

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MANGANESE AND HUMAN HEALTH

Dan Benzie
Peter Ashbrook

INTRODUCTION

Manganese (Mn) is the twelfth most abundant mineral in the earth's crust and is essential for plant and animal life (National Research Council, 1973). Manganese oxide was considered a variety of iron from antiquity through the late eighteenth century, and was later confused with the ores of magnesium. It was first recognized as an element in 1774 by Scheele (DeHuff, 1975). Ancient Egyptians and Romans used manganese to color glass and pottery. The first mining of manganese in the U.S. was for pottery coloring in 1837, followed by use in the iron and steel industries in 1839. It often occurs in nature with iron. Ferromanganese containing 25 to 30 percent Mn was first commercially mined in 1865.

Although the U.S. mines very little manganese, the total world resources are very large. It is essential for the production of steel, and this constitutes its principal use (DeHuff, 1975). Manganese is used as an alloy to add strength, toughness, hardness, and hardenability to the metal (DeHuff, 1975). Other uses of manganese include production of various chemicals, welding rods, and certain fertilizers, fungicides, and animal feeds (National Research Council, 1973). Organic manganese is currently used as a gasoline additive in place of lead and this may lead to increased atmospheric levels (Smith, 1972).

Manganese has been found in all human tissues examined, and the total body burden of a 70 kg adult averages 12 mg. It is essential for normal bone formation and the functioning of several enzymes (National Research Council, 1973). The half-life of manganese in the body is approximately 37 days; however, overexposed miners show an average of 15 days (Mena, 1974). Food is the main source of manganese intake, with a daily average of about 3 mg for an adult (Mena, 1974). Water is another source of manganese intake.

The average concentration of untreated surface water has been reported as 0.07 mg/ℓ, a level greater than the recommended limit for manganese (0.05 mg/ℓ) in drinking water by the U.S. Public Health Service (National Research Council, 1973).

The average manganese content of urban air is about 0.10 $\mu g/m^3$, while outside the urban area manganese concentrations drop below detectability (National Research Council, 1973). The major surces of manganese in the atmosphere are emissions from iron and steel production, manganese alloy production, mining operations and the manufacturing of dry-cell batteries. Smith (1972) reported that emissions from coal-fired power plants contain 60 to 400 $\mu g\ Mn/m^3$. The normal soil content of manganese has been reported by the National Research Council (1973) to be 800 to 850 ppm; however, mining activity or fertilizer applications can increase these amounts significantly.

Manganese occurs in many chemical forms (eight different valence states), making it essential to determine the form present before assessing potential health impacts. These molecules may be cations or anions. Smith (1972) reported that cations are more toxic.

OCCUPATIONAL EXPERIENCE

The primary effects of occupational exposure to manganese compounds have been neurological manganese poisoning and manganese pneumonia, both resulting from inhalation. The present threshold limit value (TLV) for manganese compounds adopted by the American Conference of Governmental Industrial Hygienists (1975) is 5 mg/m^3, expressed as Mn.

Neurological Effects

Smith (1972) reported that the primary effect of manganese inhalation is on the central nervous system with the resulting disease proportional to the

length and intensity of exposure. The symptoms he reported are shown in Table 1.

Symptoms are usually reversible by removal from exposure if diagnosed early (Smith, 1972). Chronic manganese poisoning (manganism) has been found at concentrations as low as 30 $\mu g/m^3$ of manganese dust (National Research Council, 1973). Manganism is clinically indistinguishable from Parkinsonism, a progressive neurological disease resulting from destruction of the cells of the basal ganglia (Smyth et al., 1973).

Smyth et al. (1973) reviewed the literature and found 400 cases of manganese intoxication since it was first reported over 100 years ago. They also examined 71 workers exposed for 8 hr/day to ferromanganese fume or dust and 71 controls with no exposure. Five cases with the symptoms and signs of central nervous system impairment suggestive of manganism were found. All were in the exposed group and early treatment reversed the symptoms.

Respiratory Disease

The National Research Council (1973) reported that inhalation of manganese may also result in manganic pneumonia, a form of labor pneumonia unresponsive to treatment with antibiotics. The average dose causing pneumonia is not known. Brezina (cited in National Research Council, 1973) first reported the disease in 1921 when five of ten workers in an Italian pyrolusite factory died of pneumonia after six months of exposure.

The National Research Council (1973) found seven reports of manganic pneumonia by foreign authors; however, none reported by Americans. Davies (cited by National Research Council, 1973) found an incidence of pneumonia of 26/1000 men exposed to manganese oxides compared to an incidence of 0.73/1000 in an unexposed group. The calculated concentrations for the exposed group ranged from 0.7 to 38.3 mg/m^3 as MnO_2.

NONOCCUPATIONAL EXPERIENCE

Very little work has been done in assessing community or non-occupational exposures to manganese compounds; however, several incidents have been mentioned in the literature.

The National Research Council (1973) cited a waterborne epidemic of manganese poisoning reported by Kawamura and colleagues. Old batteries buried near a family's well-water supply resulted in sickness among all six family members and ten neighbors who had drunk the water. Symbols were those of manganism. Chemical analysis showed high concentrations of manganese and zinc in the water, and in the blood and urine of the patients.

Smith (1972) reported that the production of ferromanganese, which results in higher concentrations of atmospheric manganese, historically has resulted in damage to the health of people living in the surrounding communities. No specific data were presented, however.

One of the major forms of manganese with potential health effects is the organic manganese used in gasoline. The National Research Council (1973) reported that 99 percent of the organic manganese is consumed in combustion, and the exhaust discharge is, therefore, inorganic. However, they found no studies on long-term exposures to these substances, and concluded that this area requires further study. Mena (1974) reported that manganese from gasoline combustion may be the major health concern in the future even though the maximum inhalation from gasoline is in the range of the normal daily absorption. The reason for this concern would be that the adult population is protected from manganese by intestinal and blood brain barriers which may not be effective in the fetus, newborn, and young infants. Also, the clinical consequences of iron deficient patients who absorb more manganese are undefined.

ANIMAL STUDIES

Respiratory Disease

Zaidi et al. (1973) reported that infective agents may be partially responsible for the pneumoconiosis seen in manganese workers. They inoculated guinea pigs intratracheally with *Candida albicans* (a common commensal of the upper respiratory tract of miners), with MnO_2 dust (particle size <5μm) and with a combination of the two. A dose of 50 μg MnO_2/1.5 mℓ produced a benign type pneumoconiosis after 180 days. The fibrotic reaction was comprised of thick reticulin fibers. When the guinea pigs were inoculated with *C. albicans,* slight lymphoid hyperplasia developed, but no fibrosis. A combination of the MnO_2 and the organism produced thick reticulin and collagen fibrosis. They concluded that the two substances interact and develop mature lesions earlier than either would alone.

Maigetter et al. (1976) showed exposure to MnO_2 altered the resistance of mice to bacterial and viral pneumonias. Mice exposed to MnO_2 aerosol daily for three or four days (average concentration of 109 mg/m^3) and then challenged with *Klebsiella pneumoniae* showed twice the mortality as mice without the MnO_2 exposure. Mice infected with airborne influenza virus 24 to 48 hours before initiation of MnO_2 exposures also showed increased mortality rates.

Maigetter et al. (1976) hypothesized that the cytotoxic effects of MnO_2 on alveolar macrophages may be responsible for the increased mortality observed in the above studies. The phagocytic activity of these macrophages plays an important role in the body's protective mechanisms against bacterial respiratory infections.

Gastrointestinal Effects

Chandra and Imam (1973) reported that oral administration of manganese chloride

induced alterations in the gastrointestinal mucosa of guinea pigs. A dose of 10 µg/kg given for 30 days resulted in the loss of some enzyme activities and patchy necrosis of the stomach and small intestines. Excess manganese in the gastrointestinal tract produced functional and structural alterations in the mucosal cells. The administration of large doses of manganese into the stomachs of animals has resulted in the corrosion of the gastric walls and intestines (Chandra and Imam, 1973).

Effects on Reproductive System

Singh et al. (1974) studied the changes occurring in the brain, liver, and testes of rats treated with $MnSO_4.4H_2O$ for 25 days. They found the testes to be the most vulnerable organ. Daily intraperitoneal injections of 6 mg Mn/kg dissolved in saline solution caused complete absence of spermatocytes. The seminiferous tubules had degenerated and were accompanied by biochemical alterations. They concluded that the observed inhibition of several enzymes (succinic and lactic dehydrogenases) suggested that manganese might affect the energy metabolism. These enzymes were inhibited in all three organs studied.

Chandra et al. (1973) reported that a single intratracheal injection of manganese dioxide (250 mg/kg) to rabbits resulted in marked destruction and calcification of seminiferous tubules after eight months. They also observed significantly reduced activity of acid phosphatase, adenosine triphosphatase, and succinic dehydrogenase.

Alteration of levels of various amino acids was thought to be caused by inhibition of certain enzymes. These biochemical alterations led to destruction of the seminiferous epithelium and finally calcification and sterility.

Chandra et al. (1973) also mentioned that sexual impotency had been observed in humans with chronic manganese intoxication. No data were presented, however.

Other Effects

Chandra et al. (1973) reported that the neurological syndrome is produced in experimental animals in 9 to 24 months. Singh et al. (1974) observed marked enzymatic alterations in rats' brains without any detectable histopathological changes after treatment with manganese sulphate.

Interactions with other compounds have also been observed to influence the effects manganese may have on experimental animals. Mena (1974) reported that iron deficient rats had an increase in plasma binding of manganese, leading to increased entrance to the brain.

Sunderman et al. (1974) reported that intramuscular injections of manganese to rats inhibited the tumorigenesis produced by nickel subsulfide (Ni_3S_2). In control groups given 2.1 mg of manganese, no sarcomas occurred. Rats receiving Ni_3S_2 alone had an incidence of 96 to 100 percent sarcomas, while those receiving both Mn (62 percent elemental Mn and 36 percent MnO_2) and Ni_3S_2 had an incidence of 63 percent after 24 months. Aluminum, copper, and chromium did not inhibit the effects of Ni_3S_2.

Although no recommended dietary intake has been established, a deficiency of manganese does appear to result in certain diseases. Hurley (1976) reported that manganese deficiency results in skeletal abnormalities and ataxia. Ataxia may include lack of coordination, loss of equilibrium, and head retraction, as has been observed in chickens, rats, mice, and guinea pigs.

