

### III. BIOLOGIC EFFECTS OF EXPOSURE

#### Extent of Exposure

Tungsten (atomic number 74) is listed in the periodic table under period 6 of the transition elements, along with chromium and molybdenum. Tungsten closely resembles molybdenum in all of its physical and chemical properties. In the pure metallic state, tungsten is grey and has a luster somewhat like that of steel. The physical and chemical properties and formulae of tungsten and of some of its important organic and inorganic compounds are given in Table XII-1 [2-6]. The commercial tungstate minerals are wolframite (Fe,Mn)WO<sub>4</sub>), scheelite (CaWO<sub>4</sub>), ferberite (FeWO<sub>4</sub>), and hubnerite (MnWO<sub>4</sub>). Worldwide, wolframite is the most important ore containing tungsten, whereas scheelite is the principal domestic ore [7]. Most tungsten deposits are low-grade and are upgraded by concentration techniques. The tungsten concentrates produced contain at least 60% tungstic oxide.

The total US consumption of tungsten concentrate in 1975 was 14.0 million pounds, of which 5.6 million pounds were domestically produced, 6.6 million pounds were imported primarily from Canada, Thailand, Peru, the People's Republic of China, and Portugal, and the remainder was released from government stockpiles [8].

In 1975, the United States produced 12.634 million pounds of tungsten products and consumed 12.934 million pounds, including 72.5% in alloys for cutting and wear-resistant materials, 11.5% in mill products from metal powder, 9.2% in steel, 2.9% in super alloys, 2.4% in chemicals and

ceramics, 0.03% in cast iron, and 1.47% in miscellaneous products [8].

Fairhall [9] stated that the principal health hazards from tungsten and its compounds arise from inhalation of aerosols during mining and milling operations. The principal compounds of tungsten to which workers are exposed are ammonium-p-tungstate, oxides of tungsten ( $WO_3$ ,  $WO_5$ ,  $WO_2$ ), metallic tungsten, and tungsten carbide. In the production and use of tungsten carbide tools for machining, exposure to the cobalt used as a binder or cementing substance (Figure XII-1) [10,11] may be the most important hazard to the health of the employees. Since the cemented tungsten carbide industry uses such other metals as tantalum, titanium, niobium, nickel, chromium, and vanadium in the manufacturing process, the occupational exposures are generally to mixed dusts. Potential occupational exposures to sodium tungstate are found in the textile industry, where the compound is used as a mordant and fireproofing agent, and in the production of tungsten from some of its ores, where sodium tungstate is an intermediate product (Figure XII-1). Potential exposures to tungsten and its compounds are also found in the ceramics, lubricants, plastics, printing inks, paint, and photographic industries. Some of the occupations with potential exposures to tungsten and its compounds are listed in Table XII-2 [12].

NIOSH estimates that at least 30,000 employees in the United States are potentially exposed to tungsten and its compounds, based on actual observations in the National Occupational Hazards Survey.

### Historical Reports

In 1927, at Essen, Germany, it was discovered that, if tungsten carbide was mixed with cobalt, a very serviceable cemented tungsten carbide (ie, hard metal) was obtained [7].

About 10 years after the commercialization of cemented tungsten carbide, the first report appeared on the associated health problems of the exposed workers. In 1940, Jobs and Ballhausen [13] examined 27 German workers exposed to unspecified concentrations of hard-metal dusts for 2 years. Radiographs of the chests of eight men showed areas of fine nodulation in the lungs suggestive of early pneumoconiosis.

In 1945, Schwartz et al [14] investigated the incidence of dermatitis among employees in a tungsten carbide plant for the US Public Health Service. About 20 of the 1,200 workers examined had red, papular dermatitis on the face, neck, and extremities. Although the dust was abrasive, patch tests of six workers showed that it was sensitivity to cobalt that had caused the dermatitis in those six.

Fairhall and associates [15], in 1947, conducted an epidemiologic survey of 1,802 workers in the cemented tungsten carbide industry for the US Public Health Service. They found inflammation of the conjunctivae and of the mucous membranes of the respiratory tract. Radiographs of 36 workers' lungs revealed granular or conglomerate markings, but 23 (64%) of these men had previously worked in unspecified mining or metal fabricating industries. Some workers were found to have pruritus due to sensitivity of the skin to cobalt.

