Copper-Nickel Mining, Smelting and Refining as an Environmental Hazard to Human Health

A Review of EpidemiologicLiterature and Study Recommendations

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by

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Summary and Recommendations

It is only through epidemiologic studies -- studies of disease occurrence in a population or subset thereof -- that the risk of an environmental hazard to that population or a subset can be measured adequately. Clinical studies may provide data on the pathogenetic mechanisms of a toxic agent from the environment, but only epidemiologic studies can provide the data for causal relationships. Animal experimental studies similarly provide information on mechanisms of action of the agent, but extrapolation of dosages and effects to man is at best treacherous and provide little, if any, information on population risks and their magnitude. Thus, in this summary we have taken the liberty of outlining the nature of epidemiologic inquiry and its methods so that the literature review on copper and nickel as toxic agents in our environment and, in particular, in relation to mining and smelting operations can best be seen in perspective, the reasons for current gaps in our knowledge of risks be made clear, and the recommendations for continuation of efforts in assessing the risks justified.

Epidemiologic studies, through a description of a disease in a population and the determinants of that distribution, attempt to ascertain factors of possible etiologic significance. The vast majority of such studies are observational and rarely are intervention or experimental studies performed to obtain definitive proof of a causal relationship between a factor and a disease. Thus, conclusions regarding the etiologic importance of a given factor must be made with respect to associations or the strength of the relationship between a disease and the characteristic under study. The causal significance of an association can be assessed in terms of five factors: the strength of the association (as measured by the relative risk or odds ratio), the consistency of the association (whether a number of

studies in different areas on different populations employing various methodologic approaches all reach the same conclusion), the temporal relationship of the association (does the presence of the factor precede the occurrence of the disease?), the specificity of the association (the precision with which one component of an associated pair can be utilized to predict the occurrence of the other) and the coherence of the association (is the relationship coherent with known facts in the natural history and biology of the disease?).

Most epidemiologic studies are either descriptive or analytic. Descriptive studies describe the distribution of a disease in terms of characteristics of the person (age, sex, race, socioeconomic status, etc.), place (local, state, national and international variation, urban-rural differences, etc.) and time (secular trends, seasonal cyclicity, etc.). The basic purposes of these studies are to assist in the formulation of hypotheses or to evaluate the consistency of an hypothesis in terms of the known distribution of a disease. Analytic studies which are of two basic types, case-control and cohort, have as their basic purpose the testing of etiologic hypotheses. Case-control or retrospective studies begin with a group of individuals with a disease and a comparable group of individuals without the disease under study and seek an answer to the question, "Is the frequency of prior exposure to a factor greater among the cases than among the controls?" Cohort or prospective studies begin with a group of individuals exposed to the factor and a comparable group not exposed and seek to answer the question, "Is the frequency of disease greater among those exposed to the factor than among those not exposed?" Both approaches with their relative advantages and disadvantages can only provide information on whether an association exists between a factor and the disease.

This report includes a critical review of the relevant epidemiologic studies on populations (occupational and non-occupational) exposed to copper-nickel mining and smelting. Also included, are selected references from the experimental and clinical literature for illustrative purposes or to facilitate explanation of a possible pathogenetic pathway or mechanism of disease production. Clearly a considerable literature exists in these latter areas but a comprehensive review of these areas was beyond the scope of this initial report on the potential health effects of copper-nickel mining and smelting. Rather, only those features of the experimental and clinical literature relevant to an understanding of the population effects have in part been reviewed.

Nickel

Experimental Studies

Many experimental studies have demonstrated the carcinogenicity of a variety of nickel compounds in several species of laboratory animals. Compounds of nickel have commonly been administered intra-femorally, intra-muscularly or through inhalation. Nickel compounds given intravenously are highly toxic and, therefore, this route cannot be used to advantage in studying carcinogenesis. It is important to keep in mind the differences in results for experiments where the inhalation route was employed rather than other routes since this exposure would most closely mimic the occupational situation. However, one should always keep in mind the limitations involved in extrapolating from results of animal experiments to the situation of human disease. With regards to intra-femoral or intra-muscular injection of nickel compounds, nickel salts seem to induce tumors in inverse proportion to their solubility. Thus, lowly soluble nickel sulfide (Ni_3S_2) is highly carcinogenic whereas highly soluble nickel

sulfate ($NiSO_4$) is poorly or non-carcinogenic. Metallic nickel (usually administered in gelatin or some other suspension such as animal fat) has also been found to be carcinogenic when injected. Nickel carbonyl absorbed through inhalation is highly carcinogenic. No one, however, has been able to demonstrate the carcinogenicity of metallic nickel when administered to experimental animals through inhalation. Two studies are often referred to as demonstrating the carcinogenicity of nickel when inhaled by laboratory animals. The results of these studies, however, are based on extremely small numbers and the descriptions of the results are shaded with nebulous, cautious and uncertain language. It must be concluded that thus far it has not been possible to demonstrate the carcinogenicity of metallic nickel through inhalation in the laboratory.

Animal studies have confirmed the high toxicity of nickel carbonyl. The pulmonary parenchyma was found to be the target tissue regardless of the route of administration. The animal data give an extrapolated $L.D._{50}$ for humans of 15 mg./liter (30 minute exposure) though the investigator carrying out this work considered that value to be high. The accepted maximum allowable concentration (MAC) is 1 ppm. Multiple exposures were not found to have a cumulative effect with regards to toxicity, but many small exposures seemed to afford some protection against subsequent exposures.

Some work has been done on the effects of nickel on the reproduction systems of rats. Rats that are fed nickel in their diets and allowed to reproduce freely, produce more runts with premature deaths than do control animals. Nickel injected into male rats produces lesions in the germinal cells of the testicles.

Occupational Studies

Many studies from several countries, including Great Britain, Canada and Norway, have indicated that workers involved in the refining of nickel experience an increased risk of developing cancer of the nasal passages and of the lungs. The exact nature of the exposure that contributes to this elevated risk cannot be stated with certainty. Early investigators emphasized the role of nickel carbonyl, a highly toxic compound which plays a central role in the Mond process of nickel refining. Nickel carbonyl is certainly carcinogenic but nickel refining which does not involve nickel carbonyl has been found to be equally hazardous. Arsenic found in the nickel ore and in other compounds associated with the processing, as well as various salts of nickel, have also been considered. It is very difficult to determine the exact nature of the responsible agent or agents from existing epidemiological evidence alone and studies entertaining conclusions in this regard should be interpreted with caution. Many studies also claim that the risk of developing respiratory cancers resulted from conditions of extremely poor industrial sanitation and that the risk was alleviated when the working environment was improved. This is true to the extent that the exposures seem to have been reduced greatly after about 1940. However, some danger in some plants certainly existed as late as 1960. The most recent occupational studies have emphasized morbidity from chronic respiratory diseases rather than cancer mortality.

With the dangers of respiratory cancers resulting from occupational exposures related to nickel refining well documented, recent attention has turned towards morbidity from respiratory disease. One thorough study has been completed by the Ontario Ministry of Health. Workers who experienced a heavy exposure of sulfur dioxide, metal dusts and fumes were compared to

workers who experienced a light exposure. Histories of chronic bronchitis and respiratory function tests were compared. The high exposure groups had significantly more chronic bronchitis and significantly poorer respiratory function test results than the lower exposure groups, but the respiratory function test results in these groups were still within accepted normal limits.

Nickel carbonyl has been known to be a highly toxic substance ever since its discovery soon after the turn of the century. Sunderman is the only investigator who has presented a paper dealing solely with nickel carbonyl poisoning. In this paper he reviewed previous reports and described the results of a study which he undertook following an industrial accident in which 100 men were exposed. The initial acute symptoms of nickel carbonyl poisoning were usually mild and transitory, being relieved when the exposed person was removed to fresh air. The delayed symptoms occurred several days after and in these men death was uncommon.

Dermatitis in the nickel occupational setting is recognized as very common. The rash is generally considered to be aggravated by heat. In the only study made exclusively on nickel dermatitis in the occupational setting, Bulmer concluded that the rash was solely due to alkalosis which in turn is due to exposure to heat. This is probably an oversimplification of the true situation.

Community or Non-Occupational Studies

Only two community-wide surveys of respiratory disease and pulmonary function in relation to relevant atmospheric pollution have been found in the literature. One survey compared a heavily polluted (sulfur dioxide and particulate) city, Berlin, N.H. in which, however, nickel refining was not involved, with a pollution-free city, Chilliwack, B.C. When the results were standardized for cigarette smoking, the prevalence of respiratory

disease in the population did not seem to be associated with the degree of air pollution. Rather "cigarette smoking was found to be the most important single factor associated with respiratory disease." A second study compared the populations of Ottawa and Sudbury, the site of a large nickel refinery. Generally, the residents of Ottawa had better respiratory function test results and less chronic bronchitis. The authors suggest that occupational exposure rather than general exposure account for the disparities that were seen. Age specific disparities in respiratory disease prevalence within the authors' own data tend to contradict their conclusion.

Exposure to nickel, other than in specific nickel manufacturing occupations, has been found to be a very common cause of skin irritation. It is often reported to be aggravated by heat and perspiration. Recent studies have found that most reported cases occur as a result of exposure in small non-nickel fabricating industries such as dentistry, retailing (cashiers), tailoring etc. as well as from contact with personal items such as nickel - containing jewelry. Thus, in regard to dermatitis as a general population hazard, no evidence exists for other than direct contact with nickel in its compounded or alloyed states.

Copper

Copper is ubiquitous 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. Numerous scientific investigations have, in fact, failed to reveal any substantial deleterious health effects of metallic copper when it is encountered at "normal" levels and through the usual (non-occupational) routes of exposure. When metallic copper is encountered in such an unextraordinary fashion, it is accumulated by the human body. The concentrations of copper that are maintained vary, depending on what tissue is examined and the residence, age, sex and race of the subject from whom the specimen is obtained. Tabulations of these "normal" tissue values have been prepared and some are presented in this report. Though copper is found only in trace amounts in the human body, its presence as a cofactor is required for the normal functioning of several essential enzyme systems. All mammalian species possess mechanisms to regulate the absorption and transportation of copper within the body to ensure that proper levels are maintained.

Under certain circumstances, however, exposures to high levels of metallic copper, to copper salts, to dusts and fumes of copper or copper ores, or to the many substances that are found in conjunction with copper, or ore used in or result from the processing of copper, can lead to deleterious health effects of varying severity. High exposures to copper can be detected and monitored with accuracy and reliability by applying existing analytical techniques to specimens of human hair, nails, urine or serum. However, since the deleterious exposure is more commonly an exposure to an amalgam of substances associated with copper or the processing

of copper, the identification and monitoring of the specific responsible agent is often difficult or impossible. In such cases it is often possible only to associate exposure to an entire industrial process with certain disease conditions.

Experimental Studies

Studies utilizing laboratory animals have been conducted in an attempt to elucidate the effects of copper and its compounds under varying conditions of concentration and routes of administration. Copper sulfate, when it is injected into rats at relatively high levels, is found to cause an excess in mortality; a decrease in body weight among the survivors; an accumulation of copper in the liver, kidney, intestines and brain; inflammation of the adrenals and, at very high loading levels, decreases in the activity of certain enzyme systems, primarily hepatic enzyme systems. Copper oxide and copper sulfide are among the many metal salts which have been tested for carcinogenicity. It has been found that neither of these compounds are carcinogenic in rats and mice when they are implanted intrafemorally. Metallic copper has been found to effect the reproductive systems of rats. Injections of metallic copper cause inflammation of the testicular tissue and some interference with spermatogenesis. None of these changes, however, were irreversible.

Occupational Studies

The health effects of copper and associated compounds are most apparent in the occupational situation where the exposures are the very most intense. It should be reiterated that under these circumstances, it is often difficult or impossible to pin-point a specific compound as the causative agent of a certain disease condition. Workers who are engaged in the smelting and refining of copper experience an elevated mortality from heart disease, respiratory cancer, tuberculosis, and cirrhosis of the liver. In addition,

these workers may suffer excess morbidity from chronic respiratory disease; arsenical melanosis, dermatosis and perforation of the nasal septum; and lesions of the liver and gall bladder. The suspected responsible agents are arsenic, sulfur dioxide and, to a lesser extent, osmium. Depending on the geological situation, copper can be mined using either underground or open-pit mining. When underground mining is employed, the workers involved suffer many of the maladies commonly associated with other types of underground mining. Copper miners have been found to experience a greater than expected mortality from heart disease, respiratory neoplasms, tuberculosis, and influenza and pneumonia. In addition, an excess in morbidity from pneumoconiosis and accidents was encountered. Metal polishers and other workers exposed to the dusts of copper and other metals occasionally develop metal fume fever. This condition is characterized by transitory chills, headache, fever, nausea and malaise. No permanent effects have been observed.

Community or Non-Occupational Studies

The presence of a copper refining industry in an area has a substantial effect on the health of the entire community. Persons, who reside in one of the 36 counties in the United States which has a major copper, zinc or lead industry, have been found to develop lung cancer at a greater rate than other Americans. People from mining communities have also often been found to experience excess morbidity from chronic and acute respiratory disease. Several environmental and population studies have indicated that people living in the vicinity of a copper smelter are exposed to a high level of sulfur dioxide and particulate air pollution and that their tissues often contain a higher than expected concentration of arsenic.