TABLE 1: SYMPTOMS OF MANGANISM

languor
sleepiness
weakness of the legs
mask-like facial expression
muscular twitching
tremors of the hands, arms or legs
uncontrollable laughter
speech difficulty
hallucinations
mental confusion
insomnia

SOURCE: Smith (1972)

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NITROGEN OXIDES AND HUMAN HEALTH

Peter Ashbrook

INTRODUCTION

Nitrogen oxides include the following seven gases (Urone, 1976): nitrous oxide (N_2O), nitric oxide (NO), nitrogen dioxide (NO_2), nitrogen trioxide (NO_3), nitrogen sesquioxide (N_2O_3), nitrogen tetroxide (N_2O_4), and nitrogen pentoxide (N_2O_5). Only three of these, nitrous oxide, nitric oxide, and nitrogen dioxide, are important in the atmosphere (Knelson and Lee, 1977). Two hydrates, nitrous acid (HNO_2) and nitric acid (HNO_3), may exist in air. Particulate forms of nitrogen, such as aerosols of nitric acid, and salts, mainly ammonium nitrate (NH_4NO_3), have also been found.

Nitrous oxide, although having a relatively high background concentration of 0.25 ppm (Urone, 1976), is of little significance as an atmospheric pollutant. It is formed mainly by bacterial action in soil (Knelson and Lee, 1977) and is used as a mild anesthetic (laughing gas). Natural sources emit 59×10^7 tons/year with an average atmospheric residence time of four years (Stern et al., 1973).

Nitric oxide and nitrogen dioxide are often referred to as NO_x and are the most important components of nitrogen oxide air pollutants. Natural background levels in North America have been estimated to be 0.5 to 4 ppb and 0.2 to 2 ppb for nitrogen dioxide and nitric oxide, respectively (Stern et al., 1973). Nitric oxide is a colorless, odorless gas, and slightly soluble in water (United States Environmental Protection Agency (USEPA), 1971). It is formed naturally by bacterial action under anaerobic conditions. Nitrogen dioxide is a reddish-brown-orange gas with a pungent odor (USEPA, 1971). Although its boiling point is 21.2°C, the low partial pressure of nitrogen dioxide in the atmosphere restricts it to the gas phase at usual atmospheric temperatures. Manmade sources of nitrogen oxides arise chiefly from combustion processes when the temperature exceeds 1093°C (2000°F). Nitric oxide is generally produced first, but is

rapidly converted to NO_2 in air. Natural sources of NO and NO_2 amount to 43×10^7 tons/year and 66×10^7 tons/year, respectively. Manmade sources of NO and NO_2, combined, have been estimated to be 5×10^7 tons/year. The calculated atmospheric residence time for these two compounds is five days (Stern, et al., 1973).

Explosives, such as the ammonium nitrate-fuel oil mixture used on the Iron Range, can give rise to nitrogen oxides. The concentration of nitrogen oxides is several hundred parts per million in cigarette smoke, but only a small fraction exists as nitrogen dioxide (Cooper and Tabershaw, 1966). Potential sources of nitrogen oxides from copper-nickel mining activities would include explosives (such as ammonium nitrate-fuel oil), diesel machinery, and, to a lesser extent, the increased traffic that mining activities would generate, smelting, and power generation.

OCCUPATIONAL EXPERIENCE

The Threshold Limit Value (TLV) for occupational workers is 5 ppm (9 mg/m^3) for NO_2 and 25 ppm (30 mg/m^3) for NO (American Conference of Governmental Industrial Hygienists, 1975). Occupations for which high levels of nitrogen dioxide has been a recognized hazard, include silo-fillers, welders, chemists, firemen, workers in nitric acid plants, and those which use explosives (Knelson and Lee, 1977).

Respiratory Diseases

Cooper and Tabershaw (1966) wrote that "the proven effects of NO_2 in man... are confined almost entirely to the lower respiratory tract." Nitrogen dioxide is able to penetrate to the lower respiratory tract because of its low solubility. Acute effects such as odor perception, nasal irritation, discomfort on breathing, acute respiratory distress, pulmonary edema, and

death are observed as nitrogen dioxide concentrations increase.

Müller (1969) described the clinical course of seven men exposed to nitrogen dioxide following a blast in construction of a tunnel:

> "Shortly after the explosion a thick and dark smog developed and was blown by wind towards the spectators. Many of them felt a pressure in the chest and became dyspnoeic shortly thereafter."

The latent period between onset of symptoms varied from 14 hours to four weeks in five of the subjects, three of whom had to be hospitalized. Bronchitis, cough, sputum and external dyspnea were the most frequent complaints. Increased lung markings and pleural adhesions were the most frequent findings in chest radiographs of the hospitalized patients. Pathophysiological changes at seven and fourteen months after the accident were minimal. However, two patients still had symptoms (heavy bronchitis with massive sputum production) fourteen months after the accident. Both had evidence of preexisting mild bronchitis. The author did not give any estimation of nitrogen oxide concentrations.

Becklake et al. (1957) described six gold miners who had been exposed to nitrous fumes--five following an ammonium nitrate dynamite blasting operation, and one following exposure to acrid brown fumes resulting from the interaction of nitric acid with wood. Exposure ranged from 5-75 minutes. The latent period before development of pulmonary edema was 3-27 hours. Time lost from work ranged from 17 to 248 days. Four of the six patients had persistent symptoms of mild to moderate dyspnea, while two appeared to recover completely. Functional changes observed could not be attributed to early stages of pneumoconiosis. Reduction in maximal breathing capacity and increase in expiratory resistance were the most common physiologic changes. It should be noted that the authors did not know the exact composition

and concentration of the constituents of the nitrous fumes, but referred to an estimate of 52 percent nitrogen dioxide content in ammonium nitrate dynamite explosion fumes.

Lowry and Schuman (1956) described four patients who had been exposed to nitrogen oxides in silos one or two days after filling with corn silage. Cough, dyspnea, and severe weakness were immediate symptoms. About three weeks later, a second phase showed fever, progressively more severe dyspnea, cyanosis, and cough. Two of the four patients died shortly after this second phase occurred. Bronchitis obliterans was observed in all four cases.

These cases illustrate the generalizations made by Cooper and Tabershaw (1966) that repeated or continuous exposures to high concentrations of sufficient magnitude can lead to delayed or chronic pulmonary changes. Brief exposures to high concentrations of nitrogen dioxide have been found to have greater adverse effects than longer exposures to low concentrations. Threshold estimates for short term and long term effects of nitrogen dioxide are shown in Tables 1 and 2.

Combined Effects with Other Agents

According to the United States Environmental Protection Agency (1971), the effects of nitrogen dioxide and sulfur dioxide on odor perception and pulmonary function are additive.

NONOCCUPATIONAL EXPERIENCE

Currently the United States' ambient air standard for nitrogen oxides is 0.05 ppm (100 $\mu g/m^3$) as an annual arithmetic average. Knelson and Lee (1977) state that this standard is expressed as an annual mean for lack of persuasive data to establish a short-term standard.

Respiratory Disease

The most extensive study of the effects of nitrogen dioxide were conducted in Chattanooga, the site of a large TNT production plant (Shy et al. 1970a, b). Over 900 second grade children from four different sections of the Chattanooga Standard Metropolitan Statistical Area were studied. One of these areas was high in nitrogen dioxide, one high in particulates, and two were controls. Socioeconomic differences were minimized by careful selection of the areas. Air quality was monitored for nitrogen dioxide suspended nitrates, suspended sulfates, suspended particulates, and soiling index. Teams of volunteers measured the three-quarter-second forced expiratory volume ($FEV_{0.75}$) for each child weekly over the course of the four month study. These volunteers were rotated among the schools to eliminate a potential team-school bias. Nitrogen dioxide levels in the air averaged 0.083 ppm, 0.055 ppm, 0.063 ppm, and 0.043 ppm in the high nitrogen dioxide, high particulate, and two control areas, respectively. Within the high nitrogen dioxide area, the levels measured near the three schools averaged 0.109 ppm, 0.078 ppm, and 0.062 ppm.

Compared with the controls, children in the high nitrogen dioxide area had a significantly lower $FEV_{0.75}$ ($p<0.05$). However, within the high nitrogen dioxide area, neither the gradient of exposure to nitrogen dioxide nor the nitrogen dioxide concentrations on the day of testing were found to be significantly correlated with ventilatory performance.

Acute respiratory illness in these children, their siblings, and their parents was examined as well. Each household was asked to respond to the question, "Did anyone in your household have a new cold or sore throat in the past two weeks?", with a yes-no answer. All affirmative- and non-respondents were contacted to ensure a total response and severity of illness as determined by

presence of fever, length of home confinement and consultation of a doctor. All family segments in the high NO_2 area had a consistent excess (average of 18.8%) of respiratory disease over the controls during the 24 week period of the winter of 1968-69. Again, a gradient could not be found among the three subsections of the high nitrogen dioxide area. However, confounding variables such as family composition, economic level, and prevalence of chronic conditions could not explain the differences found between the high nitrogen dioxide and control areas. Nitrogen dioxide exposure alone appeared to be the most probable explanation for differences in illness rates. The authors noted that the high nitrogen dioxide concentrations observed were similar to those resulting from high-density traffic in large urban areas.

Two studies (Motley et al. 1959, and Remmers and Balchum, 1965--both cited in Goldstein, 1971) showed that patients with chronic obstructive lung disease had improved pulmonary function when breathing decomtaminated air as compared with breathing Los Angeles smog. However, particulates and ozone were also absent from the decontaminated air. Some investigators have been unable to find any correlation between low levels of nitrogen oxides and pulmonary function in patients with chronic obstructive pulmonary disease.

Other Effects

Knelson and Lee (1977) discussed the possible effects of suspended particulate nitrates. One study cited found that asthmatics living in the New York-New Jersey metropolitan area had a significant increase in asthmatic attacks when ambient suspended nitrates were increased, but only when the temperature was above $10^{o}C$. Another study in two southeastern communities produced similar, but less consistent, results.