In 1953, Miller et al [16] were the first to report cases of "hard-metal disease" (interstitial pulmonary fibrosis) in hard-metal grinders.

Three men who had ground finished tools for 6.5-8.5 years complained of persistent coughing, with production of sputum and exertional dyspnea. Radiologic chest examinations showed that prominent hilar shadows and lung markings abated in one worker, but persisted for more than a year in the other two workers after they had been removed from the work atmosphere. However, the clinical signs and symptoms disappeared in all three men when they were no longer exposed to the workplace dust. The authors recognized that the workers were exposed to various combinations of powdered metals but concluded that cobalt was the most likely cause of the disease.

#### Effects on Humans

Occupational exposures to tungsten and its compounds have been reported to have primary effects on the respiratory system. In the cemented tungsten carbide (hard-metal) industry, exposure to a combination of cobalt and tungsten sometimes has resulted in hard-metal disease. The pulmonary involvement presented in a number of reports was characterized clinically by upper respiratory tract irritation, coughing, exertional dyspnea, and weight loss. As the condition of the workers worsened with prolonged exposure in this environment, extrinsic asthma, diffuse interstitial pneumonitis, fibrosis, pneumoconiosis, or combinations of these were evident.

Dorsit et al [17], in 1970, described three workers exposed to tungsten carbide and cobalt as having a "true, occupational, pulmonary disorder." These men, aged 30, 36, and 57 years, had been employed for 5, 11, and 16 years, respectively, in work involving the use of diamond and tungsten carbide drills, rectifiers, and sharpeners. Workplace dust

particles were under 3  $\mu\text{m}$  in diameter, and the concentration of dust in the air varied from 380,000 to 5,600,000 particles/liter of air (2.3-62.3 mg/cu m). The workers received examinations which included blood analyses, chest X-ray studies, and pulmonary function tests. All three workers had dry coughs, progressive dyspnea on exertion and subsequently at rest, roentgenographic signs of nodular reticulation of the lungs (diffuse interstitial fibrosis) of varying degrees, decreased lung capacities, oxyhemoglobin desaturation, hypercapnia, respiratory alkalosis, polycythemia, and weight loss.

Of 380 workers in the same factory, 29 men who had been employed for up to 17 years were examined for clinical signs and symptoms of respiratory disorders [17]. Of these, 15 had dry coughs, 5 showed throat irritation, 9 had worktime dyspnea, and 3 had allergic asthma (some had more than 1 symptom).

The authors [17] also reviewed published reports of exposure to cemented tungsten carbide dust and, from this study and their own work, concluded that affected workers were characterized as 30- to 50-year-old males exposed for at least 3 years. Clinical findings included dyspnea on exertion, a dry cough, cyanosis of lips and fingers, rales, polycythemia with a concurrent rise in hemoglobin, and weight loss. Observations among workers affected included progressive decreases in circulatory and cardiac function, concurrent pulmonary infections (possibly tuberculosis), and death within 4 years of initial onset of symptoms. The authors also pointed out that pulmonary function tests were more indicative of the severity of interstitial fibrosis than were radiographs. They concluded that a mixture of tungsten carbide and cobalt appeared to be the causative

agent and advised extremely close supervision of workers in the hard-metal industry.

In 1971, Coates and Watson [18] reported 12 cases of diffuse, interstitial lung disease among tungsten carbide workers. The group consisted of 11 men and 1 woman, with a mean age of 40.5 years (range 22-55 years), who were engaged in various processes in the manufacture and grinding of cemented tungsten carbide. The exposure levels of tungsten were not given, but the processes generated particles averaging less than 2.0  $\mu\text{m}$  in diameter and produced concentrations of airborne cobalt greater than 0.1 mg/cu m. In addition to tungsten and cobalt, the processes also used titanium carbide, tantalum carbide, chromium carbide, and nickel. The mean duration of exposure before the development of symptoms was 12.6 years, with a range of 1 month to 28 years. Eight of the 12 workers died. Seven of the 12 workers were examined by one of the authors; 6 of those examined were tested for vital capacity, FEV1, and maximum voluntary ventilation (MVV).