Copper per se and its compounds, however, have a minor effect on the health of the general population. Copper sulfate is toxic to humans when

taken in large amounts and is occasionally used in suicide attempts, especially in Asia. Death usually occurs due to shock or liver or kidney complications. Exposures to smaller quantities of copper sulfate have been associated with hemolytic anemia. Chronic exposure to copper has, in a few instances, been related to the development of hemachromatosis. Cases of dermatitis due to exposure to copper in brass artifacts have been reported.

Recommendations

Further work is proposed in four major areas:

1. A continuation of the literature review to include epidemiologic studies of other elements associated with copper-nickel mining and processing which are considered potential health hazards to both occupational and non-occupational exposed groups. These elements would include arsenic, sulphur dioxide, particulate air pollution and silica. In addition, any new epidemiologic articles on copper-nickel mining and processing would be reviewed and incorporated into the report.
2. Maintain contact with current investigators in the area of epidemiologic study of copper-nickel mining and processing to ascertain findings early (pre-publication). A roster of such investigators has already been compiled and should be up-dated continuously.
3. Analyze available mortality data from U.S. counties in which copper-nickel mining and processing exists. This would include an age-sex-race-cause specific comparison of mortality data from these counties with similar data from contrast counties in which such activities do not exist.
4. Development of priorities and methodologies to obtain baseline data which would provide a comparison for subsequent morbidity and mortality which will occur in St. Louis and Lake Counties. This would include collection of disease data and physical specimens for storage and future analysis. Among the diseases or conditions which would have emphasis would be the several relevant cancers, chronic respiratory disease, congenital anomalies, significant increases in body burdens of trace elements and acute effects such as dermatitis and other systemic manifestations. The earlier need is the development of cooperative

participation among all the health agencies in these counties in a sound surveillance system which would not only provide a base for evaluation of long-term effects but would be sensitive enough to detect immediate acute phenomena related to the copper-nickel hazards.

5. Development of strategies and methodologies for the ongoing surveillance and screening of both occupationally and non-occupationally exposed individuals. This would be predicated upon the organization of the community and industry's development of comprehensive health records on employees. Data collection forms, methods of data collection, and analytic techniques will have to be developed and tested.

The first three activities mentioned above could yield useful information which would contribute to the assessment of the potential health effects of copper-nickel mining and processing. The latter two activities, although not contributing directly to the environmental impact statement, are necessary for the ongoing evaluation of the health status of the communities and of protective measures applied in the development of the industry.

GENERAL INTRODUCTION

A 1973 report (52) by the Minnesota Department of Natural Resources (DNR) provides background information on the past and future activities of the copper-nickel industry in the State. The report consists primarily of information on policy issues, technical matters and economic concerns relating to copper-nickel mining and was developed from information obtained from various state agencies, industry and private concerns. The report does not contain any data on the human health effects of copper-nickel development.

In 1974, Ronald Hays (30) of the University of Minnesota's Department of Civil and Mineral Engineering produced a contract report for the U.S. Bureau of Mines titled "Environmental, Economic and Social Impacts of Mining Copper-Nickel in Northeastern Minnesota." Like the DNR report, Hays assembled a comprehensive study relating the major environmental, economic, social, and engineering aspects of copper-nickel development (see Appendix 1). Hays included a short discussion of occupational safety within which he pointed out the relatively high accident rates associated with copper-nickel extraction and concluded, "the accident data show that mining and related activities are dangerous occupations with high accident rates and that underground mining is more dangerous than open pit or surface mining." Although his discussion of public health aspects was minimal, he did mention that "mining and associated activities may increase occupational and environmental health hazards because of mining and process technology and necessary air and water discharges." He concluded that public health hazards must be evaluated after specific mining and process technology have been proposed.

In an environmental impact statement by the Wisconsin Department of Natural Resources (91) a technical evaluation of the environmental impact of a proposed copper mine is presented. This report provides a technical description of the complete mining process and a list of chemicals used in the concentrating process of ore but disregards the potential health hazards of such a mine.

A report by Wagner (86) for the National Institute of Occupational Safety and Health provides an overview of environmental conditions in fifteen U.S. copper smelters (see Appendix 2). Airborne concentrations of heavy metals and SO_2 levels were determined. No chronic health effects were studied and, other than the collection and analysis of 250 urine samples, no systematic efforts to study any disease conditions were made. However, the data are useful in that they provide baseline indices of environmental conditions in copper smelters. The results of the air sampling showed that copper concentration generally exceeded the OSHA standard of 0.1 mg/M^3 for fume and 1.0 mg/M^3 for dust. Arsenic was found generally in concentrations below NIOSH recommendations although some samples exceeded the 0.05 mg/M^3 standard; and SO_2 levels were consistently elevated and varied widely both among and within the smelters. There was no description of the sampling procedures used in obtaining the urine specimens other than that they were collected from only 3-5% of the exposed population of workers. The author concluded that "The potential for arsenic induced cancers may exist in the industry, possibly potentiated by the relatively high atmospheric SO_2 concentrations. Epidemiologic studies would be required to evaluate the nature and extent of any health effects...."

The Ontario Ministry of the Environment (59) using data derived from acute toxicity studies obtained from short-term bioassay experiments,

described the toxicity of over 100 agents used in copper-nickel and other milling. Classes of chemicals examined included bulk chemicals, flotation chemicals, frothers, promoters, modifiers, flocculants and explosives. More specifically, the list of elements and compounds added at some part of the milling (crushing and separating) process included sulfuric acid, hydrochloric acid, ammonia, cyanide, cresylic acid and xanthates. The study concluded that mine-mill reagents vary in their relative short term toxicity. Some are persistent and will in all likelihood escape in some manner from the tailings dumped while others will not. The toxicity studies were applied to aquatic animal life and not to human health.

Although these reports provide some relevant technical information on the potential impact of copper-nickel development, they do not address the issue of the effects of such development on human health. The remainder of this evaluation deals with the epidemiologic evidence, supported by clinical and laboratory studies, of the effects of copper and nickel mining and smelting on human health. The paucity of good epidemiologic or experimental evidence renders any definitive decision difficult, however sufficient evidence is available to recommend precautionary or protective measures in the establishment of any new copper-nickel industry.

NICKEL

I. INTRODUCTION

Several epidemiologic studies [20,54,65] (80) have demonstrated that workers employed in the refining of nickel have a substantially elevated risk of developing lung or nasal cancer. This elevated risk can result from as little as one year of intensive exposure, but these diseases generally require over twenty years to manifest themselves.

The exact nature of the hazardous agent has not been determined. The highly toxic compound, nickel carbonyl, has been suspected of being responsible and this substance has been shown to be toxic and carcinogenic in animals. However, it is doubtful that any significant proportion of the reported disease can be attributed to this compound because many refineries do not employ the process which entails its use and because in those situations where it is used it is of necessity kept in a confined environment. It is more probable that the agent or agents are among the dust of the nickel ore and its products to which the workers are continually exposed. Animal studies have shown that refinery dust, metallic nickel and various nickel salts can be carcinogenic when they are injected or implanted into a variety of species of experimental animals. Generally, the less soluble the compound, the more carcinogenic it is. Studies employing the inhalation route of administration have failed to show that metallic nickel alone can be carcinogenic when administered through the route which most closely resembles the human exposure. Careful management of industrial hygiene in nickel plants has lead to a substantial

decrease in the risk of respiratory cancer; however, at least some risk was present in some of these plants as late as 1960. Extraordinary precautions for handling dusts in nickel plants are warranted.

With the risk of cancer among nickel workers fairly well established and largely under control, emphasis has recently been placed on morbidity among nickel workers. It has been found that workers exposed to the various dusts resulting from the refining of nickel experience a greater prevalence of chronic respiratory disease. It should be noted that this finding applies primarily to workers who smoke cigarettes. Nickel is also a common sensitizing agent for allergic dermatitis. Some instances (11) have been reported where dermatitis became a problem among workers, especially when the exposure was encountered in conjunction with the conditions of extreme heat associated with certain aspects of the refining process.

A few studies [2, (56)] have attempted to investigate the influence of nickel refining, with regards to respiratory disease, on the community in which the refinery is located. No definitive conclusions can be reached in this area because of inconsistancies in the results.

Animal studies [32,72 (90)] have shown tha metallic nickel may have a deleterious influence on reproduction. Pathological changes in rat testicular tissue as well as changes in the number and quality of progeny have been observed. This effect has not been noted in humans.

Several excellent reviews of the subject of the health effects of nickel have been produced. In 1975 the National Academy of Sciences published a volume entitled Nickel as part of the series Medical and Biological Effects of Environmental Pollutants (57). This work was an attempt to summarize the results of all the relevant literature which was available through 1974. No detailed description or critique of the methodologies is presented. The topics covered are the sources and prevalence of nickel in the environment, the metabolism of nickel and the health effects of nickel. In an article entitled Nickel Carcinogenesis, published in 1968, Sunderman (77) reviewed the occupational and experimental studies pertaining to carcinogenesis of nickel and its compounds. The possible biochemical mechanism of carcinogenesis were also presented. Several annotated charts summarizing these studies were given (see Tables 1 and 2).

Mastromatteo (49) presented a similar review entitled Nickel: A Review of Its Occupational Health Aspects in 1967. In addition to the occupational and experimental studies of cancers, Mastromatteo also discussed the process of nickel refining as it is done in plants in Canada, the toxicity of nickel and its compounds and the occupation-related disorders which have been associated with nickel.

As part of a series of reports on several common air-pollutants prepared for the National Air Pollution Control Administration, Sullivan (76) produced a report entitled Air Pollution Aspects of Nickel and Its Compounds in 1969. The emphasis is not on human health effects though this is discussed. Other topics include: the occurrence and sources of nickel and its compounds; the effects

Table 1. Cancers of the Respiratory Tract Among Nickel Workers[1]

Author	Date	Country	Major Industrial Process	Previously Unreported Respiratory Cancers	
				Lung	Nasal Sinuses
Bridge	1933	Wales	Nickel carbonyl		10
Baader	1937	Wales	Nickel carbonyl	36	6
Barrett	1948	Wales	Nickel carbonyl	46	31
Loken	1950 1956	Norway	Smelting; electrolysis	5	
Rockstroh	1958	Germany	Smelting; electrolysis	45	
Morgan	1958	Wales	Nickel carbonyl	52	14
Sutherland	1959	Canada	Smelting; electrolysis	19	7
Passey	1962	Wales	Nickel carbonyl	13	
Znamenskii	1963	USSR	Smelting	"several"	"many"
Tatarskaya	1965 1967	USSR	Electrolysis	1	2
Tsuchiya	1965	Japan	Not Specified	19	
Mastromatteo	1967	Canada	Smelting; electrolysis	18	9
			Total	254	79

[1]From: Sunderman, F., Nickel carcinogenesis. Dis. Chest, 54, 41-48, 1968.

Table 2. Prevalence[1] of Respiratory Cancer Among Nickel Workers

Author	Country	Years Studied	Exposure Group	Proportionate Mortality* Lung	Proportionate Mortality* Nasal Sinuses
Hill	Wales	1929-1938	All workers	16	196
Doll	Wales	1938-1956	All workers**	4.9	297
			Mond Process†	7.1	119
			Other Workers	3.4	37
Sutherland	Canada	1930-1957	All workers	2.2	
Tsuchiya	Japan	1957-1958	All workers	2.2	
Mastromatteo	Canada	1930-1965	All workers	2.9	96
			Furnace Workers‡	4.4	197
			Other workers	1.8	21

*Multiple of age specific male death rate from cancer of lung or nasal sinuses in relevant standard populations.

**From 1938 to 1956, 25.6 percent of all deaths among nickel workers in Glamorganshire, Wales were due to lung cancer and 9.9 percent were due to cancer of nasal sinuses.

†Men whose last employment was in the Mond nickel carbonyl process.

‡Men who worked $\geq$ 3 years in the cupola furnace.

[1]From: Sunderman, F., Nickel carcinogenesis. Dis. Chest, 54, 41-48, 1968.

of nickel and its compounds on animals, plants and materials; and the standards, costs and methods of controlling nickel in the environment.

II. EXPERIMENTAL EVIDENCE FROM ANIMAL STUDIES

A. Introduction (25,26,36,) (37,38,64,79)

Numerous investigators (12) have studied the experimental production of tumors with nickel, nickel salts and organic nickel compounds. Various routes of administration were employed and intramuscular and intrafemoral injection were commonly used. Intravenous injection was not often used because nickel compounds were usually highly toxic when received through this route. Respiratory inhalation was also commonly used since this was the route of greatest importance to human health. The results were often different when different routes of administration were used. Caution should be taken when extrapolating experimental results in animals to man.

B. Carcinogenesis

Campbell (12) was one of the earliest investigators to study nickel carcinogenesis. Fifty to sixty mice in each study and control groups were subjected to the inhalation of a variety of dusts. Two of the agents studied were "diluted nickel dust" and "sulfur dioxide plus nickel dust." In the "diluted nickel dust" group, 30% of the test animals as opposed to 13% of the controls developed tumors. The author stated that some significance was indicated by these results but provided no numerical evidence. There was no statistically significant difference in the number of animals that developed

tumors in the "sulfur dioxide plus nickel dust" group as compared with controls. The exact composition of the "nickel dust" and cell types of the tumors were not specified. Furthermore, no rationale was provided as to why nickel dust should be carcinogenic by itself but not carcinogenic when combined with sulfur dioxide.