Several authors have suggested the possibility that suspended nitrates

could be converted to nitrosamines. If this occurred to a significant extent, there would be a risk of carcinogenesis. Dimethylnitrosamine was found (Fine et al. 1976) in concentrations ranging from 0.01-1.0 ppb in air samples from Baltimore, Maryland and Belle, West Virginia. These relatively high concentrations were attributed to chemical companies. Shapley (1976) discussed the possible relationship between NO_x and nitrosamines and correlations with urban cancers.

The mutagenicity of nitrogen oxides has been reviewd by Fishbein (1976). Most of the studies appear to have concentrated on nitrous acid (HNO_2) and nitrosamines, both of which are mutagenic. However, there has been a report that nitrite (NO_2) suppresses the mutagenicity of dimethylnitrosamine which, if true, could limit the potential significance of human exposure to these two agents.

EXPERIMENTAL EVIDENCE

Human Studies

Goldstein (1971) cited two studies of human volunteers demonstrating impairment of pulmonary function after exposure to nitrogen dioxide. In one study, exposure to 4-5 ppm of nitrogen dioxide for 10 minutes increased expiratory and inspiratory flow resistance in health adults. In another, exposure to 50 ppm nitrogen dioxide for one minute was shown to cause significant nasal irritation and pulmonary discomfort.

Von Neiding et al. (1973) found a significant decrease in carbon monoxide diffusing capacity in healthy males exposed to 5 ppm nitrogen dioxide for 15 minutes. The same authors, studying chronic bronchitics, found a relationship between inhaled (30 breaths) concentration of nitrogen dioxide and increase in airway resistance over the range 1.5 to 5 ppm nitrogen dioxide;

no effect was observed when the nitrogen dioxide concentration was below 1.5 ppm.

Orehek et al. (1976) found that 0.1 ppm nitrogen dioxide significantly increased specific airway resistance and enhanced the bronchoconstrictor effect in 13 to 20 asthmatics, who had been symptom-free at the time of the study. They concluded that the incidence of asthmatic attacks could be higher in polluted areas for at least some very sensitive asthmatics. Also, indoor sources of nitrogen dioxide, such as gas stoves and gas heaters, were judged to be possibly more detrimental for many asthmatics than outdoor exposure. Morrow (1975) cited a study by Smidt and von Nieding who found a significant increase in airway resistance in patients with chronic nonspecific lung disease when exposed to two ppm nitrogen dioxide for two minutes.

Animal Studies

Goldstein (1971) and Morrow (1975) reviewed the experimental evidence derived from animal studies. Both authors note that there is a wide range of responses among the various species. Some of the key areas are summarized below:

Pathologic findings--Pathologic features similar to human emphysema have been produced in rats exposed to 10-25 ppm nitrogen dioxide for several months. However, destructive bullous lesions (which are always present in human emphysema) were absent in the rodent models. Lower exposures, 0.8-2.0 ppm nitrogen dioxide, have only minor effects on rats, and these animals have a normal lifespan. Mice show loss of cilia, alveolar cell disruption and obstruction of respiratory bronchioles after exposure to 0.5 ppm nitrogen dioxide for three months. Pneumonitis occurs after longer exposures. Again,

the pathologic abnormalities are unlike the changes observed in humans with emphysema.

Pulmonary resistance to infection--In general, these studies have shown that nitrogen dioxide depresses pulmonary resistance to infection. Bacteria, such as *Klebsiella pneumoniae,* were used to infect both control animals and those exposed to nitrogen dioxide. Adverse effects were observed in mice (Nitrogen dioxide >0.5 ppm), hamsters (at very high concentrations), and preliminary studies on monkeys (5-10 nitrogen dioxide). Depression of pulmonary resistance by nitrogen dioxide was transient in mice.

Alveolar macrophage function--Studies conducted in vivo suggest that nitrogen dioxide inhibits alveolar macrophage function. In vitro studies have shown that very high concentrations of nitrogen dioxide (176 ppm) can kill macrophages and lesser concentrations (50ppm) can significantly reduce phagoctyic function and suppress cellular energy pathways.

Mucociliary function--Apparently few studies on this subject have been performed. These have shown that nitrogen dioxide inhibits ciliary activity and thus causes a decreased rate of particle removal. However, certain deficiencies in the laboratory models were noted.

Biological oxidation--Peroxidation of lung lipids was observed in rats exposed to 1.0 ppm nitrogen dioxide for four hours a day. In addition, vitamin E was found to be partially effective in preventing these effects when induced by nitrogen dioxide.

TABLE 1: Threshold estimates for adverse health effects attributable to nitrogen dioxide (short term).

Adverse Effect	Research Approach	Type of Estimate	Exposure	
			Level $\mu g/m^3$	Exposure
Odor Perception	Clinical	Worst Case	225	5 minutes
		Least Case	835	3 minutes
		Best Judgment	225	5 minutes
Diminished exercise tolerance	Clinical	Worst Case	1900	15 minutes
		Least Case	14500	6 hours
		Best Judgment	9400	15 minutes
Susceptibility to acute respiratory infection	Toxicology	Worst Case	2800	2 hours
		Least Case	28200	3 hours
		Best Judgment	2800	2 hours
Diminished Lung Function	Clinical	Worst Case	3000	1 hour
		Least Case	9400	15 minutes
		Best Judgment	3800	1 hour
Fatality	Toxicology	Worst Case	165,000	4 hours
		Least Case	940,000	1-2 hours
		Best Judgment	188,000	1 hour

SOURCE: Finklea (1974).

TABLE 2: Threshold estimates for adverse health effects attributable to nitrogen dioxide (long term).

Adverse Effect on Human Health	Research Approach	Type of Estimate	Exposure Level $\mu g/m^3$	Exposure Duration
Increased susceptibility to acute respiratory infection	Epidemiology	Worst Case	188	For ten percent* of hrs. or days for 3 years or less
		Least Case	564	
		Best Judgment	376	
	Toxicology	Worst case	940	3 months
		Least Case	9400	3 months
		Best Judgment	940	3 months
Increased severity of acute respiratory disease	Epidemiology	Worst Case	188	For ten percent* of hrs. for at least 1 year.
		Least Case	470	
		Best Judgment	282	
	Toxicology	Worst Case	940	For 6 or more hrs. each day for 3 or more months
		Least Case	3760	
		Best Judgment	940	
Increased frequency of chronic respiratory disease symptoms	Epidemiology	Point Estimate	No increase after 3 years exposure to levels between 188 $\mu g/m^3$ and 564 $\mu g/m^3$ on ten percent of hours or days.	
	Toxicology	Worst Case	940	For 6 hrs. or more each day for 3 months or more.
		Least Case	3800	
		Best Judgment	940	
Decrease Lung Function	Epidemiology	Worst Case	188	For ten percent of hrs. for 3 years or less.
		Least Case	564	
		Best Judgment	376	
Aggravation* of Chronic heart and lung diseases			NO DATA	
Carcinogenesis*			NO DATA	
Fetotoxicity and* Mutagenesis			NO DATA	

*Through either nitrogen dioxide or nitrous acid - nitric acid - nitrate route

SOURCE: Finklea (1974)

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NOISE AND HUMAN HEALTH

Peter Ashbrook

INTRODUCTION

Noise is unwanted sound. There is no question about the definition of noise. However, sound that is pleasant to one person may be a nuisance to someone else (e.g. your neighbor's stereo system). To understand problems related with noise, some basic information about sound, along with definition of some common terms, is necessary.

Although sound is most often thought of as waves traveling through air, it can be caused by a perturbation in any medium which can be compressed and rarefied (Rudmose, 1969) such as water, wood, floors, or walls. The frequency of these waves is measured in Hertz (Hz), which is the same as cycles per second. Frequencies of 16 Hz to 20,000 Hz can be detected by the normal healthy human ear (U.S. Environmental Protection Agency (USEPA), 1973). Sound pressure detectable without pain by the human ear, ranges from 0.0001 to 100,000 microbars (one microbar equals one dyne/cm^2). Because this wide range precludes use of a linear scale, a logarithmic scale (decibels) has been developed. Decibels (dB) are calculated using a reference pressure. For noise, the reference pressure is usually 0.0002 microbars, a pressure which equals zero decibels. An increase of 20 dB corresponds to a 10-fold pressure increase (Table 1). Noise is usually reported as dBA, meaning that it was measured on the "A" scale. Because noise almost always is composed of more than one frequency, the "A" scale gives a reading for which the pressure of each frequency has been weighted according to the sensitivity of the human hear. Levels of various noises are presented in Table 2.

Natural sources of noise include: wind, rain, thunder, water splashing, animals, birds, and insects. Potential sources of noise from mining activities include: blasting, machinery, and increased traffic.

Published literature on the effects of noise is very extensive. The purpose of this review is to provide basic information about noise and to briefly discuss the reported effects of noise.

OCCUPATIONAL EXPERIENCE

Standards--Hearing impairment has been defined as an average hearing threshold level greater than 25 decibels at 500, 1000, and 2000 Hz (American Conference of Governmental Industrial Hygienists, 1975). Threshold limit values (TLVs) have been set to prevent hearing impairments resulting from continuous or intermittent noise (Table 3). Recommendations for exposure to impulsive or impact noise, which consist of noise levels with maxima more than one second apart, are shown in Table 4. The values shown in the tables have been published to guide noise control efforts and do no represent a fine boundary between safe and unsafe levels. When exposure to noise consists of several different levels, time-weighted averages are calculated to ascertain if noise exposure is excessive.

Hearing Loss--Baughn (cited by Ward, 1969) studied hearing loss caused by exposure to noise. Exposure to occupational noise below 80 dBA appeared to cause no excess hearing loss as compared to the general population. At a continuous exposure to 95 dBA, the probability of noise causing a worker's hearing loss was 50 percent. When the level of continuous noise exposure reaches 105 dBA, hearing loss occurred in nearly 100 percent of the workers habitually exposed. The frequency most sensitive to noise-induced hearing loss is 4000 Hz. Sensitivity decreases as the noise frequency becomes farther removed from this level.

Cantrell (1974) studied the effects of exposure to intermittent noise. Subjects exposed to 80 dB for 24 hours a day for 10 days exhibited little

or no effects. Exposures to 85 and 90 dB for the same time period caused small decrements in hearing and some interference with sleep.