The authors [18] noted that the pattern of clinical signs and symptoms was strikingly similar in all the workers, varying mainly in intensity. The early stages of respiratory involvement were characterized by a cough with scanty sputum, followed by dyspnea on exertion. An average weight loss of 10 pounds was noted in seven patients. Ventilatory tests of six patients showed that the average vital capacity was 50% of the predicted values (range 37-70%); the FEV1 was between 85 and 100% of the predicted values, and the average MVV was 76% of the predicted values (range 45-92%). These findings were interpreted to indicate a severe, restrictive ventilatory pattern without airway obstruction. From the

findings of low carbon monoxide diffusing capacity and decreased oxygen saturation of the arterial blood, the authors concluded that the patients had a diffuse, interstitial, fibrotic response to the xenobiotic material that had entered their respiratory systems. In two individuals, pulmonary function changes preceded abnormal chest X-ray findings. Serial chest X-ray studies showed progressive, bilateral, nodular, and linear densities with gradual involvement of major portions of the lungs. Radiographic evidence of nonspecific, diffuse interstitial fibrosis was found.

Light-microscopic examinations of the aforementioned lung specimens showed interstitial cellular infiltration with slight to marked fibrotic tissue reaction, cystic air spaces lined by an epithelium showing a metaplastic change from a squamous to a cuboidal type, and desquamation into the alveoli of type II alveolar pneumocytes [18]. Large mononuclear and occasional multinucleated, giant cells were present. Electron microscopic findings were consistent with the changes observed by light microscopic examination. By X-ray diffraction analysis, the presence of tungsten carbide was detected in all of the lung samples analyzed. Mass spectrometric analysis revealed the presence of both tungsten carbide and cobalt. One lung biopsy sample for which quantitative data were reported contained 3.0  $\mu\text{g}$  of tungsten, 2.0  $\mu\text{g}$  of titanium, and 0.1  $\mu\text{g}$  of cobalt/g of wet lung. The authors found no correlation between the amount of cobalt in the lung specimens and the severity of the disease from which the decedent had suffered. The type of interstitial lung disease seen in these people reportedly resembled the hypersensitivity pneumonitis of "farmer's lung" and beryllium granulomatosis.

Coates and Watson [18] also briefly reported on five tungsten carbide workers with normal chest roentgenographs who were described as having occupational asthmatic bronchitis. Data such as age, sex, duration of exposure, and the nature of the work involved were not described. These workers had episodic attacks of wheezing cough which abated when they left work and recurred on their return. The authors referred to this form of lung disease as "sensitization" related to preexisting lung diseases, allergic background, or both. The authors stated that no evidence existed that this disease might progress to interstitial lung disease. They emphasized that determining workers' susceptibility to interstitial lung disease and diagnosing the disease in its early stages would help to protect workers' health. Although they presented no evidence that cobalt was responsible for the observed respiratory disorders, they believed it to be the most probable cause.

In 1974, Bech [19] described clinical and radiologic findings in 12 workers with diagnoses of hard-metal disease and in 1 worker with allergic asthma among 375 hard-metal tool grinders employed in a cemented tungsten carbide plant. These 12 men ranged in age from 33 to 69 years, with an average age of 54.3 years. Although the exposure concentrations and the compositions of the dusts to which the men were exposed were not given, the typical tools contained "80-90% tungsten, 8-18% titanium carbide, 5-25% cobalt," and occasionally small quantities of tantalum, vanadium, molybdenum, and chromium. The 12 workers with hard-metal disease had been engaged in tool grinding for an average of 25.8 years (range 15-51 years), whereas the worker who had allergic asthma had worked at tool grinding for only 2 years. Eight of the men worked only part time as tool grinders.



All workers were evaluated by physical examination and chest radiography. Lung tissue obtained by biopsy from one worker, by biopsy and by autopsy from two workers, and by autopsy only from four workers were evaluated microscopically. Pulmonary function tests also were conducted on 8 of the 12 workers with hard-metal disease.