Over a period of many years Hueper [36,37] (38) carried out an extensive series of studies on metal carcinogenesis. In the first (36) of the studies on nickel carcinogenesis, metallic nickel was administered intrafemorally to dogs, rabbits and rats; intravenously to rabbits, rats and mice; intramuscularly to mice and intrapleurally to mice. In the studies involving intrafemoral injections, none of the dogs developed tumors after five years; 27 out of 100 rats in the experimental group developed sarcomas (most involving periosteal connective tissue and other contiguous tissues) whereas none of the controls developed tumors; and one of six rabbits in the study group developed a fibrosarcoma. In the studies employing intravenous injection, no mice or rabbits developed tumors; of the 25 rats in the study group 7 developed tumors at the site of injection, 9 developed tumors at remote sites and 4 died at the time of injection. However, in the study employing intramuscular injection none of the 50 mice developed tumors. It should be recalled here that rats developed tumors in surrounding muscular tissue following spillage of nickel suspension during intrafemoral injection. In the study involving intrapleural injection, 50 mice failed to produce any signs of tumors. These studies

demonstrated the carcinogenicity of metallic nickel in animals.

In his second investigation, Hueper (37) studied the effects of metallic nickel when inhaled by mice, rats and guinea pigs. Pure nickel (from the Mond process) was administered at an average concentration of 15 mg. per cubic meter for 6 hours per day, 4 or 5 days a week for up to 21 months. The study groups included 42 guinea pigs, 160 rats and 20 mice. All of the study animals died during the exposure and an autopsy showed extensive inflammation of the lungs. Most of the guinea pigs, about one half of the rats, but none of the mice developed "adenomatoid formations." Pulmonary carcinomas developed in two of the guinea pigs. Because the identification of the tumors in the guinea pigs was not unequivocal and because only two animals developed such tumors, this evidence remains insufficient to support the contention that malignant lung tumors can be induced by inhalation in experimental animals.

Hueper's third study (38) also was concerned with the effects of the inhalation of nickel. Nickel was administered to rats and hamsters with lime dust and sulfur dioxide at the rate of 20-35 ppm with 50-65 gms. of dust exposure per day for 5-6 hours per day for up to 24 months. The dust and sulfur dioxide were added to increase the irritation of the lung tissue which was thought to facilitate the induction of lung tumors. Most of the rats showed signs of chronic inflammation of the lungs whereas few of the hamsters showed any such signs. None of the animals developed carcinomas. This study

demonstrated that even under harsh conditions, pulmonary carcinomas were not induced in laboratory animals with the inhalation of metallic nickel dust.

Gilman (26) published a very informative study of the carcinogenic properties of metallurgical dust from a nickel refinery. The composition of the dust used was found to be the following: cupric oxide (3.4%), nickel sulfate (20.0%), nickel sulfide (57.0%), nickel oxide (6.3%), cobalt oxide (1.0%), ferric oxide (1.8%), silicon dioxide (1.2%), moisture (7.3%), and miscellaneous (2.0%). Also found in small quantities (less than .1% but greater than .01%) were lead, arsenic, aluminum oxide, calcium oxide, magnesium oxide and sodium; and in trace amounts (less than .01%); bismuth, silver, tellurium, chromium, gold, and boron. In the first phase of the study the complete dust was injected intramuscularly into rats and mice. It was found that the toxicity of the dust could be reduced by washing. Both washed and unwashed dust proved to be highly carcinogenic. In the groups treated with either washed or unwashed dust 67 of (60.4%) animals produced tumors. No tumors were found among the animals treated with the supernatant which resulted from the washing of the dust. Rats developed rhabdomyoscarcomas predominantly whereas mice developed spindle-cell fibrosarcomas most often. In the second phase of the study each of the components of the refinery dust as well as several additional compounds were tested separately. Only four of the compounds, nickel oxide, nickel sulfate, cobalt oxide and cobalt sulfide, produced tumors in the animals

after 20 months. For the rats, 66% exposed to nickel oxide and 89% exposed to nickel sulfide developed tumors. Between 44% and 66% of the various strains of mice developed tumors from exposure to the nickel compounds.

Payne (64) conducted a more thorough investigation of the carcinogenicity of the various nickel salts. Nickel compounds of varying solubility were implanted with sheep fat into muscle of rats. Each treatment group consisted of 35 rats. Twelve of the rats implanted with nickel sulfide, 6 with nickel carbonate and 4 implanted with nickel oxide developed tumors. Single tumors were produced by nickel sulfate and nickel acetate. No tumors were produced by nickel chloride, nickel anhydrous acetate, nickel ammonium sulfate, nickel (+3) oxide or the fat control. The tumor types were not given. The authors concluded that the more soluble compounds were more toxic and were excreted more rapidly but that the less soluble compounds were more carcinogenic.

Sunderman (78) investigated carcinogenesis by nickel carbonyl in rats. Forty-one rats served as controls, 64 were exposed three times a week for 1 year at a low concentration (0.03 mg./L.), 32 were exposed 3 times a week for 1 year at a high concentration (0.06 mg./L.), and a fourth group was given a single exposure of nickel carbonyl at a concentration (.75 mg.L.), approximately equal to the $L.D._{50}$. Of all the animals, including the controls, 9 survived for 2 years or more, and 4 of these developed lung tumors. Two of the animals exposed to the single, very high dose developed lung tumors,

one an adenocarcinoma and the other a papillary bronchial adenoma. One of the animals exposed to the repeated doses at the low concentration developed a squamous cell carcinoma and one of the animals exposed to the repeated doses at the high concentration developed an adenocarcinoma. These results therefore seem to suggest that nickel carbonyl can induce lung tumors in experimental animals.

C. Nickel Carbonyl Poisoning

The acute toxicity of nickel carbonyl reported among humans as a result of accidental exposures has been studied in animals. Kincaid (39) performed experiments to determine the $L.D._{50}$ in mice, rats and cats. The estimated $L.D._{50}$ for 30 minutes of exposure was .067 mg./L. for mice, 0.24 mg./L. for rats, and 1.9 mg./L. for cats. In a second group of experiments, the same kinds of animals were subjected to a series of exposures of increasing intensity . In the series of ten exposures the sixth or seventh corresponded to the previously determined $L.D._{50}$. In all three species there were very few deaths among the animals that were subjected to multiple exposures. The authors concluded that several small exposures could provide protection against subsequent larger exposures. However, this would probably apply only to the short term toxic effects and not to the long term effects such as carcinogenicity. From the values of the $L.D._{50}$ determined for the various animals, Kincaid postulated the general relationship of the $L.D._{50} = 0.009 \text{ (body mass)}^{2/3}$. From this relationship the extrapolated $L.D._{50}$ for a 70 Kg. human is 15 mg./L. Kincaid considered this to be too high.

Hackett (29) made determinations of the $L.D._{50}$ for routes of administration other than inhalation. In each experiment 40 male rats were used: 5 dose groups of 8 rats each. The $L.D._{50}$ for the intravenous route was 2.2 ± 0.11 mg.Ni/100 gms.; for the subcutaneious route, 2.1 ± 42 mg.Ni/100 gms. and for the intraperitoneal route, 1.3 ± 0.14 mg.Ni/100 gms. From pathological examinations, Hackett concluded that the target tissue for nickel carbonyl was the pulmonary parenchyma regardless of the route of administration. The primary pathological changes which were noted were cellular changes of the alveolar lining cells.

D. Effects on Reproduction

A few studies which have been conducted indicate that nickel may have an adverse affect on the reproductive systems of rats.

Hoey (32) studied the effects of several heavy metal salts, including nickel sulfate, on the testicles of rats. The animals were injected with the salts in concentrations of 0.04 m-moles per kg of body weight and then killed sequentially and examined. Some animals were given multiple injections. The acute effects observed were shrinkage of the central tubules, edema, some thickening of the nuclear membrane of the Leydig cells and clumping of the chromatin. Formation of spermatozoa was not affected but separation of the head and tail of the spermatozoa was often seen. The chronic changes involved a more severe shrinkage of the central tubules, more severe nuclear changes, and damage to the Sertoli-cells. The authors

did report, however, that generally "a good deal of recovery in all cases" did occur.

The findings of Hoey have been confirmed by Waltschewa (90). In this study 30 male rats were injected with 25 mg./Kg body weight of nickel sulfate daily for 120 days. The animals were subsequently killed and the testes, livers and kidneys studied. The author reported that "severe lesions in the germ cells particularly in spermiogenesis" were found but that changes in the livers and kidneys were "scarcely observed."

Schroeder (72) investigated the various characteristics of litters produced by animals fed on diets high in specific heavy metals. The animals were fed diets of known composition and the various metals added in the drinking water. The approximate concentration of nickel in the entire diet was 5 p.p.m. Ten parameters (maternal deaths, dead litters, young dead, failure to breed, number of runts, number of litters, age at first litter, interval between litters, average litter size and male to female ratio) were studied over three generations. Among these parameters only the number of young dead and the number of runts was significantly different in the nickel-fed and control groups.

III. EPIDEMIOLOGIC STUDIES OF OCCUPATIONALLY EXPOSED GROUPS

A. Cancer

In 1932 the possibility of an elevated risk of respiratory cancers among workers at the Mond nickel refinery in Wales was first brought to the attention of the House of Commons of Great Britain (4, 3). There was no control group and no

statistical analysis was done. Also, agreement could not be reached as to whether these cancers were occupation related. By 1933, 10 cases (9 fetal) of nasal cancer were reported over an interval of 11 years (10). Again no expected values were available but it was noted that this was an extraordinary number of cases for this "little recorded site." An occupation-related etiology was strongly suspected.

Bradford Hill (31) performed the first statistical analysis of the situation in a private report prepared for the Mond Nickel Company. Hill noted that the age structure and size of the working population at the plant had not changed substantially between 1929-1938. He was able, therefore, to apply age-specific mortality rates for all of England and Wales to the "average population" of the plant to obtain the expected number of deaths from various causes. The observed: expected numbers of death were: lung cancer 16:1; nasal cancer 11: <1; other cancers 11:10 to 11; all other causes 67:72. Hill later augmented this study with data from 1948-1956. For this interval 48 deaths from lung cancer occurred whereas 10 were expected and 13 deaths from nasal cancer occurred whereas <1 would have been expected. Furthermore, Hill noted that the deaths occurred almost exclusively among "process workers" and that the elevated risk seemed to apply only to those who had started work before 1925. From the latter observation Hill concluded that the excess risk was ameliorated in 1925 when the refinery was revamped. Hill's use of an "average" population rather than a specific cohort does detract from the precision of the study. This methodology

does not account for turn-over among the workers and an inflated observed value could be obtained. In his inference concerning the risk being confined to those who started work before 1925 Hill does not seem to have properly considered the effect of age alone, that is, the workers who started before 1925 would be older and, therefore, naturally experience a greater amount of disease. His conclusion regarding the disappearance of the hazard in 1925 was not, therefore, well founded. This particular conclusion could not well be valid, but it cannot be substantiated from these data alone.

In 1949 Barnett (6) reported on this same group of workers. He noted that in the interval 1923 to 1948 there were 47 cases of nasal cancer (46 dead by the end of 1948) and 82 cases of lung cancer (72 dead by the end of 1948). No expected values were calculated. Barnet noted that there were no cases of nasal cancer and only two cases of lung cancer among those workers who had started work after 1924.

Doll (19) carried out a thorough analysis of mortality among these workers employing the vital statistics for all males who died between 1938 and 1956 in the region containing the refinery (the data were available only for certain areas within the region for the years 1938-1947). The expected numbers of deaths were obtained by employing proportionate mortality. The "other occupations" (other than heavy industrial) group was used as the standard population for determining the expected number of deaths from lung cancer. The population of England and Wales was used for the standard population in the case of nasal cancer

because it was felt that many ex-nickel workers could have been included in the "other occupations" group. Doll calculated a relative risk of 14 for lung cancer 1938-1947, 7 for lung cancer 1948-1956, 242 for nasal cancer 1938-1947, 159 for nasal cancer 1948-1956, and 196 (or greater than 29 if an expected value of less than 1 is counted as unity) for nasal cancer 1938-1956. Doll also concluded that the risk was removed or substantially reduced in 1924. This demonstration of the removal of the risk, because it is based on age-specific rates, is more thoroughly substantiated than those which had previously been offered by Hill and Barnett.

Doll (20) later performed a second study on the workers of this same plant but with more years of observation. Men who had worked for more than five years over the interval of 1939 to 1966 were followed to either death or to a termination date of January 1, 1967. There were 845 men followed; 27 additional men could not be traced. Age-specific rates for England and Wales were used as the standard rates. Again the workers were categorized by the date of their first employment. For nasal cancer among those who started work before 1925 there were 39 observed deaths as compared to 0.107 expected deaths. This corresponds to a relative risk of 364 (or 39). For those who started work after 1925 there was no elevated risk with 0 observed deaths and 0.036 expected deaths. In relation to lung cancer among those who had started work before 1925 there were 105 observed deaths as compared to 13.9 expected deaths. This corresponds to a relative risk of 7.5. For those who started

work after 1925 there were 8 observed deaths and 6 expected deaths giving a relative risk of 1.3 (no test of significance was given). Doll reiterated the fact that the risk was removed in 1925. Considering that the comparisons are based upon age-specific rates and that a sufficient period of time had elapsed between the event (the revamping of the plant in 1925) and the end of the study period (the latent period of lung cancer in this situation is generally thought to be about 25 years) it was fairly safe to conclude that the risk was, for the most part, removed in 1925.