Threshold Shifts--Threshold shifts are caused by exposure to loud noise. These shifts can be either temporary or permanent. When the temporary threshold shift is less than 40 dB, recovery proceeds in an exponential fashion and is usually complete within 16 hours. However, recovery becomes linear with time for temporary threshold shifts greater than 40 dB and may take days or weeks for complete recovery (Ward, 1969). Noises with maximum energy in high frequencies are more dangerous than those in low frequencies (ie. a screech is worse than a rumble). Intermittent noise, although more annoying, is less able to produce temporary threshold shifts than steady noise. The ear cannot be made more resistant to occasional high noise levels by exposure to lower noise levels (Ward, 1969). Drugs, time of day, hypnosis, good thoughts, or ESP have no effect on recovery from temporary threshold shifts (Ward, 1969).

Effects on Performance--Noise greater than 90 dB causes a decrease in the quality of work, but has little effect on the amount of work performed (Cohen, 1969). It has been postulated (Cohen, 1969) that high noise levels in the mining industry could be a factor behind the high accident rates observed in the industry. Studies examining the effects of noise less than 90 dB on performance have rarely shown any change in performance. Random bursts of noise are more disruptive than continuous noise.

Other Occupational Hazards--Steady noise greater than 110 dB can result in changes in the size of visual fields (Shepherd, 1974). Noise over 130 dB can cause nystagmus and vertigo (Shepherd, 1974).

Noise in the Mining Industry--The Bureau of Mines has conducted noise surveys in the mining industry. Derzay (1972) reported that levels as high as 130 dBA were found and that many levels exceeded 115 dBA. Sixty-eight different noise sources were found to create at least 90 dBA, of which four were at least 120 dBA, 14 at least 110 dBA, and 40 at least 100 dBA.

Drills powered by compressed air were the most noisy source. Drills were observed to be more noisy in harder rock formations. In general, underground mines were more noisy than open pit mines.

Results from a study of hearing impairment due to two different types and levels of noise produced by drills are presented in Table 5. In this study, 82 percent of the miners reported they used earplugs.

NONOCCUPATIONAL EXPOSURE

Effects of noise on people have not been successfully measured in terms of excess deaths, shortened lifespan, or days of incapacitating illness (Miller, 1974). Evidence of less severe effects is discussed below.

Hearing Loss--Hearing loss tends to be more common in older age groups. Loss of hearing due to the aging process is known as presbycusis. Hearing loss caused by factors other than age and occupational exposures is known as sociocusis. Examples of noise which cause sociocusis are sporting firearms, chain saws, and rock music. Two studies of hearing impairment, one on the general population and the other on a group with no excess exposure to noise (non-noise), are shown in Table 6.

Speech Interference--Perhaps the most obvious effect of noise is interference with speech. This interference, also known as masking, may cause inconvenience, disruption of work or leisure, and even potential dangers. Masking will occur if the noise level is not more than 10 dB below the speech level (Burns, 1968).

Sleep Interference--Interference with sleep is a potentially serious, but also controversial, effect of noise. There is no doubt noise can interfere with sleep. However, one can adapt to noise to such an extent that when the noise is not present, the individual may have trouble falling asleep (Burns, 1968). In addition, when an individual has not been receiving adequate sleep, the body demands more sleep, and resting periods are lengthened. Intermittent noise is more likely to interfere with sleep than continuous noise. The significance of a sound has a strong effect on sleep interference--for example, a baby's cry will awaken the mother (Burns, 1968).

Annoyance--One's attitude towards a particular noise often determines the response. For example, Cohen (1969) cited a study in which two groups of workers were exposed to the same noise. One group was told that the noise would adversely affect their performance, and it did. The other group was told that the noise would improve their performance, and their performance improved.

Jonsson and Sörensen (1970) studied the effects of attitude on annoyance reactions to noise. Responses to aircraft and motor vehicle noise were studied. One group (positive) was told that there was great concern for the residents and efforts were being made to control the noise. Another group (negative) was told that there was no concern for residents and no methods for controlling noise would be considered. There were marked differences in the responses of the two groups based on these attitudes (Table 7). Personality factors can affect response to noise (Cohen, 1979): those with greater anxiety and neurotic tendencies were more adversely affected by noise than others. Similar findings were found for introverted persons. Three generalizations can be made about the annoyance of noise (Cohen, 1969): 1) the louder the noise, the more annoying it is; 2) higher frequency sounds are more annoying; and 3) variable

sounds are more annoying than continuous sounds. Noise intruding on one's privacy can cause annoyance; that is, noise made by your neighbors is usually more annoying than the same noise produced by you (Cohen, 1969).

Complaints--Attempts have been made to relate number of complaints to the number of people disturbed by a noise. One study (cited in USEPA, 1974) found that when one percent of the people complained, 17 percent were highly annoyed as determined by a social survey. If 10 percent complained, 43 percent were highly annoyed. Based on several surveys around airports, the Organization for Economic Cooperation and Development (cited in USEPA, 1974) estimated that the percentage of annoyed people could be predicted to be equal to $2(L_{dn} - 50)$, where L_{dn} is the average day-night sound level, with a 10 dB penalty applied to nighttime levels.

Sex Differences--Miller (1974) briefly reviewed the subject of differences in sensitivity to noise between men and women. Three studies were cited that found: women shift towards lighter stages of sleep in response to noise more often than men; aircraft noise caused greater sleep disturbance in middle-aged women than middle-aged men; and women tend to wake to noises of lower levels than men. On the other hand, Siegelaub et al. (1974) found that the incidence of hearing loss among men, aged 30-59 is 2.5 to 5 times higher than women of the same age even after adjusting for previous noise exposure and smoking habits.

Effects on Children--Children may be more susceptible to adverse effects from noise than adults. Mills (1975), in a review concerning noise and children, wrote that levels of noise not interfering with speech perception in adults may interfere significantly with speech perception in children. These same noise levels may also interfere with acquisition of speech, language, and

language-related skills. Exposure of children to sufficient levels of urban noise for extended periods or during critical development periods may have deleterious effects on auditory discrimination and possible reading skills. Whether these effects are permanent or temporary is not known. Mills is extremely careful in his wording, suggesting that the effects of noise on children is highly controversial.

Mental Health--Miller (1974), in a review about the effects of noise on people, wrote, "There is no definitive evidence that noise can induce either neurotic or psychotic illness". However, noise may be able to exacerbate the effects of other stresses on mental health.

Abey-Wickrama, et al. (1969) examined psychiatric admissions to hospitals in two areas near London, one heavily exposed to aircraft noise and one which was not. Admissions were found to be significantly higher in the high noise area, attributable predominantly to older women ($\geq$45) not living with their husbands and who suffered from neurotic or organic mental illness. The authors concluded that aircraft noise could be a factor in increased rate of psychiatric admissions. A follow-up study (Gattoni, 1973) found the same trends; however, no significant differences between the high and low noise areas were found in the second study.

High Blood Pressure and Cardiovascular Disease--Some evidence exists that workers exposed to higher levels of noise have a higher incidence of cardiovascular disorders (Miller, 1974). However, other factors, such as age, dust levels, occupational danger, life habits, and other non-noise hazards could have been responsible.

Jonsson and Hansson (1977) compared 44 males with noise-induced auditory impairment greater than 65 dB with 74 males in the same industrial plant and of the same age with normal hearing (impairment less than 20 dB). Blood

pressure was significantly elevated ($p < 0.0001$) as was the proportion of hypertensives ($p < 0.05$) in those with the hearing loss.

Cantrell (1974) found that continuous exposure to intermittent noise of 80 dB caused a significant increase in blood cholesterol and plasma cortisol. When the noise was discontinued and all other conditions held the same, blood cholesterol and plasma cortisol levels decreased.

Other Effects--Higher levels of noise may be related to increased incidence of ear, nose, and throat problems, adn equilibrium disorders (Miller, 1974); but other factors may have been responsible for such findings.

ANIMAL STUDIES

Limited studies on cats and guinea pigs exposed to high-level sounds suggested that the young incur greater anatomical and physiological injuries of the inner ear than do adults (Mills, 1975).

Table 1: Formula for calculating decibels.

$$dB = 10 \log \frac{P^2}{P_r^2}$$

log = logarithm base 10

P = observed sound pressure

P_r^2 = reference sound pressure (0.0002 microbars)

Table 2: Sound pressure level of various noises.

Sound Description	Decibels	Sound Source
Threshold of feeling/pain		Rocket engine
	120	Turbojet: 7000 pounds thrust
Deafening		Propeller aircraft
	110	Nearby riveter
		Nearby thunder
	100	Jet at 1000 feet
		Subway and elevated trains
		Discotheque
Very Loud		Woodsaw, punch press
	90	Loud street noises
		Noisy factory
	80	Pneumatic drill
		Police whistle, portable sander
		Power mower at 50 feet
Loud		Noisy office
	70	Average traffic
		Normal radio
	60	Average factory
		Air conditioner at 20 feet
Moderate		Noisy home
	50	Average office
		Ordinary conversation
	40	Quiet radio
Faint	30	Quiet home
	20	Quiet conversation
Very Faint-threshold of audibility	10	Rustle of leaves
		Whisper
	0	Soundproof room

SOURCE: Bogden, 1974.

Table 3: TLVs for continuous or intermittent noise.

Maximum Duration Per Day Hours	Sound Level dBA
16	80
8	85
4	90
2	95
1	100
1/2	105
1/4	110
1/8	115*

*No exposure to continuous or intermittent in excess of 115 dBA.

SOURCE: American Conference on Governmental Industrial Hygienists 1975.

Table 4: TLVs for impulsive or impact noise.

Sound Level dB*	Number of Impulses or Impact per Day
140	100
130	1000
120	10,000

*Decibels peak sound pressure level.

SOURCE: American Conference of Governmental Industrial Hygienists 1975.

Table 5: Hearing impairment in selected occupationally exposed groups.

Percent with Hearing Impairment		
Intermittent Noise 115-120 dBA	Constant Noise 105 dBA	Age Group
2	7	20-29
20	27	30-39
26	40	40-49
65	60	50-59

SOURCE: Cited by Derzay, 1972.

Table 6: Hearing impairment in selected general population groups.

Percent with Impaired Hearing		
Non-noise (2282 tested)	General Population (20,459 tested)	Age Group
3	2	20-29
5	5	30-39
10	14	40-49
20	24	50-59

SOURCE: American Industrial Hygiene Association (1967).

Table 7: Effect of attitude on annoyance.