Of the 12 employees with hard-metal disease, 8 died of secondary consequences of their pulmonary disease [19]; four of the eight died of cor pulmonale and cardiac failure, whereas the other four died of emphysema. Except for differences in the degree and duration of the symptoms, the general course of the disease was similar in all 12 cases. Coughing (dry or with sputum production), exertional dyspnea, and occasional wheezing characterized the disease. Initially, the chest radiographic studies showed slight increases in lung markings and very sparse linear opacities in the mid- and lower zones. In later stages of the disease, there were marked radiologic changes with varying degrees of linear, micronodular, and nodular opacities in the midzones of the lung, prominent hilar shadows, and occasional honeycombing. Pulmonary function tests revealed restrictive ventilatory defects, with reduction in residual lung volume and total lung capacity (no values given). A low FEV1 and FEV and a marked reduction (50% of normal) in carbon monoxide uptake were noted occasionally. Examination of lung samples obtained by biopsy or autopsy revealed emphysema and varying degrees of interstitial fibrosis in seven workers. In one patient with hard-metal disease of recent onset, withdrawal from exposure and corticosteroid therapy produced clinical and radiographic evidence of improvement.

The worker with allergic asthma developed wheezing, tightness and discomfort in the chest, and exertional dyspnea which was later manifested in asthmatic attacks [19]. These signs and symptoms were least severe at the beginning of a workday and during the weekend. However, there were signs of bronchospasm upon auscultation of the chest. The asthmatic signs and symptoms receded 2-3 months after the worker's discharge from tool-sharpening work.

The author [19] concluded that, since hard-metal disease is progressive and potentially lethal, its early recognition is of the utmost importance. He also acknowledged that there was no correlation between the development of diffuse interstitial fibrosis and the onset of symptoms or the duration of exposure. The study does not contribute to the evaluation of the etiologic role of tungsten in the development of hard-metal disease.

In 1975, Baudouin et al [20] reported 5 cases of diffuse interstitial pulmonary fibrosis among 100 men of unspecified age who worked in a hard-metal factory where dusts of tungsten, titanium, tantalum, and niobium metals, of their carbides and oxides, and of cobalt metal were liberated during various operations. The concentrations, particle sizes, and specific compositions of these dusts were not indicated. The authors noted that most occupational exposures occurred in operations involving the mixing of powders and the grinding and machining of sintered pieces. The workers were screened for observable and radiographic anomalies of the chest. Of the 100 exposed workers, 15 (aged 22-65) had signs of respiratory irritation after 1 month-9 years of exposure. Five of these 15 workers developed pulmonary fibrosis within 6 months to 4 years after the onset of the irritative signs.

The investigators [20] found no predisposing factor in the personal or family backgrounds of the five subjects with pulmonary fibrosis. The irritation diminished or disappeared during vacations and weekends and reappeared during work. When the disease progressed to fibrosis, the authors found rapid weight loss, fine rales, and exertional dyspnea which was not reversible during vacations.

No significant changes were noted in the chest radiographs of the workers with irritative symptoms [20]. However, reticulonodular images that became gradually accentuated and more generally distributed were characteristic of the fibrotic stage. Spirography showed low volumes of residual air in the lungs, indicative of a constant, restrictive disorder. Lung diffusion studies showed resistance to transepithelial gas exchange, leading the authors to suggest that such studies could be used to diagnose fibrosis before the appearance of radiologic signs. Blood-gas analysis demonstrated decreased exchange of respiratory gases between the alveoli and the pulmonary capillaries. Baudouin and his associates [20] reported that immunologic examination revealed a cellular rather than a humoral immune deficiency.

In one worker, the progression of clinical, radiographic, blood-gas, and pulmonary function changes was similar to those described above, and both light and electron microscopic examinations of lung tissue removed for biopsy revealed that diffuse, interstitial fibrosis had evolved [20]. Electron microscopic examinations also revealed crystalline particles, possibly of tungsten carbide, in the macrophages. Examination of the ashed lung by X-ray fluorescence revealed the presence of a large amount of tungsten, of an amount of titanium greater than is usual, and of small

amounts of tantalum and niobium. The carbides of tungsten and titanium were demonstrated in the ashed lung by X-ray diffraction. The authors concluded that inhalation of dusts containing a mixture predominantly of tungsten metal or tungsten carbide caused diffuse interstitial fibrosis. Tungstosis was suggested as the name for this form of fibrosis, which was preceded by irritative symptoms and appeared 4-11 years after initial exposure. The authors suggested the registration of tungstosis as the 65th occupational disease in France. Although no component metal of the dusts was established as the causal agent, the authors [20] stated that tungstosis follows the inhalation of powders composed principally of tungsten metal or tungsten carbide.