The Sudbury district of Ontario, Candada, being the largest source of nickel for the western nations has an extensive nickel industry. Consequently, the Ontario Ministry of Health has become very interested in investigating the impact on health of this large industry. In 1959 Sutherland carried out a retrospective cohort analysis of 2355 Ontario workers involved in the nickel industry. His study was reviewed by Mastromatteo in 1967 (49). The workers were drawn from lists of employees over the interval 1930-1957 and were divided into 8 exposure categories (including several "mixed exposure" categories). The age-specific mortality rates for Ontario were applied to the accumulated person-years of exposure to obtain the expected numbers of deaths. The workers experienced fewer deaths than were expected in all categories of death except for sinus and pulmonary cancer. The observed and expected numbers of deaths for several causes are shown in Table 3. In the case of sinus cancer Sutherland noted that the magnitude of the risk increased

Table 3. Observed and expected numbers of deaths from selected causes among Ontario nickel workers, 1930-1957[1]

Cause of Death	Observed Number of Deaths	Expected Number of Deaths
All Cancers	54	43.19
Sinus Cancer	7	0.19
Pulmonary Cancer	19	8.45
Vascular lesions affecting the central nervous system	14	20.72
Respiratory diseases	13	16.21
Gastrointestinal diseases	9	16.07
All Causes	245	308

[1]From: Mastromatteo, E., Nickel: A review of its occupational health aspects, J. Occup. Med., 9, 127-136, 1967.

in proportion to the number of years of exposure to furnace work. One year of exposure to cupola furnace work and 3 years of exposure to the sintering plant seemed sufficient to lead to an elevated risk. On the other hand, no evidence was found that exposure to the calcining furnace alone contributed to sinus cancer. Workers classified as anode furnace workers, electrolytic plant workers, non-dust exposure workers and office workers had no elevated risk. Similarly, in the case of lung cancer, exposure to furnace work, other than the anode furnace, seemed to be associated with an elevated risk whereas electrolyte, non-dust, and office workers did not experience an elevated risk. Sutherland listed the risk to process workers of developing lung cancer as 2.25 times normal and the risk to furnace workers (with more than three years of furnace exposure) as 3.6 times normal.

In 1948 the sintering operations of the Port Colborne refinery were moved to Copper Cliffs. Sutherland (80) performed a second study of sinter workers who had worked at least 5 years in the interval of 1948-1967. There were 483 men included in the study; 271 of whom had worked more than five years. The age-specific mortality rates for Ontario were used to calculate the expected numbers of deaths. The number of person-years of exposure were calculated for three groups. The first group included all of the person-years of exposure that were accrued by people who had been exposed for 4 years or less. The second group included those who had been exposed 5-9 years and the third group was comprised of those who had been exposed for more than 10 years.

In this scheme a single man can contribute person-years to each of these categories if he survives more than ten years of exposure. Because of the long latent period of the diseases under consideration, this particular methodology seems to be of little value in elucidating the relationship between the length of exposure and the risk of developing a respiratory cancer. The conclusions regarding all exposure groups combined, however, are valid. There were no disparities between the number of expected deaths and the number of observed deaths for any cause of deaths except for lung cancer.

Nickel is also refined in Norway and in 1973 Pedersen (65) presented a thorough study based upon the comprehensive vital records available to the National Cancer Registry of Norway. The study included 1,916 men who had been first employed before 1961. The men were followed from 1953 to either death or 1971. The workers were divided into four exposure groups. Age-specific mortality rates for Norway were applied to the cohort at each year during the study interval to obtain the expected numbers of deaths. The greatest risk was found for those employed in roasting-smelting and electrolysis. The observed and expected numbers of deaths for each of the four employment categories for all causes, all cancers and various respiratory cancers are shown in Table 4.

In 1957-1959 Tsuchiya (84) conducted a large scale survey to determine the relationship between certain cancers and occupational exposures. In the study 400,000 subjects from 200 randomly selected enterprises were followed for three years.

Table 4. Observed and Expected Numbers of Deaths by Cause Among Norwegian Nickel Workers Employed Before 1961[1]

Type of Work	Number Employed	Total Deaths		Cancer Deaths										
				All Sites		Nasal		Larynx		Lungs		All Respiratory Organs		
		O	E	O	E	O	E	O	E	O	E	O	E	O/E
Roasting-Smelting	462	95	75.7	43	22.9	5	0.1	4	0.4	12	2.5	21	3.0	7.0
Electro-lysis	609	139	108.5	59	32.7	6	0.2	-	0.5	26	3.6	32	4.3	7.4
Other Specified Process	299	37	39.8	18	12.6	1	0.1	1	0.2	6	1.3	8	1.6	5.0
Other Unspecified Work	546	74	79.7	22	24.5	2	0.1	-	0.3	4	2.7	6	3.1	1.9
Total	1916	345	303.7	142	92.7	14	0.5	5	1.4	48	10.1	67	12.0	5.6

[1]From: Pederson, E., Cancer of respiratory organs among workers at a nickel refinery in Norway, Int. J. Ca., 12, 32-41, 1973.

Health supervisors from each of the enterprises reported all cases of cancer, all deaths from cancer and the materials which that particular enterprise handled. Expected values for the numbers of cancer deaths were obtained by applying the age-specific mortality rates for Japan for 1958. Significant positive association was found between lung cancer and industries which "handled" nickel and chromium. For these two classes combined there were 22 observed deaths from lung cancer and 10 expected deaths from lung cancer. Needless to say, the nebulous label of "industries which handle nickel and chromium" makes it impossible to relate specific exposures to the elevated risk which was found.

B. Respiratory Diseases

The only thorough study on morbidity from respiratory disease in relation to nickel refining was done by the Ontario Ministry of Health (58). In this study 310 "converter" workers and 64 "refinery" workers were studied. Converter workers were subject to exposures of sulfur dioxide, metal dusts and fumes whereas refinery workers were not. Of the converter workers, 23% (70) had a history of bronchitis whereas only 8% (5) of the refinery workers had a similar history. Among smokers, 33% (62) of the converter workers and 10% (3) of the refinery workers had a history of chronic bronchitis. Both of these disparities were significant but the difference between the two groups of smokers was more highly significant. Several indices were used to evaluate the results of the respiratory function tests but the greatest emphasis was placed on the Forced Expiratory Volume -

one second (FEV) to Forced Vital Capacity (FVC) ratio. The converter workers had significantly lower results on the respiratory function tests but these results were not lower than what the authors would have expected to find among the general population. In the no disease category (FEV/FVC > 70%) were 78% of the converter workers and 86% of the refinery workers. In the slightly diseased groups (FEV/FVC between 60% and 69%) were 13% of the converter workers and 14% of the refinery workers. In the moderately to severely diseased group (FEV/FVC 59%) were 8.4% of the converter workers and none of the refinery workers. It is important to note that in regards to smoking the authors conclude that "the different working environments did not show any determinable effects on non-smokers."

C. The only investigation of nickel dermatitis in the occupational setting was conducted by Bulmer in 1923-1925 (11) using the Inco employees at the Port Colborne refinery. All of the men who reported developing a rash during this interval were treated and interviewed by Bulmer. He noted that most of the cases of dermatitis occurred among the fair-skinned employees and those who were more susceptible to other skin irritants such as poison ivy. Bulmer was able to achieve a dramatic reduction in work hours lost, from 202 (hours lost per 105 hours worked) in 1923 to 3.7 in 1975 by treatment with oral calcium chloride and topical calamine lotion. Bulmer also applied electrolyte solutions to an unspecified number of rabbits without producing skin irritations. Because of the above evidence Bulmer concluded that "heat appears to be the

most important single contributory factor" and that "nickel rash was not directly due to contact with irritating substances." It is difficult to understand how nickel could be unrelated to dermatitis in a nickel refinery when nickel is a common cause of dermatitis and when nickel is ubiquitous in the environment. Certainly, his cursory experimental work which seemed to suggest that nickel was innocuous was inadequate.

D. Nickel Carbonyl Poisoning

Sunderman (78) reported on an accidental occupational exposure of 100 workers to nickel carbonyl. Of the 100 men, 3 were hospitalized and 2 died. As in many previous reports, the initial symptoms reported were frontal headache, dizziness, and nausea. The initial symptoms were usually mild and transitory and subsided when the patient was removed to fresh air. Several days after exposure, delayed symptoms could occur in severe cases. These symptoms included tightness in the chest, cough, dyspnea, weakness and G.I. symptoms. Death was not uncommon and resulted from loss of aerating tissue in the lungs due to hemorrhage, atelectasis and necrosis. Sunderman reported that while the urine level of nickel carbonyl declined rapidly after the first day in some patients and persisted in others, it was possible to judge the severity of the exposure by the urine level of nickel carbonyl on the first day. Sunderman considered 1.1 meq/100 ml to be a safe level. The concentrations of nickel carbonyl in the urine of the exposed men varied from 11 to 35 meq/100 ml.

IV. EPIDEMIOLOGIC STUDIES OF NON-OCCUPATIONAL EXPOSURES

A. Respiratory Diseases

In 1961 a survey for respiratory disease was conducted in the heavily polluted city of Berlin, New Hampshire. At the time of the study, it was well documented that Berlin had high levels of sulfur dioxide and particulate pollution. In 1963 a second study, employing similar methods, was conducted in Chilliwack, B.C. a city which is relatively pollution free, in order to compare the results with those found for Berlin (2). In the Berlin study 1261 persons were involved and in the Chilliwack study 557 persons aged 25-74 years were studied. The Harvard questionnaire for respiratory disease, an extensive smoking survey and lung function tests including the FVC, FEV_1, and PEFR (Peak Expiratory Flow Rate) were employed. The residents of Chilliwack were found to have generally higher results for the respiratory function test indicating better lung function. No significant difference, however, could be found in the prevalence of respiratory disease when cigarette smoking was taken into account. For males, aged 25-74, in Berlin, 38% were found to have any respiratory disease, 30% chronic bronchitis and 15% obstructive lung disease. The analogous figures for Chilliwack were 29%, 22%, and 12%. The expected Values for Chilliwack, standardized for age and smoking patterns of Berlin were 30%, 24%, and 12%; similar to those values actually observed in the Chilliwack populations. The authors concluded that smoking was the most important factor affecting respiratory disease and that, in this case, air pollution did

not seem to have a major influence on the prevalence of respiratory disease.

A second, more relevant study, was conducted in 1969-71 and 1972-73 and compared samples of the populations of Ottawa and Sudbury, the site of a major nickel refinery (56). It is generally considered that Sudbury has more sulfur dioxide air pollution whereas Ottawa has more particulate air pollution. There were 3280 residents of Ottawa and 2208 residents of Sudbury involved in the survey. The subjects were questioned concerning symptoms of respiratory disease, (using the British Medical Research Council questionnaire) smoking, residence and occupation and spirometric tests were administered. The FEV_1/FVC ratio was the index of respiratory function employed. In general the subjects from Ottawa had better results in the respiratory function tests. There were several exceptions to this, notably among the young smoker categories for both sexes. Sudbury males had a higher prevalence of chronic bronchitis (112/1000) than did males in Ottawa (72/1000). For females both Sudbury and Ottawa had an overall prevalence rate for chronic bronchitis of 81/1000. The authors interpreted these findings as indicating an effect of occupational exposures on the males of Sudbury. It is precisely the working-age males, however, who have less disease in Sudbury than in Ottawa. The prevalence of chronic bronchitis among males aged 25-44 years in Ottawa is 97/1000 whereas in Sudbury it is 95/1000. For heavy smokers (25+ cigarettes per day) in this group the prevalence is 245/1000 in Ottawa and 170/1000 in Sudbury. Moderate smokers in this age

class also have a higher rate in Ottawa than in Sudbury. Light smokers and non-smokers have a greater prevalence in Sudbury than in Ottawa. This anomaly in the data makes any definitive interpretations very difficult.

B. Dermatitis

Fisher (22) described 198 cases of nickel dermatitis taken from the files of the New York Skin and Cancer Unit during 1949-1959. Among the recorded cases of dermatitis from this unit, nickel was the second most common agent. Only paraphenylene-diamine produced a greater number of positive reactions among the patients who were seen; 180 of the cases were females and 18 were male. Common sites of irritations were ear lobes, thighs, and hands. The topical distribution and the sex disparities suggested the importance of jewelry and other personal items. Of the 40 subjects who were retested, 36 had retained their sensitivities over several years. The dermatitis was often reported to be aggravated by sweating.

A similar study was reported by Marcussen (48) who described 621 cases from the Finsen Institute in Denmark over the period 1936-1955. Fourteen percent of the cases were judged to be occupation-related. Occupations which were found to be associated with nickel dermatitis were: platers, hairdressers, tailors, nurses, doctors, dentists, cashiers and shop assistants. These occupations were considered to involve high risk because 70% or more of the cases who worked in these occupations reported dermatitis on the hands. Twenty-four or 4% of the cases were employed in the plating industry. The authors concluded that

few cases of nickel dermatitis resulted from exposures in major industries. Most exposures, they contend, were encountered in small industry and through contact with personal items containing nickel.

COPPER

I. INTRODUCTION

Copper, atomic number 29, has played a dominant role in civilization since the Stone Age. Hammered copper artifacts date from the 6th and 5th millenia B.C. Food has been cooked in copper vessels since the metal was first worked.

In 1953 the Bureau of Mines began issuing a series of papers "on important metals, the mining and processing of which may constitute a health hazard to those exposed thereto." The first in the series was a literature review of health hazards of copper done by Davenport (17) in 1953, which referenced 230 papers most published before 1935. The historical review up to 1900 shows a continuous controversy among the scientific community on health effects of copper. Sections on dietary copper, especially in milk and water, offer strong evidence of the safety of copper ingestion. A rather long portion (56 pages) of this 114 page paper was devoted to a discussion on copper in the treatment of disease; including cholera, tuberculosis, cancer and anemia. Copper poisoning in industry concerned itself with "metal fume fever." No articles were reviewed on health of miners nor were any historical descriptions included on mines or mine workers. Aside from the use of from twenty to one hundred year old research to validate conclusions of safety, one is impressed that over half the report is on material on the stated beneficial uses of copper. This review article is still often referred to in the literature.