	Positive (n = 92)	Negative (n = 93)
	Percent	Percent
Aircraft Noise		
Serious disturbance	14.1	59.1
Considerable Disturbance	25.0	31.2
Not much, slight, or no disturbance	60.9	9.7
Motor Traffic		
Serious disturbance	27.2	75.3
Considerable disturbance	35.9	22.6
Not much, slight, or no disturbance	36.9	2.1

SOURCE: Jonsson and Sörensen, 1970

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PROCESSING CHEMICALS AND HUMAN HEALTH

Peter Ashbrook

INTRODUCTION

Processing chemicals are used in most mining operations to extract desired metals and nonmetals from the mined ore. The cost of the chemicals is such that the mining industry generally attempts to use them wisely and efficiently (Hawley, 1972). However, these relatively small amounts of chemicals (usually less than 0.5 pounds per ton of ore) added up to more than 1.75 billion pounds in 1975 in the United States (Bureau of Mines, 1976).

Potential hazards to human health from processing chemicals arise in a number of ways. Safety hazards may be present with the storage, handling, and disposal of all chemicals. Accidental spills present additional hazards. Some chemicals have toxic vapors, or may form toxic vapors upon decomposition or interaction with other substances present. Decomposition of chemicals and interactions with other substances may form hazardous products which enter the environment through water or soil as well as through air. Even if the processing chemicals do not decompose or interact, the discharge of the chemicals alone may have potential adverse implications.

This review will give a brief overview of the various types of chemicals and why they are used. Potential impacts on health of some of the more common chemicals used by the copper-nickel industry will be discussed briefly; however, the large variety of chemicals which might be used precluded all but a cursory examination of processing chemicals. It is hoped that this report will provide a foundation for more detailed studies.

PHYSICAL DESCRIPTIONS AND POTENTIAL HAZARDS

A comprehensive description and brief review of the toxicity of processing chemicals has been prepared by Hawley (1972). The information presented below is based on that document unless otherwise indicated.

Collectors

Froth flotation has been used for many years to concentrate ores. Ore is finely ground and introduced into the flotation cell as a slurry at 25-40 percent solids by weight. Air is introduced and dispersed throughout the slurry. Minerals are floated to the surface by the air bubbles, which accumulate in a froth at the surface to be skimmed off to form a concentrate.

Collectors are the most important flotation agents. These substances generally contain a polar and nonpolar group on each molecule. Mineral sulfides are attracted to the polar group, giving the molecule a nonpolar or hydrophobic character, and thus easily floated to the surface. Xanthates and dithiophosphates are the most commonly used collectors.

For copper-nickel flotation, xanthates would probably be the collector employed. Xanthates, technically known as dithiocarbonates, have the general structure given in Figure 1. In solution, xanthates coexist in equilibrium with their oxidized products, dixanthogens (Figure 1) which function as collectors also. Typical conditions of xanthate usage are 0.1 pounds per ton of ore at a pH of 8.5-10 (Rao, 1971). Known decomposition products include carbon disulfide (CS_2), hydrogen sulfide (H_2S), and sulfur dioxide (SO_2). At low concentrations of xanthates, low pH, and temperatures above 30°C, decomposition occurs quite rapidly.

Carbon disulfide has been related to cardiovascular disease, neurologic abnormalities, and possibly adverse effects on the reproductive system

(Bronson, 1977). These effects have been observed in the viscous-rayon industry (Bronson, 1977) which uses xanthates; however, there have been no reports in English literature of excess carbon disulfide exposure in the mining industry. Hydrogen sulfide has an obnoxious odor at very low concentrations and is toxic to humans at higher levels. The threshold limit values (TLVs) for carbon disulfide and hydrogen sulfide are 20 ppm and 10 ppm, respectively (American Conference of Governmental Industrial Hygienists (ACGIH), 1975). It has been reported that the National Institute of Occupational Safety and Health (NIOSH) has recommended a reduction of the TLV for carbon disulfide to one ppm (Bronson, 1977). Sulfur dioxide is discussed in another document (Regional Copper-Nickel Study, 1977).

Frothers

Frothers are used to stabilize the bubbles to which the minerals are adhered. Ideally, a frother will stabilize bubbles long enough for the froth to be removed and then break down immediately afterwards. Organic substances, having one part polar and one part nonpolar, tend to be the most effective frothers. Pine oil, cresylic acid, and certain alcohols, such as methyl isobutyl carbinol and polypropylene glycol derivatives, are the most widely used. The constituents of frothers are volatile substances, which are also found in the essential oils used in perfumes. Hence, many have a pleasant fragrance.

Pine oil is composed of terpene hydrocarbons, terpene ketones, and terpene alcohols. It appears to be readily degradeable (half-life of one day in a sewage treatment plant).

Cresylic acids used industrially are most often xylenols, but cresols are also used. Both are phenol derivatives. Methyl isobutyl carbinol (MIBC),

also known as methyl amyl alcohol, is the most commonly used frother in the U.S. (Bureau of Mines, 1976). Animal experiments have suggested that the toxicity of methyl isobutyl carbinol is similar to normal butyl alcohol. The threshold limit value of methyl isobutyl carbinol is 25 ppm (ACGIH, 1975).

Modifiers

Modifiers, for purposes of discussion, are generally used for pH control. Hence, there are two major categories: acids and bases.

Sulfuric acid is the most common acid used in the U.S. (Bureau of Mines, 1976). However, other acids, such as hydrochloric acid, are occasionally used. Acids will cause burns if spilled on exposed skin and can cause irritation to the eyes and respiratory tract. Although nonflammable, sulfuric acid may cause ignition of organic and other combustible materials (e.g. nitrates, carbides, chlorates and metallic powders). Upon contact with iron or steel, acids may cause the generation of hydrogen gas, which is quite flammable also. If acid containing waters are discharged additional adverse effects may arise due to lowering of pH and increase in total dissolved solids concentrations. Sulfuric acid is discussed in more detail elsewhere (Regional Copper-Nickel Study, 1977).

Lime (calcium hydroxide, or calcium oxide) is the most common modifier used and in fact, accounts for more than half (by weight) of all processing chemicals used in the United States (Bureau of Mines, 1976). Other less commonly used bases include ammonia, caustic soda (sodium hydroxide), and soda ash (sodium carbonate). Bases may cause tissue damage upon contact with the skin, and some are respiratory irritants. Like acids, they may alter the pH and total dissolved solids concentrations of receiving waters, if discharged. Concentrations of acids or bases which would alter pH depend upon the buffering capacity of the waters into which they are discharged.

Activators

Activators are used in the flotation process to increase the affinity of the mineral to be floated by the collector. Copper sulfate is the most widely used activator for sulfide ores. For oxidized copper ores (e.g. copper carbonate), sodium sulfide is frequently used as an activator.

Copper sulfate is widely used to control algae. Humans appear to have a relatively high tolerance for copper sulfate. Sodium sulfide, depending on the pH, can form H_2S, a toxic gas.

Depressants and Flocculants

Depressants, as their names suggest, are used for the opposite reason as activators. Sometimes separation of two minerals is difficult because the two minerals have similar affinities for various collectors. A depressing agent can be chosen to inhibit one mineral, so that it will remain in the pulp while the other mineral is floated.

Flocculants are generally used after flotation to aid in filtration of the products or to aid thickening of the finely ground pulps. Inorganic agents, such as alum or lime, can be used, as well as organic materials such as guar, starch, and polyacrylamides. These agents are also widely used in water treatment plants for public water supplies.

Very little information is readily available concerning the effects of these compounds on health.

EXPECTED USE OF PROCESSING CHEMICALS FOR COPPER-NICKEL MINING

Collectors and frothers would be used in all flotation processes. Typically, these agents would be xanthates and methyl isobutyl carbinol, respectively.

Other types of agents (modifiers, activators, depressants, and flocculants) may be used depending on the actual conditions, but these are not always necessary.

Figure 1. Structure of xanthates and dixanthogens.

R = alkyl group

X = alkali metal (K or Na)

SOURCE: Rao, 1971

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SILICOSIS

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INTRODUCTION

Silica is ubiquitous in the environment; it is composed of silicon and oxygen, which are contained in most of the compounds in the earth's crust. Silica (SiO_2) occurs in nature in three forms: quartz, cristobalite and tridymite (Ziskind et al., 1976).

Quartz is the most common of all minerals and a constituent of most rocks. It is very resistant to mechanical and chemical alterations. Breakdown of rocks containing it yields smaller quartz grains which form sand (National Institute of Occupational Safety and Health (NIOSH) 1974). Quartz is associated with feldspar and muscovite and occurs in large amounts as sand in stream beds, lakeshores, and soils.

Cristobalite and tridymite are chemically identical to quartz; however, their crystal structures differ (NIOSH, 1974). They generally occur together as silicate minerals in volcanic rocks.

The uncombined forms of these minerals are called "free silica" to distinguish them from silicates, which contain cations. Silicates and noncrystalline or amorphous silica are not considered to be associated with health problems (Ziskind et al., 1976).

Silica is an important industrial material used in the manufacture of glass and silica bricks, in mortar, and as an abrasive (NIOSH, 1974). In powdered form it is used in paints, porcelain, scouring soaps, and as a woodfiller. Presently there are more than 200 industrial processes where silica inhalation is a health hazard (Baum, 1965). The most frequent reports are from mining, tunneling, quarrying, highway construction, foundry work, sandblasting, and pottery industries.

In high doses over long periods of time silica may accumulate in the lungs and produce silicosis, a chronic fibrotic respiratory disease. The symptoms are not unique, and usually include cough, dyspnea, wheezes, and repeated nonspecific chest illnesses (NIOSH, 1974). Whereas normal lungs contain less than 0.2 grams of silica, those with silicosis may contain 15 to 20 grams (Ziskind et al., 1976). Silicosis is an occupational disease by definition and there have been no reports of any community health effects.

OCCUPATIONAL EXPOSURE TO SILICA

Silicosis is probably the oldest occupational disease known (Baum, 1965). Lung diseases have been produced from exposure to free silica or dust since the beginning of mining. Agricola mentioned a pulmonary disease produced by dust in his Treatise on Mining written in 1556. Technological advances supplying powerful energy sources have greatly increased the amount of dust produced. In the early 1900's this type of disease was widespread in metal grinders, gold miners and granite workers, and in 1866 Zenker named these diseases as the pneumoconioses (Ziskind et al., 1976).