Scherrer [21] described pulmonary interstitial fibrosis in three male workers exposed to tungsten, cobalt, titanium, tantalum, and niobium dusts at unspecified concentrations. The men, aged 34, 38, and 58 years, had been exposed for 3, 1, and 8 years, respectively. In each case, clinical symptoms, vital capacity, and chest radiographic findings were reported. A sample of lung was removed from the 38-year-old worker for biopsy, examined under a light microscope for histologic changes, and was analyzed spectroscopically and histochemically for the presence of tungsten and cobalt.

Although the course of the disease was somewhat different in each worker, the chief signs and symptoms were similar [21]. The illnesses of the three workers began with dyspnea, coughing, fever, and general malaise. The symptoms of the two younger workers were somewhat relieved when they left the dusty work environment. The condition of the 58-year-old man, whose illness had developed more slowly, continued to deteriorate even

after he left work. For the 38-year-old worker, a diagnosis of hard-metal pneumoconiosis (pulmonary interstitial fibrosis) was made on the basis of chest radiographs showing miliary reticulation, wet rales heard over most lung areas, decreased pulmonary functions, and hypoxemia and on the results of examination of specimens of lung removed for biopsy. In this worker, the alveolar septae were thickened by fibrotic processes, and the air spaces were decreased by excess mucus and hyperplasia of the alveolar epithelium. Macrophages containing numerous foreign materials were present. Both spectroscopic and histochemical analyses of biopsy specimens of lung indicated the presence of 200 times the normal amount of tungsten, but no cobalt was found. The 34-year-old worker was able to return to work in an area free of the dusty exposures; the other two were severely restricted in their ability to work.

Scherrer [21] recommended that vital capacities be determined as early as possible in suspected exposure cases, since these measurements seemed to permit the earliest detection of abnormalities in hard-metal pneumoconiosis or fibrotic interstitial lung disease. The disease was not attributed to any one component of the hard-metal alloy. However, the author noted that individual susceptibility to hard-metal pneumoconiosis was a significant factor.

In 1972, Rochemaure et al [22] described the development of fibrosis in a 46-year-old woman who had worked with hard-metal mixtures and thus had been exposed to tungsten carbide and cobalt at unspecified concentrations. She was a nonsmoker with no history of bronchopulmonary problems. Three years after beginning such work, she developed a persistent, dry cough that lasted for 12 months and became productive during the following 6 months.

At the end of this period, exertional dyspnea and a weight loss of 8 kg were noted. About 3 months later, the woman was hospitalized after X-ray studies of her chest revealed bilateral, reticulonodular opacities.

Except for crepitant rales, physical examination of the woman did not reveal any abnormalities [22]. Pulmonary function tests showed a decrease of more than 50% in vital capacity and decreased carbon monoxide diffusion (50% of the theoretical value). Blood-gas determinations showed a tendency toward respiratory alkalosis. Differential blood cell counts and liver function test results were normal. Chest radiographs revealed reticulonodular opacities on both sides of the chest, but mainly on the right side and in the basal areas of the lungs. Expectations contained mucus, many bronchial cells, and macrophages, and bronchial aspirates contained, in addition, large amounts of blood and some inflammatory, cellular elements.

Ocular microscopic examination of a specimen of lung taken for biopsy 2 months after initial hospitalization revealed fibrosis with deposits of collagen, lymphocytes, and plasmocytes around the bronchi and vessels, which caused thickening of the alveolar septa [22]. Hyperplastic squamous or cuboidal epithelial cells lined the damaged alveoli, which contained macrophages and leukocytes and showed some evidence of edema. Emission spectrographic analysis of the lung specimen revealed no detectable levels of tungsten, titanium, or cobalt. The investigators attributed these negative findings to the small sample size.

The patient's clinical, radiologic, and pulmonary function tests showed significant improvement when she left the work environment [22]. Coughing, dyspnea, and reticulonodular opacities recurred when the patient

resumed work 3 months later. Because of the severity of her signs and symptoms, the patient again stopped work after 3 weeks. At this time, pulmonary function tests showed that her vital capacity had decreased to 60% of the predicted value and that there was a 66% decrease in carbon monoxide diffusing capacity. The authors stated that the recurrence of her signs and symptoms when she returned to work indicated that tungsten carbide dust played an important role in her illness, but they pointed out that cobalt was the most toxic agent to which she had been exposed. The authors suggested that individual susceptibility differences might have caused only some workers to experience coughing and dyspnea and still fewer to develop pulmonary fibrosis.