In 1966 Walshe (89) presented a review of the literature on copper appearing between 1955 and 1967. Topics of normal copper levels in humans, copper metabolism and copper turnover were thoroughly discussed. The section on Wilson's disease with emphasis on the role of

chelating agents in treatment represented much of the work done by the author in this area of research. Toxicity, aside from Wilson's disease, was only briefly described and the occupational hazard was dismissed by a reference to Davenport's article.

In 1972 Louria et al.(45) reviewed the medical toxicology of twelve trace metals including copper. Emphasis was placed on industrial sources of intoxication, clinical manifestations and possible relationship to some relatively prevalent diseases. The discussion on copper centered around normal values, Wilson's disease and copper levels in other disease states. Toxicology was discussed in terms of acute poisoning due to ingestion of metallic copper in in food and of copper sulphate in suicide attempts.

In 1974 Cohen (15) reviewed the health hazards from copper exposure concentrating on copper dust, fumes and salt intoxication. Although admitting the paucity of industrial-linked copper intoxications in the literature, Cohen felt that the presence of the dust and fumes in a variety of settings could be a definite hazard to the health of the exposed worker. Reviewing the manifestations, he described effects on the skin, eye and respiratory, gastrointestinal, hematalogic, renal, cardiovascular and neurologic systems. Diagnosis and treatment were also elucidated with the suggestion that the chronically exposed individual should have ongoing surveillance including a screening test of 24 hour urine levels. He suggested that elevated levels, in the absence of pregnancy or some intercurrent disease, should be regarded as a reliable indicator of excess copper, though he provided no evidence to support this. Urine level surveillance should not exclude the application of the most commonly employed method of detection,

measurement of the concentration of copper fume, dust, salt mist, etc. in the ambient atmosphere of the work place. In 1965 Schroeder et al. (71) surveyed human exposures to copper, reporting on levels in twenty-two human tissues from the U.S. and eight human tissues from several other areas of the world (See Tables 5 and 6). He analyzed copper levels in food and water and called attention to the ubiquity of copper in the biosphere. Mean levels in man varied considerably from place to place with Orientals having especially high values. The brain was the only organ showing changes with age with concentrations increasing from birth to maturity. Mean hepatic copper levels in areas with soft water were significantly higher than mean values for cities with hard water.

All plant material showed copper. Copper in food showed highest values in oysters and a predilection for lipids. All terrestial animals studied contained copper with the "Standard Man" containing 100 mg. of copper, the sixth most abundant trace metal in human tissue. Copper is toxic to organisms lacking barriers to absorption which includes all living species except mammals. Monogastric animals appeared to have higher resistance than multigastric animals.

In a two part article in 1961 Adelstein and Vallee (1) reviewed the literature of the 1950's and described various aspects of copper metabolism in man. Copper concentrations in human organs and body fluids were tabulated. The physiology of copper was discussed and two metabolic disorders, albinism and hepatolenticular degeneration (Wilson's disease) were related to copper. These are inheritable disorders characterized by failure to synthesize a cuproenzyme.

Table 5. COPPER IN HUMAN TISSUES, ACCORDING TO GEOGRAPHICAL AREA
(p.p.m. ash; mean±S.E.M.)

Area	No. cases	Aorta	Brain	Heart	Kidney	Liver	Lung	Pancreas	Spleen
CHILDREN									
U.S.	23	120±16	290±20	340±26	250±14	1300±260	140±8.7	160±17	100±7.1
African	5	—	270±50	440±69	880±630	1700±450	700±570	170	—
Indian	9	240±60	510±99	350±24	380±55	1100±270	360±85	220±31	130±14
Japanese	3	180±44	350±100	310±28	410±78	2000±590	190±10	170±35	140±22
ADULTS									
U.S.	150	97±4.6	370±12	350±7.5	270±6.4	680±50	130±2.9	150±6.4	93±3.1
San Francisco	27	82±12	460±25	370±14	220±28	670±51	100±4.8	150±8	100±4
African Negroid	41	110±17	540±35	340±16	410±74	960±110	150±9.3	—	200±88
Caucasoid	13	150±22	390±37	410±74	340±69	480±87	220±37	140±14	140±15
Switzerland	9	110±59	340±45	350±30	240±42	810±120	130±5.3	140±19	100±11
India	25	200±28	450±29	320±24	540±170	1100±140	390±170	190±16	140±5.6
Lebanon	7	—	—	—	400±59	550±61	230±20	96	470±370
Japan	20	280±68	440±36	400±44	660±160	2000±340	470±190	310±65	240±35
Taipei	10	450±110	720±92	750±120	1000±110	1500±190	570±93	310±60	280±52
Hong Kong	10	140±20	310±42	370±24	560±150	1400±230	220±21	140±14	170±20
Philippines	9	240±33	520±53	350±20	560±190	1100±390	210±21	280±130	220±56
Thailand	10	150±15	400±33	280±17	690±160	1800±360	230±38	170±17	130±12
Hawaii	10	180±24	490±120	420±26	410±40	680±150	210±19	180±18	150±10

Children are those subjects under 20 years of age; nine were in the first and 14 in the second decade of life. Cases from San Francisco were treated separately [44] and are so shown. Subjects from Honolulu were largely Asiatics. The gross causes of death according to geographic area have been reported [60]; accidental deaths made up 62 per cent of the total from the United States mainland and 25 per cent of the total from foreign countries.

Table 6. COPPER IN OTHER HUMAN TISSUES, UNITED STATES VALUES

Items	No. cases	p.p.m. ash (mean ± S.E.M.)
Adrenal	13	210±15
Muscle	136	85±5.8
Diaphragm	91	150±4.2
Esophagus	66	140±10
Stomach	130	230±5.8
Duodenum	67	300±20
Jejunum	101	250±7.7
Ileum	84	280±14
Cecum	31	220±11
Sigmoid colon	108	230±7.8
Rectum	42	180±9.0
Larynx	50	59±9.4
Trachea	60	65±7.9
Ovary	16	130±8.7
Uterus	32	110±9.5
Bladder	110	120±4.6
Prostate	50	110±6.8
Testes	71	95±12
Omentum	75	190±9.4
Skin	22	120±11
Thyroid	20	100±14
Fat	28	235±14

Cartwright and Wintrobe (13) brought together data gathered since 1944 concerning various aspects of copper metabolism in normal and pregnant women subjects. Determinations (mean and 95% confidence limits) of total serum copper were 109 (81-137) µg/100 ml in men and 100 (87-153) in women. Total copper in µg/wet tissue was determined on five otherwise healthy males between the ages of 25 and 45 who died from traumatic causes. The results were: 5.1 µ/gm for the liver, 3.0 µg/gm for the heart, 2.0 µg/gm for the kidney, 0.8 µg/gm for the spleen, and 0.9 µg/gm for the muscle. Results on pregnant women showed that total serum copper increased during the third trimester of pregnancy and was as high as 346 µg%. Daily turnover of copper was estimated to be 0.6-1.6 mg absorbed per day, 0.5 to 1.2 mg excreted in the bile, 0.1-3 mg passed directly into the bile, and .01-.06 mg appeared in the urine per 24 hours. This was one of the classic papers on copper metabolism and has been referred to often in subsequent articles.

Other assay techniques for copper levels on normal subjects included spectrographic analysis of human skin, nails and hair as described by Goldblum (28). Specimens of skin, nails and hair were obtained from 18 normal, white males ranging from 15-70 in age. Copper values in skin ranged from 0.00074% to 0.00088% of dry tissue, in black hair from 0.003% to 0.013%, and in nails from 0.00094% to 0.0081%. Precision in the analysis was poor and confidence limits might have revealed more information than choosing the mean of the nine values ~~grouped in the~~ grouped in the center of the log distribution. Contamination during specimen collection in using tap water, beakers and paper towels may have influenced the results.

Tessmar, et al. in 1973 (83) showed that race, sex and age significantly affected serum copper levels (SCL) in children with no

significant interraction. Mean SCL and standard deviations were given for each age group and a regression line was plotted which showed the relationship of SCL to age in the age group 6-12. Significantly higher values in Negroes were found at all age levels as opposed to those among white and Mexican-American children where values were not significantly different. Nomograms giving a proposed correction factor for age in the two racial groupings made this a useful paper.

Copper assay in relationship to disease entities is also of interest. Hrgovcic et al.(35) did serum copper observations in patients with malignant lymphoma. High serum copper levels (means = 142.8 to 157.9 mg %) were observed in active disease in both male and female cases with non-Hodgkins lymphoma. Mean levels decreased (113.6 mg %) in remission. There was a significantly higher level in generalized as compared to localized disease. Comparisons with Hodgkins disease cases indicated a similar pattern but a group of patients with prostatic carcinoma showed no relationship between SCL and disease or radiotherapy.

An opportunity to study chronic exposure to low levels of copper presented itself in the use of metallic copper as an intrauterine contraceptive agent. Tatum (82) in 1973 reviewed some of the biological aspects of copper relevant to the reproductive processes. The concentration of copper in the endometrium, uterine fluid and cervical mucous rise to a peak during the 2-3 cycles after insertion and return to normal after removal. Serum copper levels appeared to remain constant in the control cycle but after removal fell by 10% making one wonder if oral contraceptive use in the control cycle may have already

increased copper levels as previously reported (70). The author compared theorized liver values after absorption of a daily copper loss from the I.U.D. (87.7 µg/gm) with hepatic copper values in Wilson's disease (604.7 µg/gm) in making claims of safety. A more realistic comparison would have been to use the normal adult hepatic copper (31.5 µ g/gm) as a reference point, rather than a genetic metabolic aberration.

Reproductive function and copper levels have been studies by many investigators. Schenker et al. (69) looked at serum copper levels in normal and pathologic pregnancies and found the average serum copper level in healthy men to be 108 µg% as compared to 129 µg% in normal, nonpregnant women. In normal pregnancy serum copper levels showed a progressive increase (139-297 µg%) with the advancement of gestation with a peak in the first trimester. Serum copper levels were elevated in cases of toxemia of pregnancy and hypocupremia was found in cases of prematurity, premature rupture of the membranes, and spontaneous abortion as compared to normal pregnancies.

Trace metal contents of maternal head and pubic hair and neonatal hair were studied by Baumslag (7) and a significant correlation was found between copper in maternal hair and lead in infant hair. Factors altering transfer of lead to the fetus were suggested. Correlation of zinc, copper and iron in maternal hair and their levels in the infants indicated the essentiality of these metals and the fact that the mother's hair levels may monitor the status of both mother and infant. There was a decrease in copper and zinc with increased parity in black women. The direct relationship between scalp and pubic hair probably reflected the same metabolic pool permitting use of pubic hair as biopsy material.

The influence of copper in the reproductive process has been studied in the area of contraception. Schenker (70) determined serum copper levels on 502 ambulatory females who were taking oral contraceptives both in combination and sequentially. A mean of 207 µg% was found. In 42 cases treatment was discontinued and the SCL slowly declined to normal values 4-6 weeks later. No control serums were utilized in this study to validate the technique.

The inhibition of sperm mobility described by Ullman (85) showed that under well-controlled conditions copper wire affected sperm migration and caused subsequent immobilization. Copper, added after spermatozoal penetration of the media, caused sperm motility to be arrested within 15-20 minutes with no return to motility after removal of the wire.

II. EXPERIMENTAL EVIDENCE FROM ANIMAL STUDIES

Copper toxicity has been studied experimentally by Owen (61). Accumulation of copper over time in rats, after ingestion of excess copper, was determined by organ system and mean values were compared. The three organs known to handle ionic copper directly were the ones accumulating the most copper. These included the liver (65 fold), kidney and small intestine (5 fold), large bowel (3 fold) and brain (2 fold). Urine levels increased five fold. Copper content of lung, heart, bone marrow, testes and erythrocytes remained the same. Comparisons were made between the mean values of tissue copper in Wilson's disease and those in normal and copper-loaded rats.

In 1974 Lal et al, (44) observed the effect of copper loading on various tissue enzymes in the rat. Copper treated animals showed an increased mortality after 6 weeks and, in survivors, a decrease in

body weight. The relative protection of liver enzymes and the absence of any effect on renal enzymes from the copper may have been related to the intracellular distribution and binding of the metal, localization of the enzymes and various protective mechanisms. The adrenal glands were markedly increased in size in the copper-treated rats and this may have been an indicator of chronic stress.

Chronic exposure as related to carcinogenic activity of a metallurgical powder was studied by Gilman [26,25]. A particular refinery dust, a proven potent carcinogen, was analyzed for carcinogenic activity of each component. Tumor response and average latent periods of responders were observed. Strong tumorific responses were found in the NiO, Ni_3S_2 and CoO. No carcinogenic activity up to 20 months was seen at a 20 mg site dosage of cupric oxide and 5 mg site of ferric oxide and nickel sulfate. Further studies were performed to observe the action of sulfide and speculation was presented that, since neither iron nor copper sulfide induced tumors, the sulfides had no carcinogenic activity per se but may have been true co-carcinogens. Studies were done on rats and mice with some qualitative differences in tumor effect.