The current Threshold Limit Value (TLV) for occupational exposure to crystalline or free silica, expressed in million particles per cubic foot (mppcf), is calculated by using the formula: 300/(percent quartz +10) (American Conference of Governmental Industrial Hygienists, 1975). The major health problems with silica occurred before this standard was set or when malfunctioning equipment or carelessness allowed concentrations to exceed these levels for long periods of time.

Workers in iron foundries and the pottery industry have been shown to have increased rates of silicosis. NIOSH (1974) reported an investigation done in 1948 of 18 iron foundries in which 9.2 percent of the workers were

found to have pulmonary fibrosis. Air samples showed that 90 percent of the airborne dust was 3 μm in diameter or less, and free silica ranged from 13 to 29 percent. An earlier study (NIOSH, 1974) had shown workers in the pottery industry had a rate of 7.8 percent silicosis.

Granite workers also had very high rates of silicosis in the early studies, but improved environmental controls have greatly reduced the dust levels and the silicosis rates. An early study of 614 granite workers exposed to dust concentrations of 37-59 mppcf, reported silicosis in 100 percent of the workers after four years (NIOSH, 1974).

A recent study by Davies et al. (1973) reported a prevalence rate of 3.0 percent in granite-cutters, and there was no evidence of pneumoconiosis in workers exposed for less than 20 years.

Effect of Silica on Respiratory System

Respiratory System

In order to understand how silicosis develops, it is necessary to first understand the basic protective mechanisms within the human respiratory system. Information in this section has been taken from Zenz (1975) and Rogan (1972).

Particles in the atmosphere are inhaled through the nose or mouth, and then travel through the pharynx, larynx, trachea, bronchi, and, if small enough, may reach the alveoli in the lungs. The body has two mechanisms to handle these intrusions, depending on where in the respiratory tract they are deposited.

The upper portion, containing the pharynx, larynx, trachea, and first several bronchi is referred to as the conducting zone, while the lower

portion containing the remaining bronchi and the alveoli is called the respiratory zone.

The particles generally tend to flow with the air in which they are suspended; however, they each possess an independent movement which may cause them to touch the wall of the respiratory tract. The wall is lined with cilia (small hairlike structures about 0.5 micron long), and these are coated with a layer of mucus which will cause the particles to stick. The cilia move in a wave-like motion and move the mucus toward the pharynx. This system will transport any insoluble particles out of the conduction zone and into the esophagus within 24 hours, where they will be swallowed and eventually eliminated from the body.

Smaller particles may pass through the conducting zone, and reach the alveoli in the respiratory zone. There they will be engulfed by macrophages within a few hours, but may not reach the mucus ciliary system for many months. Some of these particles may be retained within the lung where they are capable of causing tissue damage.

The particles deposited in the conducting zone may damage the mucosa and cause bronchitis, while those accumulating in the lung may cause pneumoconioses such as silicosis. The very soluble substances may be absorbed from all parts of the system, and the site of deposition is unimportant.

Silicosis

When silica is introduced into the body the characteristic reactions, as described above, usually occur. However, disease may result when certain sizes and concentrations of particles occur over a long enough exposure time. Particles larger than 5 μm in diameter are almost entirely deposited in the nose, pharynx, trachea and bronchi (Zenz, 1975). These particles would then

be removed by the ciliary mucus system, most within several hours, and all within 24 hours (Rogan, 1972). Particles smaller than this, however, may accumulate in the lung and result in a progressive fibrosis.

The exposure time necessary to cause silicosis is generally 5 to 30 years, but in extreme cases disease may develop within 1.5 years (Baum, 1965). Ziskind et al. (1976) reported that chronic silicosis may result from moderate exposure to dust containing less than 30 percent quartz for 20 to 40 years, and accelerated silicosis may result from higher doses for 5 to 15 years. The pathology is the same for both forms of the disease.

The numerous theories which have been proposed as to the mechanism of this reaction are generally based on the physical shape of the particles, their solubility, their cytotoxicity to macrophages, or their crystalline structure (NIOSH, 1974). Ziskind et al. (1976) have reviewed the mechanism of silicosis. The following steps are thought to occur: 1) inhalation of the silica particles, penetration to the lung tissue, and retention, 2) ingestion of the particles by macrophages, 3) death of the macrophages, 4) release of the contents of the killed cells, including the silica, 5) ingestion of the silica by other macrophages and their deaths, 6) gradual accumulation of cells, 7) production of collagen, 8) hyalinization (degeneration of the fibrous tissue), and 9) sometimes complications. The pathological stages of the silicotic lesions are related to the exposure concentration of free silica, the duration of the exposure, and the length of time the retained dust is permitted to react with lung tissue (NIOSH, 1974). The silicotic nodule produced in the lung can vary in size from 2 or 3 mm to several cm (Rogan, 1972). The earliest lesions occur in the walls of the respiratory bronchioles, and appear to form from aggregations of macrophages. The small isolated nodules formed in mild cases may never progress, a condition called discrete nodular silicosis (Rogan, 1972).

In more severe cases the large nodules may be so close together that a continuous mass of fibrous tissue is formed; this is called massive conglomerate nodular silicosis. Another form of the disease, progressive massive fibrosis, arises from a single mass of fibrous tissue and is present in the other pneumoconioses as well as silicosis (Rogan, 1972).

Complications of Silicosis

The major health effects of silica are often the complications developing from a case of silicosis. The most frequently reported is tuberculosis. Others which may develop include chronic bronchitis, emphysema and cor pulmonale. Ziskind et al. (1976) reported that the association between silica exposure and later development of tuberculosis has not been confirmed; however, Rogan (1972) reported that the association is too frequent to be coincidental. Baum (1965) reported an increased incidence of tuberculosis among silicotics and mentioned that prior to the introduction of chemotherapy for treatment the mortality rate was very high. A study of Rhodesian copper miners (Paul, 1961) showed that the attack rate of pulmonary tuberculosis was approximately 30 times greater in silicotics than nonsilicotics. Table 1 shows the attack rates observed over a ten year period.

Emphysema is another complication frequency associated with silicotic miners. In conglomerate silicosis the areas of conglomeration fibrose and contract, leading to more emphysema (Baum, 1965). The workers become breathless, begin coughing with more sputum, and become susceptible to pulmonary infection. As the fibrosis and emphysema progress, the strain on the right ventricle of the heart is increased and cor pulmonale may develop. This is often the terminal event in advanced silicosis (Baum, 1965).

Other health problems associated with silicosis include: calcified lymph nodes; perforation of the bronchial tree leading to infection and hemorrhage;

and paralysis of the phrenic or recurrent laryngeal nerves (Ziskind et al., 1976).

There is also evidence that inhalation of dusts containing only small amounts of silica (less than 10 percent) may produce nodular fibrosis (Zenz, 1975). The mining of iron ore has produced a disease known as siderosilicosis, which is though to result from the interaction so iron oxide and silica. Zenz (1975) reported that other mixed-dust pneumoconioses may result from interactions of silica, iron oxide, alumina, graphite and possibly talc.

EPIDEMIOLOGICAL STUDIES OF METAL-MINERS

The first major investigation of the silicosis problem in metal mines was carried out by the Bureau of Mines and the Public Health Service in 1914-15 (Flinn et al., 1963). Among 93 miners examined in the Joplin, Missouri mining district, 64 (68.8 percent) showed definite evidence of pulmonary disease. Thirty-nine of these 64 miners also had symptoms of tuberculosis. Samples showed that concentrations as high as 6 to 7 mg dust/100 liters of air were common. Of another 720 miners examined, 65.5 percent had silicosis, and 21.8 percent of these had pulmonary tuberculosis.

NIOSH (1974) cited an investigation of 1,018 copper mines carried out in 1916-19. Dust injury to the lungs was found in 42.4 percent of the miners, however, no dust concentrations were reported. Another early study cited by NIOSH showed 66 cases of silicosis among 727 metal miners, for an incidence rate of 9.1 percent. Dust exposures in these mines ranged from 3-37 mppcf, while free silica content ranged from 1-99 percent.

An extensive survey of silicosis in the U.S. metal mining industry was carried out by the Public Health Service and the Bureau of Mines from 1958 to 1961 (Flinn et al., 1963). They studied 67 underground mines employing approximately

20,500 persons. Environmental studies determined the concentrations of dust present and identified the occupations with the highest exposure, while the medical study diagnosed workers with silicosis and classified them according to symptoms, previous illnesses, age and length of employment.

The environmental study included 789 full-shift weighted average exposures of which 13.2 percent exceeded the 1962 threshold limit value. Although some mines had no weighted average exposures over the limit, all mines had some individual samples containing excessive dust. The type of mining operation and the sampling location within the mine affected the dust levels found. They also took 14,837 impinger samples and found slightly less than 10 percent showing excessive dust. The excess dust often resulted from improper ventilation or air recirculated from another dust-producing area. Other causes of excess dust included insufficient use of water, defective or dusty equipment, dry roadways, dry drilling, and excessive use of blowpipes. Nine percent of the impinger samples in the mills, and 21 percent collected in the crushers contained excessive dust. Dust in the mills was primarily from cleanup operations, spillage from conveyors and lack of dust control at transfer points along the conveyor. The dust at the crushers was due to improper maintenance of equipment, lack of dust collecting systems, and lack of effective ventilation. The shops and other surface locations contained excessive dust in 6.7 percent of the samples. This was from cleaning with compressed air, work in the assay labs and work in the concrete plants.

The medical study included x-rays of 14,076 workers in 50 mines. There were 476 x-rays classified as consistent with a diagnosis of silicosis, resulting in a crude prevalence rate of 3.4 percent. Thirteen of the mines studied had less than one percent of their employees affected with silicosis and five mines had greater than seven percent. The symptoms most frequently reported by the silicotic patients were chest illness and shortness of breath.

Certain jobs within the mining operation showed much higher rates. The prevalence of silicosis was highest in faceworkers in underground mines. Five percent of this group had silicosis, accounting for 62.5 percent of all diagnosed cases. The highest rate for surface workers was 3.5 percent among the mill workers. The overall prevalence among underground workers was 4.1 percent, while that for surface workers was 2.2 percent.

Silicosis rates were shown to be influenced by the age of the workers and the number of years employed in mining (Table 2). Silicosis was not observed in x-rays of miners less than 35 years of age, while 31.7 percent of the miners 65 and over had evidence of the disease. No cases occurred in workers with less than five years of exposure and 16.9 percent of those working for more than 30 years had silicosis.