In 1966 Hoey (32) did a series of experiments to determine the effect of five metals (silver, copper, tin, nickel and cobalt) administered subcutaneously on the histology and functioning of the testes and epididymis of the rat. All five metals produced acute and chronic changes in the histology of the testis and interfered, to some degree, with spermatogenesis. None of the metals produced irreversible damage to the testicular tissue. The metal which produced the most lasting damage to both tissues and spermatogenesis in all the experiments performed was copper.

III. EPIDEMIOLOGIC STUDIES OF OCCUPATIONALLY EXPOSED GROUPS

A. Introduction

Lee (42) summarized and reviewed the issue of arsenic, a by-product of copper smelting, as an occupational hazard. He stated that all compounds of arsenic are toxic. In occupationally exposed men it causes dermatitis, perforation of the nasal septum and skin ulcerations. Arsenic is usually included on the list of substances suspected of being carcinogenic to humans. The most common sites of suspected arsenic-induced cancer include the skin, lung and liver. However, Lee maintained that the evidence was not conclusive and the carcinogenicity remains "potential." He suggested that diet should be taken into account (sea food especially) in the assessment of occupational exposure by urinary arsenic determinations. Despite his recommendation, few studies have heeded this advice.

Smith (74) in a review article on an occupational hazard in the copper-nickel industry dealt with the precious metal osmium. Osmium, a rare metal of the platinum series, is produced as a by-product of the copper refining process. The national annual production of osmium amounts to only 1228 troy ounces. Therefore, although it is known to be toxic to the respiratory system in its tetroxide form, Smith does not consider it a serious environmental contaminant due to its extreme rarity. Until quantitative data are available on osmium losses to the environment during copper-nickel ore beneficiating and refining, the importance of osmium cannot be definitively established.

B. Cancer

Pinto and Bennet (66) conducted a study of the causes of death among 229 employees during 1946-1960 and pensioners of the same copper smelter that Milham and Strong (50) studied eleven years later. They compared the mortality in this group by cause of death and arsenic exposure to state-wide mortality data. Environmental exposure and measurements of arsenic concentrations were determined on the basis of materials handling, air analysis and urinalysis in 1953. Thirty-eight individuals were then placed in the exposed catagory. According to the authors, there was no evidence that chronic arsenic trioxide exposure would cause cancer or fatal cardiovascular diseases (see Table 7). Confounding variables such as age, diagnostic acumen and completeness of follow-up were assessed. As in other studies of this time period plant conditions markedly improved over time making quantification ~~of~~ of precise exposures in the past difficult. A number of unproven assumptions are made by the author. For example, "there is a tolerance range in which arsenic can be present in the body and does not produce cancer" was used to support the statement "that arsenic trioxide absorption of the range we have described in industry does not cause cancer." Both statements are written as facts where in reality the former is speculation and the latter is an improper inference. Another example was the sentence, "At present we can say arsenic trioxide was not one of the possible external factors associated with this (excess respiratory cancer in the non-arsenic exposed group) problem." A further assumption was that arsenical dermatitis was "a measure of personal hygiene

Table 7. Comparison of Smelter Mortality Distribution for Period 1946-1960 With State of Washington Male Deaths for 1958

Cause of Death	Washington State Mort. 1958, Males 15-95	Observed Smelter Mort.	Expected Smelter Mort.
Cancer	2,184	43	36.7
Cardiovascular	8,123	150	134.8
Accidents	1,020	11	16.9
All others	2,432	25	40.4
Total	13,759	229	228.8

[1]From: Pinto, S. and Bennett, B. M. Effect of arsenic trioxide exposure on mortality. Arch. Env. Hlth., 7,583-591, 1963.

Table 8. Observed and Expected Deaths for Selected Conditions, with Standardized Mortality Ratios (SMR), by Cohort, 1938-63

Cohort	Cause of Death											
	Respiratory cancer			Diseases of heart			Cirrhosis of liver			Tuberculosis		
	Observed	Expected	SMR	Observed	Expected	SMR	Observed	Expected	SMR	Observed	Expected	SMR
1	61	13.0	469*	280	258.3	108	2	5.0	40	15	12.1	124
2	37	10.0	370*	138	115.0	120†	11	4.2	262*	5	4.6	109
3	10	4.3	233†	68	51.9	131†	5	2.1	238	6	3.2	188
4	15	5.6	268*	87	60.4	144*	3	2.8	107	3	3.4	88
5	24	11.8	203*	152	128.4	118†	12	6.0	200†	15	7.8	192†

*Significant at 1% level.
†Significant at 5% level.

[1]From: Lee, A. M. and Fraumeni, J. Arsenic and respiratory cancer in man: An occupational study. J. Natl. Ca. Inst., 42, 1045-1052, 1969.

and is not a measure of the amount of arsenic absorbed by these men" - a statement totally without any scientific evidence. Analysis of the cancer data itself was incomplete. Fifteen and three lung cancer deaths were observed in the "non-arsenic" exposed and arsenic exposure groups respectively as compared to expected values of 7.2 and 1.4. Regarding these figures, the authors state, "This comparison shows there were a few more deaths in the non-arsenic-exposed respiratory cancer group than were to be expected by calculation, and further study of these cases is continuing." However the increase of lung cancer deaths for the two groups combined was in fact significant ($X^2_{(1)} = 10.27$, $p < .005$).

In contrast to the former paper, Lee and Fraumeni's 1969 study (42) was well conducted. This study, similar in design to Pinto's study, compared death records of 8,047 white male smelter workers exposed to arsenic trioxide to the white male population of the same state. The data were age adjusted, and socioeconomic, genetic, diagnostic acumen and urbanization factors were considered. Ninety percent of the group was followed up and during the period 1938-1963, 1877 were known to have died. Overall, there was a 15% excess of deaths over expected. Tuberculosis, respiratory cancer, heart disease and cirrhosis showed significant excesses as causes of deaths. When analyzed by length of employment, respiratory cancer was in excess in all time and exposure cohorts, and a gradient by degree of arsenic exposure was seen (see Table 8). The latent period for respiratory cancer was established to be 34-41 years. Sulphur dioxide exposure was positively related to cancer, though the gradients were not as consistent, suggesting

that it may contribute to or enhance the effect of arsenic induced cancer. The authors were unclear as to how the arsenic trioxide exposure was measured. Most importantly, the types of smelters involved in the study were not identified.

The first study of mining and lung cancer was carried out by Wagoner (87). Death certificates of 930 miners out of 75,000 engaged in mining at different mines from 1948-1959 were analyzed. Causes of death were classified according to the 6th revision of the International List of Diseases and Causes of Death. The objective of the study was to determine the influence of fifteen or more years of underground metal mining on mortality. The mortality rates for the white population of the states in which the mines were located were used for comparison. The data were age adjusted and cigarette smoking, country of birth, socioeconomic status, genetics and diagnostic acumen were considered. The standardized mortality rates were significantly greater than 100 for virtually all causes of death with the exception of vascular lesions affecting the central nervous system, motor vehicle accidents, and suicide and homicide (see Table 9). The causes for the observed excess in mortality were not, and could not, be adequately assessed in this paper. Atmospheric pollution from nearby smelters may have affected the observed results. The type of metal mining varied from mine to mine and was not quantitated by the author. It was mentioned that, "In addition to silica the ore from the mines in this study contains the following substances, in order of diminishing quantities: sulfur, iron, copper, zinc, manganese, lead, arsenic, calcium, fluorine, antimony and silver."

Table 9. Standardized Mortality Ratios, with Numbers of Expected and Observed Deaths According to Cause, among Metal Miners, January 1, 1937, through December 31, 1959.

CAUSE OF DEATH	LIST NO.*	COHORT I			COHORT II			TOTALS		
		EXPECTED DEATHS	OBSERVED DEATHS	STANDARDIZED MORTALITY RATIOS	EXPECTED DEATHS	OBSERVED DEATHS	STANDARDIZED MORTALITY RATIOS	EXPECTED DEATHS	OBSERVED DEATHS	STANDARDIZED MORTALITY RATIOS
Tuberculosis	(001-019)	8.9	61	685†	7.5	68	907†	16.4	129	787†
Respiratory	(001-008)	8.5	61	718†	7.1	65	915†	15.6	126	808†
Other	(010-019)	0.4	--	---	0.4	3	750‡	0.8	3	375
Malignant neoplasms	(140-199)	36.2	64	177†	37.7	71	188†	73.9	135	183†
Digestive system	(150-159)	17.4	24	138	16.8	27	161‡	34.2	51	149†
Respiratory system§	(160-164)	7.0	22	314†	9.1	25	275†	16.1	47	292†
Other	(140-148, 165-170, 177-181, 190-199)	11.8	18	153	11.8	19	161	23.6	37	157‡
Vascular lesions affecting central nervous system	(330-334)	25.4	14	55‡	23.8	20	84	49.2	34	69‡
Diseases of heart	(400-443)	107.5	166	154†	118.5	146	123‡	226.0	312	138†
Influenza & pneumonia	(480-483, 490-493)	10.0	21	210†	8.2	19	232†	18.2	40	220†
Accidents	(800-962)	18.5	23	124	23.0	38	165†	41.5	61	147†
Motor vehicle	(810-825, 830-835)	5.1	2	39	6.9	6	87	12.0	8	67
Other	(800-802, 840-962)	13.4	21	157	16.1	32	199†	29.5	53	180†
Suicides & homicides	(963-964, 970-979, 980-985)	6.4	2	31	8.3	1	12†	14.7	3	20†
All other causes	(Residual)	65.1	97	149†	65.9	119	181†	131.0	216	165†
Totals		278.0	448	161†	292.9	482	165†	570.9	930	163†

*6th revision of International Lists of Diseases and Causes of Death.[1]
‡Significant at 5% level.[5]
†Significant at 1% level.[5]
§All except 2 patients observed had cancer of lung or bronchus.

[1]From: Wagoner, J., Miller, R. W. Usual cancer mortali among a group of underground metal miners. Ne ng. J. Med., 269, 284, 1963.

From this, one can infer that copper mines were investigated, but as to what percentage of the entire study population they comprised cannot be determined.

Osborne (60) studied lung cancer among gold miners. Since the suspected carcinogen was arsenic, commonly implicated as a carcinogen among copper smelters and miners, this paper is of relevance. This was a descriptive study of 37 lung cancer patients who had worked in the Gwanda Gold mines and who were hospitalized during the period 1957-63. Incidence rates were computed and work history and smoking data were collected. The results showed that male miners had a lung cancer incidence of 205.6 per 100,000 population as compared to the general male rate of 33.8. A review of available mining histories showed that 25 of 28 men had worked underground in dusty conditions in mines with "highly" arsenical ore bodies. Only 6 cases were non-smokers, leading the author to suggest that arsenic and smoking acting together is responsible for the high incidence of lung cancer in this population. The exposures were poorly quantitated, a large percentage of the study population had incomplete mining histories, and the analyses were incomplete.

C. Respiratory Diseases

Morbidity studies related to occupation, especially in the area of respiratory disease, have used various approaches. Laenhart (43) in 1968 reported on two field studies conducted from 1958-1965 on the prevalence of pneumoconiosis diagnosed by standard 14x17 inch chest roentgenograms of 14,076 actively employed metal miners and 2,546 bituminous coal miners. Prevalence

of x-ray evidence of pneumoconiosis in coal miners was three times that of metal miners in all three major classifications; suspected, simple and complicated disease. The age distribution was similar but coal miners had spent 9 more years underground. Metal miners showed more extensive disease with, on the average, larger and more extensive opacities. No non-miner controls in the same geographic area were studied. Retired or non-working, but previously exposed, employees could have been included and may have influenced the results. The description of the diagnostic criteria was very thorough and included a copy of the International Labor Organization's Classification Chart on x-ray diagnoses.

The relationship between the concentrations of fourteen substances, including copper, found in lung tissue at autopsy and coal-workers pneumoconiosis was studied by Sweet et al.(81) who analyzed 164 specimens of lung tissue from 19 deceased bituminous coal miners from Raleigh County, West Virginia in 1967. A small control group of three non-miners and 12 female residents was also examined done. Increasing degrees of lung damage correlated with increasing trends in levels of magnesium, beryllium, vanadium, free silica, coal dust and total dust. No relationship was found between the severity of coal-workers' pneumoconosis and chromium, copper, iron, manganese, nickel, titanium, zinc and non-coal dust. Significantly higher copper levels were found in class 2, that is, in subjects showing the earliest effects of coal-workers' pneumocomosis. Neither age nor length of exposure were considered. Since the control group was so inappropriate their inclusion in the study did not contribute to a clarification of the results.

Ayer et al.(5) in 1968 obtained subjective evaluations by a panel of industrial hygienists on classification of occupational groups by degree of exposure to airborne particles, irritant gases, organic vapors, and temperature extremes. The degree of hazard was compared with ranked proportional morbidity rates of certain conditions. Chi-square tests showed a number of significant differences, the most striking being the association of particulate exposure to excess disability from emphysema. No association was found between particulate exposure and disability from lung cancer.

In 1968 Fuentes and Kendrick (24) reported on a study of 130,000 workers disabled (as defined by the Social Security Administration) because of respiratory conditions. The proportional morbidity ratio for respiratory conditions in males was 2.34 for miners and 1.64 in foundry workers. A comparison made between skilled and unskilled workers showed a lower morbidity ratio in unskilled foundry workers (1.19) and a higher ratio in unskilled mineral extraction workers (2.04 vs. 1.83 for skilled or semi-skilled). There was no difference between skilled and unskilled groups of metal fabricators.

In 1963 Flinn et al. (23) prepared a report on silicosis in the metal mining industry for the Bureau of Mines. In this descriptive report the authors sought to determine the prevalence of silicosis and to assess the environmental conditions in the metal mining industry. Included in the report were 11 copper mines employing 7,250 men (representing 35% of the entire study group). Open pit mines were not included in this review. The overall

prevalence rate of silicosis among all miners was 3.4%, and among copper miners was estimated at 3.6%. The data also showed that silica content of the dust was much more an important determinant of silicosis prevalence than was the type of commodity (copper, lead, zinc, etc.) produced. Significant steps have been taken since the 1940's to reduce the dust hazards to most metal miners, and throughout the industry an apparent decline in the number of silicosis cases can be seen. However, because a few locations have not provided effective dust control and the long time inherent in evaluating the effects of recently instituted hazards and controls, the current silicosis danger, while reduced, is difficult to assess. The report contains important baseline data necessary for the planning and evaluation of future studies, in addition to important measures for controlling dust. Since the publication of this report, more advances have been made in industrial hygiene related to dust control.

Silicosis was studied in Rhodesia copper miners by Paul (63) in 1961. Here, the incidence of silicosis and silico-tuberculosis was determined from the author's examination of 370,000 x-ray films of 100,000 individuals over a 10-year period. The results of the study showed that silicosis had dropped significantly, from 4.0 to 0.6 per 1,000 miners, coinciding with improvement in ventilation and dust suppression techniques. Other findings were that pulmonary tuberculosis was about 30 times greater in silicotics than in nonsilicotics, the prevalence of chronic bronchitis was low (.1%) and, not surprisingly, the highest risk group for silicosis was among those engaged in drilling.

Yakshina and Makarov (92) calculated the rates of silicosis among Russian copper miners in the Central Urals. A total of 6,000 workers were examined from three different mines over a 10-year period. A five-year "incidence" rate of 0.35/100 miners examined was offered as evidence that the measured decline in dust content was associated with a drop in the silicosis incidence, a lengthening time of silicosis development, and other favorable clinical signs. This conclusion was based on a comparison of the American rate as derived by Flynn of 3.6/100. However, in the Russian study incidence was determined while the American study measured prevalence. Soviet miners received regular obligatory medical examinations while the American miners did not and this, according to the authors, was reflected in the type (high silico-tuberculosis) and severity of the cases that did come to medical attention in the U.S. The second part of the study compared questionnaire responses of silicotics and healthy miners. The questionnaire was filled out before the diagnosis thus eliminating any bias due to knowledge of an individual's disease status. The analysis of the questionnaire data showed that the newest silicosis cases were related to infringement of dust regulations, drilling without hydraulic dust suppression, and poor ventilation. The analysis was incomplete in that only percentages and not rates were given. The authors concluded their report by saying, "final eradication of this occupational disease in copper mines calls for a steady reduction in the dust content in the air to levels not exceeding 2 mg/m^3."

Mokronosva et al. (53) reported on a retrospective study of 1234 cases of silicosis among miners who worked in the copper mines of the Sverlorsh region in the central Urals and who entered or left employment between 1946 and 1970. The purpose of the study was to analyze the mortality of workers before and after 1948, the year in which new hygienic measures were implimented in the mines. The workers were initially divided into two groups depending on whether the major proportion of their working life occurred before or after 1948 and then further subdivided according to the stage of the disease at the time of diagnosis. Probabilities of death were calculated for each group for intervals of 5, 10, 15 and 19 years after diagnosis. In general, the length of survival after diagnosis was greater for those whose longest work exposure occurred after 1948 and this improved survivorship was attributed to a decrease in the magnitude of exposure to dust. Tuberculosis, cardiovascular insufficiency and lung cancer were found to be the major causes of death. Although the authors indicate that earlier diagnosis and improved treatment methods, particularly for silicotuberculosis, could have confounded the results, no attempt was made to determine the influence of these factors on the results.

Results of occupational health investigations by Lucenko (46) in 3 ore-dressing works in the Urals revealed that workers were exposed not only to copper dust but to gases such as hydrogen sulfide liberated by Flotation agents. Medical examinations of 257 workers with the highest seniority disclosed that 4% had first stage pneumoconiosis. Animal

experiments using white mice and rats showed that inhalation of dust from copper concentrate was associated with a general toxic reaction in the liver, kidney, and lung tissue. Dust from sulphide copper ores was associated with a fibrogenic respiratory response. The author recommended that a threshold limit value of 4 mg/m.^{3} be fixed for dust from sulphide copper ore with a free silica content of less than 10%.

A more acute respiratory syndrome associated with the polishing of copper plates was described by Gleason (27) in 1968. Three men came down with complaints resembling cold symptoms and called "metal fume fever." Air samples revealed 0.12mg/m^3 of copper in the polishers' breathing zone; copper dust was two to three times higher at the front of the polishing wheel than in the general air in the middle of the room. After local ventilation was applied, employee complaints ceased. As the author pointed out, the data did not permit any broad generalizations about the toxicological aspects of fine, airborne copper dust; it merely justified exhaust control. They concluded that "metallic copper is generally believed to be of little significance in industrial hygiene."

D. Dermatitis

In 1951 Holmquist (33) presented a comprehensive and systematic report of arsenical dermatitis in employees of a Swedish copper ore smelting works. In addition a thorough review of the subject was presented. His data showed that sick leave was granted 1,462 cases of arsenical dermatitis between 1932 and 1948. Technical improvements led to a noticeably

declining incidence in the later years. Peak incidences of summer dermatitis and winter perforations of the nasal septum were noted. Resistance as well as "adaptation" ~~was~~ were also described.

Oyanguren's paper (62) in 1966 was actually on two studies: one of 124 copper workers exposed to arsenic in a copper mine and processing plant and the other, various community-related lead poisonings from a different lead mine and smelter. Only his work on arsenic exposure is of relevance to this report. Two control groups were assembled to compare with the exposed population; one consisted of 21 workers who worked at least one kilometer away (control A), and the other 20 people in a city with no exposure (control B). Among the cases, arsenical melanosis was diagnosed in 7%, arsenical dermatosis in 5.6% and perforation of the nasal septum in 1.6% (2 cases). None of the manifestations were encountered in the controls. Both the cases and control A showed a significant absorption of arsenic in the urine over control B, as well as significantly increased sensitivity to a patch test for arsenical hypersensitivity. Relevant environmental measurements included air levels of arsenic in the roasting plant which ranged from 0.3 to 81.5 mg/M^3 (the TLV is 0.5). The paper lacks any description of the control group and their method of selection and provides no information on the methods used to determine arsenic concentrations.

Morris (55) stated in 1952 that contact dermatitis due to brass had not been previously reported. Large numbers of cases

of contact dermatitis had failed to implicate brass and influenced clinicians against testing for it and insurance companies against accepting brass exposure as a basis for payment. He reported on 5 cases of proven brass dermatitis among over 2,000 cases of industrial dermatitis. All cases revealed a positive patch test for brass. Two cases were tested for copper and zinc, as well as other trace metals found in brass, and only copper was positive.

E. Accidents

Shattock (73) conducted a descriptive study of 5,000 miners producing 90,000 tons of ore a month. The investigation showed that accidents accounted for a serious loss of workdays and increased morbidity and mortality. The highest frequency of accidents were finger injuries caused by flying rock. In most cases, carelessness in handling explosives was the cause. The accident rate overall was high in the first year of service, declined until the sixth year, then rose sharply.

F. Other Conditions

Mallory (47) reported that during one year, 1922-3, out of 288 autopsies done at Boston City Hospital, 10 cases (3.4%) showed findings of hemachromatosis, a condition characterized by deposits of hemafuscin in the liver changing over time to hemosiderin and involving other tissues. Nine other cases occurring before or since were also studied. For a year after this unusual cluster not one case was seen. On investigation of the occupational history, 4 of the 10 had had prolonged copper exposure, some accompanied with alcoholism. Three other

cases with death due to other diseases but with long copper exposure had early signs of the disease. Animal studies and prospective studies on all autopsies for hemofuscin in the liver showed that chronic copper exposure may merely cause a slight but persistent destruction of red blood cells. Although not finding a causal association with hemachromatosis, these studies added to the body of knowledge on chronic copper exposure. The author's conclusions that small amounts of copper can be eliminated without damage, but that large amounts over time are dangerous with susceptibility playing a part have been validated in subsequent studies.

Mills (51) conducted a descriptive study of the possible relationship of copper to disease in the Korean people who used brass as the universal material to manufacture food bowls, spoons, wine bottles and cooking pots. Not only did this exposure to copper not appear to affect the people, the author felt that brass utensils were actually protective against disease. Observations of brass workers showed that the work was done in the open air or semi-open rooms. The workmen appeared symptomless with no apparent common disease among them. In one hundred autopsies, investigation for hemachromatosis was negative.

In 1948, Wallgren (88) described 20 cases with symptoms of metal-fume fever of which 17 were employed in the copper industry and 3 in zinc or brass. Evaluation of serum copper levels showed that 8 of the 13 workers with the typical symptoms of fume fever had serum copper levels greater than 160 mg%. Normal values obtained from other studies ranged from 100-130 mg%.

High serum copper levels and illness were attributed to inhalation and absorption of copper dust present in the factories. Since no controls were examined, this result must be interpreted with caution.

A study of 230 copper smelter workers from 4 copper smelting works in the Urals revealed that 40% of these workers with 15 years or more employment suffered from lesions of the liver and gall bladder (75). The workers were found to be exposed to silica concentrations of about 0.30 mg/1., metal dusts containing free or combined silica, iron and zinc oxides, magnesium compounds and minute amounts of lead.

IV. EPIDEMIOLOGIC STUDIES OF NON-OCCUPATIONAL EXPOSED GROUP

A. Cancer

Blot and Fraumeni (9) identified 89 counties engaged in primary smelting and refining of non-ferrous metallic ores. Thirty-six of these had copper, lead or zinc installations and 18 were counties with copper smelters (apparently, no counties contained more than one type of smelter). Cancer mortality rates for each county were calculated from "U.S. Cancer Mortality by County: 1950-69," by Macon and McKay. Demographic and socio-economic data were obtained from census statistics for 1960, the midpoint of the study period. A multiple regression model was used to test for significance. The general results showed that lung cancer mortality was significantly higher among males ($p < .001$) and females ($p < .05$) in the group of 36 counties with copper, lead, and zinc industries than the rest of the U.S. For these 36 counties standardized mortality ratios were 17%

and 15% higher for males and females respectively, and in the 3 counties with the highest percentage of the total population employed in the smelting and refining industries, the excess was 92% and 36%. Confounding variables such as urbanization, socio-economic factors or other manufacturing processes were taken into account. Smoking habits were thought not to be any different among counties with copper, lead, or zinc industries. Two unpublished reports were cited which showed that the smoking habits of workers in copper smelters were not unusual. Further analysis is needed to differentiate the contribution of mining (and type) from that of smelting and refining.

The Tacoma Smelter specializes in smelting and refining of copper ores rich in arsenic and other impurities. In fact, this smelter is unique in that it is the only commerical source of arsenic trioxide in the free world. In 1972, Milham and Strong (50) conducted a two part study on the potential health hazards associated with this smelter. Part one was a survey of arsenic levels in hair, urine, and vacuum cleaner dust. The hair and urine studies were on a small number of children who were in one of two schools; one next to the smelter and the other eight miles away. Hair determinations averaged over 50ppm in the exposed but less than 3ppm in the unexposed. Children in the school next to the smelter had much higher urinary arsenic levels than those in the control school. The second part of the study involved all members of six families in which urine values were observed to change in synchronous fashion indicating inhalation as the most likely route of exposure. Both urine

samples and vacuum cleaner dust showed an inverse relationship of arsenic concentration with distance from the smelter. It was also determined that younger children had consistently higher urinary arsenic levels than older children or adults. The second part of the study was a death record analysis using county death certificates that listed place of employment and cause of death. The 39 deaths due to respiratory cancer among smelter workers from 1950-1971 was compared to the expected number of 18. In addition, urine levels were only based on one sample per child. Other variables such as wind direction and length of residence were not taken into account.

B. Respiratory Disease

Kubota (40) undertook a study to determine trace elements in humans who live in different parts of the U.S. Copper, zinc, cadmium, and lead were determined in 243 blood samples of male residents of 19 medium sized cities in 16 states. The mean concentration of copper in whole blood agreed closely with other reported normal values as stated by the author although no value was given. The overall mean of 89mg% included the value for Billings, Montana (174mg%) which had a significantly higher blood copper level than the other cities. The ranges of copper concentrations of residents of Billings (92-348) and El Paso, Texas (37-201) were wide and could have been associated with the presence of ore smelters located there but this suggestion was not validated in any way. No adjustment for age was made even though age disparities between areas could influence values. No reason was given to explain why whole blood values

rather than serum levels were chosen to monitor environmental exposure. Erythrocyte levels could influence the results in a manner not connected with exposures but with nutritional status, altitude, and anemia. In order to determine the effects on red blood cells, it is necessary to analyze the separate fractions of the blood. Serum copper level tests are also a well-utilized technique with good reproduceability.

In 1974 Corridan (16) took head hair samples from 21 children from a primary school in rural Ireland which was situated within one-quarter mile from an open-cast metal mine. The mine produces zinc and copper and the processing of the ore results in the production of mercury and arsenic. An environmenal study was done on samples of grass between the school and mine and showed 60-5,000 ppm of trace metals as compared to recommended food limits of 0.5-20 ppm. Significantly ($p < .001$) higher levels of arsenic were found in the study children as compared to two control groups. Lead and mercury levels were lower than those in urban Irish children. It was not possible to determine whether exposure occurred at school or at home since the parents would not give permission for any further study of the children possibly because of fear of the economic consequences if the mine were closed.