The silicosis prevalence rates were found to vary according to commodity produced at the mines: iron mines, 4.2 percent; lead-zinc mines, 4.8 percent; copper mines, 3.6 percent; uranium mines, 3.1 percent; and all others, 3.7 percent.

The conclusions from this extensive investigation were that considerable progress had been made in the metal mining industry in the prevention of silicosis. Workers employed before 1935 had a substantially higher prevalence of silicosis. This is when many of the dust monitoring and control systems were begun or improved. There were, however, 128 cases of silicosis among men working since 1935, and this along with the excessive dust concentrations found, indicated the need for more dust controls. The authors concluded that combined medical and environmental surveillance and control can pervent the development of clinically significant silicosis among miners.

A study by Yakshina and Makarov (1966) of copper mines in the Central Urals reported on 0.35 percent incidence of silicosis. They, too, reported

that although the dust content had been reduced considerably in recent years, excessive dust was still a problem in many of the operations. The major problem areas were dry drilling, improper ventilation and use of outside air which had already been contaminated.

The improved conditions in these mines had, however, decreased the number of cases of silicosis, prolonged the time necessary for the development of silicosis, and changed the clinical pattern of the disease (Yakshina and Makarov, 1966). Their suggestions for prevention of silicosis in copper mines included: flushing during drilling operations; dust suppression in blasting; spraying of ore and rock during loading; spraying of the walls and roof of haulage and ventilation drifts and working mine faces; and mine ventilation for removal of dust and purification of intake air.

A study of copper miners in northern Rhodesia (Paul, 1961) showed a reduction in incidence of silicosis from 0.35 percent in 1950 to 0.06 percent in 1959. No workers whose dust exposure began after 1950 were found to have silicosis. This was attributed to improvement of ventilation and suppression of dust. The most frequent symptom of those suffering from silicosis was dyspnea; however, chest pain and an unproductive cough were reported by some workers. Paul (1961) also found that drillers had a higher incidence than other occupations even though the dust concentrations they were exposed to were often less. He suggested that this may be due to particles being freshly produced, and that the proportion of submicroscopic particles was higher. Generally, however, the concentration of dust, its silica content and the duration of exposure were found to correlate well with the chest x-ray appearances.

A study of underground metal miners in the U.S. reported by Wagoner et al. (1963) showed an increased mortality among the miners. The increase was partly due to malignant neoplasms of the respiratory system; partly to silicosis and

its complications, tuberculosis and cor pulmonale; and partly to influenza and pneumonia.

NIOSH (1974) reported that the metal mining industry in the United States had 76,000 workers in 1970, most of whom had exposure to free silica. However, a recent review (Ziskind et al., 1976) concluded that protective measures adopted in the past have almost eliminated clinical silicosis among metal miners.

ANIMAL STUDIES

Silicosis has been well documented in humans and there is little need to review the many animal studies which have been done. It is helpful however, to examine some of the studies considered by NIOSH (1974) in recommending an occupational standard for silica exposure. Silicosis has been experimentally produced in rats, guinea pigs, rabbits, dogs and monkeys. Several studies have shown that the most fibrogenic form of silica is tridymite followed by cristobalite and then quartz. Other studies cited by NIOSH (1974) found that maximal fibrogenicity was produced in rats by intratracheal injection of 50 mg quartz-cristobalite dust in the particle size range of 0.5-2 μm. Chronic inhalation studies with guinea pigs produced lesions with most of the characteristics of the silicotic nodules seen in human silicosis. The dust concentrations were 4,400 mppcf (respirable dust of 90 percent quartz) for 8 hours/day, 6 days/week for two years.

Nine separate studies cited by NIOSH (1974) have found evidence suggesting that the cytotoxic and fibrogenic activity of silica is due to the rupture of the macrophage lysosomal membrane and the release of a factor (probably lytic enzymes) which produces cytoplasmic damage as it diffuses into the surrounding medium. Once lysis of the macrophages has occurred the free silica particles cause further damage to fresh macrophages.

Rogan (1972) mentioned injection and inhalation studies which produced nodular pulmonary fibrosis. The lesions however were not quite the same as those found in humans.

Kuncova et al. (1972) examined the lung function, biochemistry and histology in silicotic and control rats. The silicosis was produced by intratracheal injection of 50 mg of quartz dust, and pulmonary function was tested four months later. Increases occurred in frequency of breathing, functional residual lung capacity, lung resistance, and oxygen consumption, while decreases occurred in lung compliance and oxygen tension of aortic blood. There was a five-fold increase in the wet weight of the silicotic lungs and many fibrotic nodules were visible. They concluded that their animal model demonstrated all of the basic functional changes of respiration present in human silicosis.

TABLE 1: Attack rate of tuberculosis on silicotic and nonsilicotic copper miners in Rhodesia.

	Silicotics			Nonsilicotics		
Year	Total	No. Developing Tuberculosis	Rate per 1,000	Total	No. Developing Tuberculosis	Rate per 1,000
1950	122	8	65.6	15,966	26	1.6
1951	124	8	64.5	16,589	17	1.0
1952	100	4	40.0	17,135	18	1.1
1953	142	6	42.3	17,384	16	0.9
1954	176	2	11.4	17,748	20	1.1
1955	194	5	25.8	18,308	18	1.0
1956	198	2	10.1	18,819	16	0.9
1957	210	3	14.3	21,389	36	1.7
1958	190	6	31.6	17,979	22	1.2
1959	169	3	17.8	20,305	13	0.6

SOURCE: Paul (1961)

TABLE 2: Percent of metal mine workers (including uranium miners) with x-ray evidence of silicosis according to age and years at metal mines.

Age in Years	YEARS AT METAL MINES					
	Total	<10	10-29	20-29	30-39	>40
Total	3.4	0.1	2.2	9.1	16.9	14.4
<20	---	---	---	---	---	---
20-29	---	---	---	---	---	---
30-39	0.2	---	0.4	2.4	---	---
40-49	3.3	0.4	2.4	6.8	15.7	---
50-59	9.8	0.9	5.7	11.9	16.0	6.6
≥60	14.2	---	5.0	12.8	19.9	18.3

SOURCE: Flinn et al. (1963)

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ZINC AND HUMAN HEALTH

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INTRODUCTION

The first descriptions of "zinck" were written by Paracelsus in the 16th century; however, evidence of its use goes back over 2000 years (Cammarota et al., 1975). Zinc oxide in calamine was mentioned in the Ebers Papyrus in 1550 B.C. (Anonymous 1975); zinc bracelets have been found dating to 500 B.C.; and the Romans used zinc alloys to make coins as early as 200 B.C. The technology of smelting was brought to Europe from China about 1730 (Cammarota et al., 1975). The U.S. first produced zinc in 1835, and was the world leader between 1901 and 1971.

Uses of zinc include: coating on iron and steel building material and battery cases, manufacture of brass, an alloy with other metals, a dust in dyes and paints and in plating in place of cadmium (Browning, 1969). It also has important uses in the transportation industry, the construction industry, electrical equipment and machinery; and chemical uses in photo-copying, rubber manufacturing, paints, and ceramics (Cammarota et al., 1975).

Zinc is a constituent of all living cells, and is essential for human life (Schroeder et al., 1967). It is an essential component of nearly 70 metal-loenzymes and is invloved in the metabolism of proteins and nucleic acids (Falchuk, 1977). Foods with high levels of zinc include seafoods, meats, whole grains, dairy products, legumes, nuts and yeast (Schroeder et al., 1967). In human tissue, zinc was found to be highest in the prostate, liver and kidney, and lowest in ectodermal tissues, brain, lung and spleen. Schroeder et al. (1967) found the approximate daily intake to be 12.6 mg (12.0 mg from food, 0.5 mg from water, and 0.1 mg from air), and concluded that zinc compounds are relatively nontoxic to living organisms, especially mammals.

OCCUPATIONAL EXPERIENCE

The most prominent health problem associated with workers exposed to zinc is metal fume fever. This can occur from inhalation of a variety of metal compounds, but is primarily due to inhalation of zinc oxide. There have also been incidents reported involving gastrointestinal effects, and effects on the skin. The American Conference of Governmental Industrial Hygienists (1975) established several threshold limit values (TLVs) for zinc depending on the chemical form present. Zinc chloride fume has a TLV of 1 mg/m^3, zinc oxide fume has a TLV of 5 mg/m^3, and zinc stearate and zinc oxide dust are classified as nuisance particulates with TLVs of 10 mg/m^3.

A NIOSH survey (Wagner, 1975) reported values of zinc in the air of U.S. copper smelters to average from <0.01 to 0.12 mg/m^3 depending on where in the smelter it is measured. These are well below the workroom standard of 5.0 mg/m^3.

Effects of Inhalation

When zinc or an alloy of zinc is burned, melted or heated to greater than 930°F, fine particles of zinc oxide are formed. Formation of fine particles of zinc oxide can occur during bronzing, galvanizing, copper rolling or welding of zinc or galvanized iron (Rohrs, 1957). Inhalation of these particles results in a disease which has been referred to in the literature as, "metal fume fever", "brass founder's ague", "zinc fever", "zinc chills", Spelters shakes", "metal shakes", (Rohrs, 1957), "glavo", "braziers disease", and "Monday fever" (Anseline, 1972).

Drinker (1922) reviewed the literature of zinc toxicity and reported the symptoms of "brass founder's ague". Thackrah was the first to recognize the disease in 1831, but zinc oxide was not confirmed as the etiological

agent until the experiments of Lehmann on himself and others in 1906. Several hours after exposure, a dryness in the throat occurs which gives rise to a cough. General lassitude, oppression in the chest, and occasional vomiting are other early symptoms. Upon leaving the area of exposure, chills are induced, and these develop into shakes with a rise in temperature. Copious sweating reduces the temperature in several hours, and there is a desire for warm drinks. The patient may feel weak in the morning, but rarely misses work.