In 1976 the Environmental Protection Agency (21) published a report titled "Health Consequences of Sulfur Oxides: a Report from the Community Health and Environmental Surveillance System (CHESS)" which contains a series of extensive epidemiologic investigations of selected, acute and chronic disease indicators

(see Table 10) and their relationship with air pollutants and burdens. The different studies sought to determine the safety and adequacy of the National Primary Act Quality standards. Acute effects were measured against the daily variation in pollutant levels while chronic effects were identified by contrasting disease prevalence in high and low exposure communities. The report concluded that the standards were supported for long term exposures, but adverse effects were noted for levels of suspended sulfates below their daily standard. CHESS investigations were conducted in 1971 in several Salt Lake Basin communities, where the primary pollutant source was a copper smelter, west of Salt Lake City. Other CHESS studies were conducted in Idaho and Montana, but the presence of lead and zinc processing plants, in additon to copper smelters, render any interpretation of the etiologic significance of the copper smelters alone difficult.

One of the CHESS studies was designed to provide long term pollutant exposure information which could be used for correlation with health effects. The report deals with the important issues of pollutant measurement methods and location of sources.

A second CHESS report provides data relating SO_2 and suspended sulfates in the air to the prevalence of chronic respiratory disease. Four communities were chosen on the basis of aerometric, meteorologic, and topographic data to represent a gradient of sulfur dioxide exposure. The high exposure community was 5 miles from a large copper smelter and the low exposure community was 38 miles from the smelter. The entire study population numbered

Table 10. CHESS HEALTH INDICATORS

Exposure	Indicator	Sample size per CHESS community	Frequency of response
Short-term (<4 days)	Frequency of asthma attacks	50 to 75	Daily
	Aggravation of chronic respiratory symptoms	50 to 75	Daily
	Aggravation of cardiac symptoms	50 to 75	Daily
	Acute irritation symptoms during episodes	400 to 1000	3 to 4 times yearly
	Daily mortality	Variable	Daily
Long-term (usually >1 year)	Pollutant burdens	800 to 1200	Once in 2 years
	Impairment of lung function	1500 to 2000	3 times yearly
	Incidence of acute respiratory disease in families	1000	Once every 2 weeks
	Frequency of acute lower respiratory disease in children	1500 to 3000	Once in 2 years
	Prevalence of chronic respiratory disease	1500 to 3000	Once in 2 years

[1]From: Environmental Protection Agency. Health Consequences of Sulphur Oxides. A Report From CHESS. 1970-71. U. S. Government Printing Office, 1974.

7,635 adults of which 4,327 were nonsmokers and 1,155 were exsmokers. Health and demographic data were collected by a self-administered questionnaire adopted from a standardized version from the British Medical Research Council. Information was obtained about the presence and duration of cough, phelgm, and shortness of breath. Results indicated an increased prevalence of chronic bronchitis among smokers and nonsmokers of both sexes after 4-7 years exposure to ambient air levels of SO_2 suspended sulfates and total suspended particulates.

Another of the CHESS reports presented data on the frequency of acute lower respiratory disease in children. Parents of children less than 12 years of age were interviewed to obtain information on respiratory symptoms in their children. The sample size numbered about 2,000 from each of our communities. Definitions were carefully constructed from interviews with a large sample of area physicians. Asthmatic history, age, socio-economic status, cigarette smoking in the home and recent family migration were correlated separately. The paper concluded, "The frequency of one or more episodes of acute lower respiratory illness signficantly increased after exposures to elevated levels of SO_2 and suspended particulates lasting over 2 years." The magnitude of the observed morbidity excesses (compared to the non-exposed community) ranged from 42% among children in the high exposure community reporting total lower respiratory illness increase, to 8% in the intermediate community. "In the high exposure community, puzzling, unexplained, statistically insignificant deficits were observed in pneumonia attack rates

and hospitalizations." The relevance of this study beyond the children's exposure to the copper smelter is in the specific age group studied. Children provide a unique opportunity to assess the effect of air pollutants on the respiratory tract. "(They are more sensitive, and) unlike adults, children have not usually been subjected to self pollution by cigarette smoking, to occupational exposures, to respiratory irritants, or to ...(residential...) changes."

The aggravation of asthma by air pollutants in the Salt Lake Basin was also discussed in the CHESS reports. The data were obtained through a cohort study of asthmatics. Four groups totaling 211 asthmatics reported their asthma attacks using weekly diaries for a 6 month period in 1971. Data analysis was based on multiple regression techniques. The most significant effect on asthma attack rates was lowered ambient air temperatures, but pollutant levels, especially suspended sulfates, were also significantly correlated with excess attack rates.

C. Dermatitis

Birmingham (8) in 1965 described an outbreak of arsenical dermatoses in a gold mining community. Examined in the study were 40 children from two community schools and 18 mill workers. The clinical findings showed that 32 of the 40 students had one or more types of suspect arsenical dermatoses (defined as eczematous contact dermatitis, folliculitis, furunculosis, pyodermas and ulcerations). It usually involved the face and areas of flexural contact. Similar lesions were seen in about half of the mill workers. Only one case, an ore roaster worker,

had an elevated urinary value of arsenic (2.06 mg/liter). Overall the results of urinalysis revealed values of arsenic which compared favorably with the daily average arsenic excretion of 0.82 mg/liter that American Smelting and Refining Company has shown to be benign on the basis of 20 to 30 years of exposure (66). Animal experiments were able to reproduce the arsenical ulcerations observed clinically at the gold smelter by applying arsenic trioxide-containing material to an albino rabbit. Patch tests were performed on volunteers from among the school children and mill workers who had experienced arsenical dermatoses of eczematous or follicular nature. There were 3 positive reactions among 14 subjects tested which indicated that allergic dermatoses to arsenic trioxide could occur. The quantitative exposures for each individual were not determined. The pet population was also examined for similar disease. Unfortunately, the animals had almost all succumbed to illness, the lone survivor being a dog with multiple ulcerations. Of significance is the fact that the authors were unable to find a relationship between the dermatoses and urinary arsenic levels despite the obvious cause-effect relationship of arsenic and the skin lesions. Therefore, non-elevated urinary arsenic levels are not necessarily indicative of non-siginificant exposure.

Chowdhuri (14) in 1966 described dermatitis due to bronze ornaments in 12 cases who were affected on the lower half of the forearm, neck, and ear lobes. The irritation first occurred after the cases began wearing bronze ornaments. Patients gave a history of profuse sweating. The condition improved when the

ornaments were removed and in the 4 cases who would not discard the ornaments severe reactions were observed with vesiculation, oozing, and scale formation. Bronze metallic alloy is 90% copper and 10% tin according to the author and tin is "partically insoluble."

Saltzer (68) described a case of allergic dermatitis on the left wrist, fourth finger ring area, and occasional pruritis of the nose area under eyeglasses. Patch tests were done with seven metallic salts or alloys and all were eliminated except for a reaction to copper sulfate and pure copper metal. A tissue specimen from the copper metal site substantiated the diagnosis of allergic contact dermatitis due to copper.

D. Copper Poisoning

Case reports of copper intoxication include an autopsy report on acute copper sulphate poisoning of 7 cases reported by Deodhar (18). Copper sulfate is commonly used for suicidal purposes among low-income groups in India. Of 5,092 autopsies performed, there were 7 cases (4 males and 3 females) of acute copper sulphate poisoning. Six were between the ages 22-26 and one was 51. Five cases expired from shock within an hour of admission and two deaths occurred on the fifth day due to renal/hepatic complications. The stomach, intestine, liver and kidneys were the important organs showing changes and hemoglobin casts in the kidney sections indicated hemolytic activity.

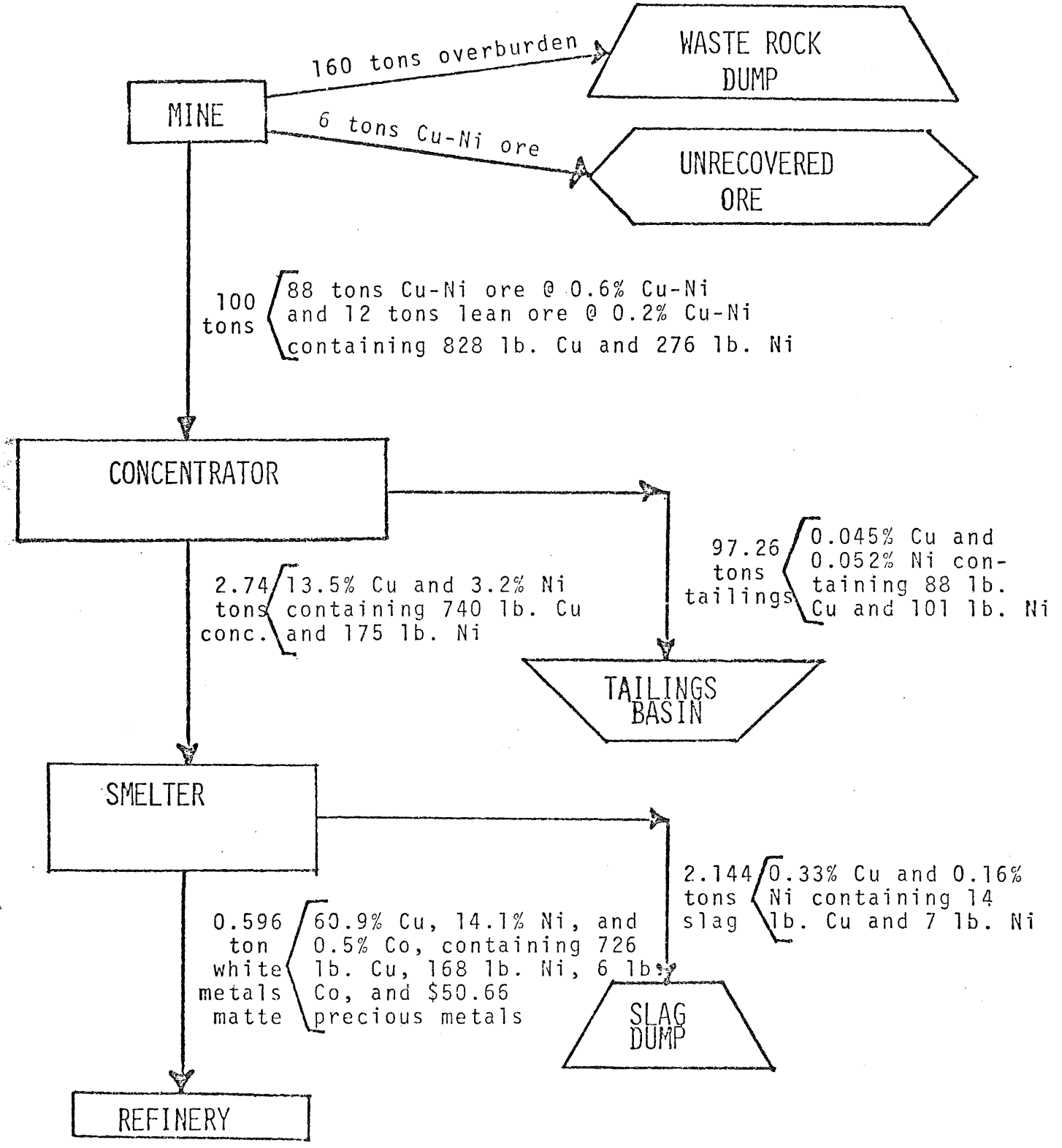
In 1966 Holtzman (34) reported on a case of copper intoxication in a child who absorbed large amounts of copper after debridement of burned skin with copper sulfate over a nine week period. The authors suggested that when ceruloplasmin is

deficient, copper may not be readily excreted and may build up to toxic levels and that the body increases ceruloplasmin directly in response to increased body copper and toxic effects occur during the lag period. Treatment with penicillamine, a copper chelator, was effective.

A case of a 15 month old infant with chronic copper poisoning was described by Salmon and Wright (67) in 1971 who believed this to be the first such case report. Symptoms included prostration, red extremities, hypotonia, photophobia, peripheral edema, and weight loss. Significant findings were high serum copper levels and no urine copper. Therapy with a copper chelator was successful. Investigation showed that the family had recently moved (90 days) to a new home with a copper hot-water system. A family idiosyncrasy was that all water for cooking came from this tap which was found to contain high levels of copper. The authors felt the child was subjected to high copper intake over three months and showed abnormal sensitivity to the metal.

APPENDIX I

MATERIAL FLOWSHEET FOR OPEN PIT MINING MODEL



[1]From: Hays, R. M. Environmental, Economic and Social Impacts of Mining Copper-Nickel in Northeastern Minnesota. 1974.

APPENDIX 2

PRIMARY COPPER SMELTERS IN THE UNITED STATES

American Smelting and Refining Company
- El Paso, Texas
- Hayden, Arizona
- Tacoma, Washington

The Anaconda Company
- Anaconda, Montana

Cities Service Corporation
- Copperhill, Tennessee

Inspiration Consolidated Copper Company
- Inspiration, Arizona

Kennecott Copper Corporation
- Garfield, Utah
- Hayden, Arizona
- Hurley, New Mexico
- McGill, Nevada

Magma Copper Company
- San Manuel, Arizona

Phelps-Dodge Corporation
- Ajo, Arizona
- Douglas, Arizona
- Morenci, Arizona

White Pine Copper Company
- White Pine, Michigan

From: Wagner, W. Environmental Conditions in U.S. Copper Smelters, National Institute of Occupational Safety and Health, H.E.W., Washington, 1975.

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