Rohrs (1957) reported three cases of workers exposed to zinc oxide. The first case was a welder who was working in a poorly ventilated area for six hours welding galvanized iron pipes. He gradually developed a metallic taste in his mouth, and a bitemporal headache. He then experienced the onset of shaking and shivering, and soon developed a fever, nausea, and a dry cough associated with dyspnea. Examination indicated coarse breath sounds, rales, and wheezes throughout the chest. The symptoms subsided within six hours of onset without any treatment. The other two cases were workers buffing zinc coated surfaces. Both cases were initially misdiagnosed, one as infectious mononucleosis, and the other as pneumonia. The symptoms were similar to those of the first case, with the exception of the chest sounds, and both were completely recovered within 12 hours. These latter two cases were not exposed to zinc oxide, but the zinc particles produced from buffing were small enough to produce the symptoms.

Papp (1968) reported that many cases of metal fume fever may be misdiagnosed. The symptoms exhibited by the patient depend on concentration of zinc oxide inhaled, duration of the exposure, and length of time since the exposure. After four to six hours of exposure, there may be pharyngeal irritation, a metallic or sweet taste in the mouth, and an unquenchable thirst. By the end of the working day, the patient may be experiencing nausea, lethargy, and have a

nonproductive cough. Several hours later fever usually occurs (seldom over 102°F), followed by 1 to 4 hours of chills and profuse perspiration. The fever will then drop and the patient may complain of weakness or abdominal pain associated with repeated emesis, and the symptoms are usually gone within 24 to 48 hours following exposure. Depending on when the patient is seen, the clinical presentation may be that of upper respiratory infection, influenza, grippe, viremia, malaria, acute bronchitis, pneumonia, aseptic process, or a high gastrointestinal obstruction. Papp (1968) reported the case of a 32-year old welder complaining of chills, fever, muscle ache, soreness in chest, and fatigue. He had experienced these symptoms many times before and had been variously diagnosed as having flu, pneumonia, viremia, a cold, and an upset stomach.

Anseline (1972) described a 25-year old painter who was burning zinc wire to produce zinc oxide pigment. Several hours following exposure, he experienced a sudden onset of shivering, chest tightness and shortness of breath, followed by generalized myalgia and weakness, nausea, frontal headache, and paresthesia in both feet. A chest x-ray showed an increase of bronchovascular markings, but within 24 hours these were gone. Anseline concluded that particles less than 1 micron in diameter, when inhaled, can cause acute febrile illness from irritation of respiratory and alimentary systems. The mechanism is probably due to absorption of zinc oxide and release of modified proteins due to alveolar damage. Anseline also suggested that many cases of zinc-fume fever go unreported because symptoms are not sufficient to bring the patient in to a physician; and when they do, the patient may be misdiagnosed. The National Institute of Occupational Safety and Health (NIOSH) (1975) concluded that although the effects of zinc fume fever appear to be transitory, chronic respiratory effects cannot be ruled out.

Gastrointestinal Effects

NIOSH (1975) reviewed some of the early reports indicating gastrointestinal effects. They mentioned that in 1934, Kapp published a report of two cases with gastrointestinal disturbances. The first case, a mechanic, did not recover promptly from an episode of metal fume fever and experienced pressure in the stomach region, nausea, and weakness. A medical ulcer regimen alleviated the symptoms. The other case had daily exposure to fumes from a zinc oven. His symptoms included coughing, vomiting and cramp-like pains in the upper abdomen which had developed over six months. Both cases had temporary symptoms of zinc-fume fever, and indicated possible gastrointestinal effects from prolonged exposure.

Another early report was that of Chrometzka, (1936, cited in NIOSH, 1975) of 58 welders. Many of the workers complained of pressure or distention of the stomach, loss of appetite, and cramp-like pains in the abdomen. Gastritis was diagnosed in only one case, but 12 others showed signs of gastric irritation.

Hamdi (1969) studied 12 furnace workers in a brass foundry, with chronic exposure to zinc oxide, and compared them with 10 nonexposed controls. He found the concentrations of zinc to be significantly higher in the blood corpuscles, whole blood, and gastric juices of the exposed group. However, there were no symptoms or abnormalities evident in any of these workers. Anseline (1972) reported that there may be a chemical reaction which takes place between zinc oxide and gastric acid in the stomach. He indicated that milk and antacids may reduce this reaction.

Workers studied by Guja (cited in NIOSH, 1975) complained of debility, abdominal pain, acid rebound, heartburn, and loss of weight after chronic exposure to 50 mg ZnO/m^3 as zinc.

These studies appear to be inconclusive, but do indicate a potential for gastrointestinal effects from long-term exposure to zinc oxide.

Effects on Skin

NIOSH (1975) cited several early studies which indicated zinc exposure may cause an occupational dermatitis. In 1921, Turner reported that 14 of 17 men manufacturing zinc oxide had experienced a dermatitis which they called "oxide pox". These were small red papules which occurred on the arms, pubic region, scrotum and thighs. They were determined to be caused primarily by lack of personal hygiene. The workers found that if they took daily baths, the lesions did not occur.

NONOCCUPATIONAL EXPERIENCE

Health Effects from Over-exposure

The only nonoccupational health effects of zinc reported in the literature are from food-poisoning, or other accidental exposures. These will be mentioned only briefly.

Several outbreaks of food-poisoning have been reported by Brown et al. (1964). In the first case, 300 to 350 people became ill after attending a celebration at which 400 were present. The symptoms, which occurred 3 to 10 hours after eating, included severe diarrhea and abdominal cramping with half showing blood in their stools. Tenesmus was also present, and there was occasional nausea and vomiting. The average duration was 18 to 24 hours. Testing revealed zinc concentrations of greater than 2500 ppm in a galvanized tub in which chicken and spinach had been prepared, and levels as high as 1200 ppm in stools of patients. Another episode involved 100 people served an alcoholic fruit punch which was prepared in a galvanized container. Within 20 minutes nausea and vomiting occurred. Other symptoms observed included

hot taste and dryness in the mouth, diarrhea, and later, general discomfort and muscular pain. All the patients recovered within 24 hours. The concentration of zinc in the container was found to be 2200 ppm, and the dose received was calculated to be from 225 to 450 mg.

The relationship between zinc and cadmium (which is known to be toxic to mammals) may be vital in determining health effects. Schroeder et al. (1967) stated that the acute "zinc intoxication" which has been reported from ingestion of acidic foods in galvanized containers, may actually be due to cadmium.

Several other accidental exposures have been reported. These included a patient on home hemodialysis who experienced acute nausea, vomiting and fever (Gallery et al., 1972) and a boy who ingested elemental zinc and suffered from lethargy and light-headedness (Murphy, 1970). The hemodialysis patient was using rainwater which had been stored in a galvanized tank, and the symptoms disappeared when this was replaced with deionized water. The other case was a 16-year old boy who had ingested 12 grams of metallic zinc to hasten the healing of a minor laceration. His symptoms were removed with administration of a chelating agent, and there were no apparent after-effects.

The only reported deaths from zinc exposure are those which occurred in 1943 from the burning of smoke generators (Evans, 1945). Zinc chloride fumes produced from the burning of smoke generators were inhaled by 70 people in a nearby tunnel. There were 10 deaths, and symptoms included dyspnea, constriction of the chest, restrosternal and epigastric pains, nausea, red and running eyes, and a cough with copious expectoration. The harmful effects were thought to be due to the very high zinc concentrations (0.2 lb/yd^3), and the heat of the particles. In the survivors, there was some damage to the mucous membranes of the nasopharynx and respiratory tract.

Health Effects of Deficiency

Being an essential element, problems may also arise from zinc deficiency. Pories et al. (1968) reviewed the diseases associated with zinc deficiencies, and suggested that zinc may be a limiting factor in the normal growth and development of infants. Deficiencies were found in burn patients, and those with wounds. Healing was improved by addition of $ZnSO_4$ to the diet. Low zinc levels were also associated with cirrhosis, lung cancer, myocardial infarction, certain hematological disorders and atherosclerosis.

Halsted and Smith (1970) reported that plasma-zinc levels in patients with a variety of conditions were significantly lower than the 96 µg/100 mℓ found in healthy adults or the 80 µg/100 mℓ found in healthy children. The conditions involved included alcoholic cirrhosis, other liver diseases, active tuberculosis, indolent ulcers, uremia (before and after hemodialysis), myocardial infarct, nontuberculous pulmonary infection, Down's symdrome, cystic fibrosis with growth retardation, growth-retarded Iranian villagers, pregnant women and women taking oral contraceptives. Falchuk (1977) also reported the mean serum zinc of normal patients to be 96 µg/100 mℓ, while the serum zinc from acutely ill patients ranged from 40 to 92 µg/100 mℓ. The patients suffered from a variety of illnesses including: bacterial infections, renal insufficiency, pulmonary disease, neurologic disease, heart disease and carcinomas. The mean serum zinc values for all categories of disease studied were significantly reduced.

ANIMAL STUDIES

NIOSH (1975) reviewed animal studies with respect to inhalation and ingestion. Inhalation studies reported in the 1920's were inconclusive. Some reported no evidence of metal fume fever while other studies found well-defined adverse effects. More recent studies have also proven to be inconclusive. The

ingestion studies required very high concentrations (0.5 percent of diet) of zinc to produce symptoms, and these were thought to be a result of zinc-induced copper deficiency.

A survey of metal carcinogenesis by Furst and Haro (1969) indicated that injection of zinc compounds into the testes of rats produced tumors, and that the administration of zinc sulfate accelerated the growth of experimental sarcomas. Pories, et al. (1972) reported that the zinc is essential for normal proliferative processes, and may be essential for tumor growth. Growth of tumors decreased in rats fed on a zinc-deficient diet, and the survival of the rats increased. Leukemia and lung tumors were also inhibited by zinc deficiency.

In a review article, Bremner (1974) reported that most animals have a high tolerance for zinc. Levels of 500 µg/ Zn/(g of food) produced no toxic symptoms in beef cattle, and levels of 5,000 to 10,000 µg Zn/g were required to produce anemia in pigs and rats. This was thought to be caused by the animals eating less because the food was unpalatable. Reproductive failure did occur in rats fed diets containing 0.4 percent zinc. Most of the toxic effects reported (Bremner, 1974) were from interactions with other essential elements including copper, iron and calcium. When copper intake was inadequate, the clinical effects could be produced in rats with doses of 200 to 400 µg Zn/g of food.

Schroeder (1970) studied the relationship between cadmium and zinc in rats. Hypertension which was produced by the administration of cadmium could be removed by adding zinc. The determining factor appeared to be the ratio of cadmium to zinc.

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