In 1967, Bruckner [23] diagnosed extrinsic asthma in a 45-year-old grinder of tungsten carbide-tipped tools. The worker had smoked for 17 years before being employed in the tungsten carbide industry but had not smoked during the present employment. During the 4 years before the diagnosis, the subject had done rough grinding of tungsten carbide for about 16 months. He used silicon carbide and aluminum oxide wheels and had later performed fine, dry grinding using diamond wheels. When the worker changed to the latter type of grinding, he experienced shortness of breath, chest tightness, audible wheezing, and productive cough during work. His symptoms decreased or disappeared during weekends and vacations. The composition and concentration of dusts in the workplace air were not described. Because of progressive deterioration in his health, the worker was hospitalized twice for severe shortness of breath with audible wheezing and a cough productive of yellow sputum.

Physical examinations disclosed evidence of respiratory distress, hyperresonance of the chest to percussion, a depressed diaphragm, and use of the accessory muscles of respiration [23]. Skin tests revealed a positive intracutaneous reaction to house and mattress dust. The dust in the patient's work atmosphere was not among the substances used in skin tests. The chest radiographs were reported to be within normal limits. Films of the paranasal sinuses showed marked to moderate clouding with some signs of scarring from an old disease. Except for eosinophilia, all the values of the blood and urine analyses were within the normal ranges. When the patient returned to work following his second hospitalization, severe asthmatic episodes recurred within 1-3 minutes after he began work. The patient stopped working until a respirator designed to remove particles with a diameter of 0.6  $\mu\text{m}$  or more was made available to him. However, he continued to experience asthmatic symptoms when wearing the respirator. Bruckner concluded that either cobalt dust or a combination of tungsten carbide and cobalt dust was responsible for the patient's symptoms. He suggested that the patient's reaction was mediated through a hypersensitivity mechanism because he exhibited the symptoms within 1-3 minutes after beginning work. Although Bruckner found eosinophilia in the patient, he did not point it out as evidence of hypersensitivity.

Schwartz and colleagues [14], in 1945, reported the results obtained in studies of 1,200 persons who worked with tungsten, tantalum, and titanium carbides, carbon, and cobalt in a cemented tungsten carbide manufacturing plant. No specifics regarding age and sex were given. Work assignments for the group were also not mentioned. Approximately 20 of the workers were found to have an erythematous, papular type of dermatitis



which was limited primarily to the sides of the neck, flexor portions of the forearm, and backs of the hands. In a few cases, the dermatitis was generalized and two sweepers each had contact dermatitis on the heel and ankle of one foot. This was the foot which was kept advanced during sweeping and was therefore exposed to the most dust. All of the affected workers had been employed for at least a month before the dermatitis appeared.

Patch tests were performed on six of the workers with dermatitis and on two control subjects not exposed to the aforementioned dusts. The reactions were read at 24 and 48 hours. The tests revealed that no subject with dermatitis reacted to the oxides of tungsten, tantalum, or titanium, or to carbon [14]. However, all six had positive reactions to metallic cobalt powder, to the unfused tungsten carbide, to mixtures or powders of cobalt, and to other materials used to make the hard metal. The control subjects showed no reaction to any test material. The authors concluded that, since the distribution of the skin eruptions was most marked in the areas of friction, the abrasiveness of the dust facilitated the development of sensitization. They concluded that sensitivity to cobalt caused the dermatitis and that this sensitivity was accentuated by the abrasiveness of the dust.

In 1963, Skog [24] described the incidence of skin disorders among workers in the Swedish hard-metal industry. Of 360 workers (sex and age not specified), 34 who had various skin disorders were examined by a dermatologist. They worked with tungsten carbide, titanium carbide, tantalum-niobium carbide, and cobalt. The durations of their exposures were not mentioned. The industry employed good general and local exhaust

ventilation and cleaning procedures, and the workers had used soap and cold cream with an organic solvent for the past 10 years to facilitate cleaning the hands and forearms. All workers with skin problems were given further dermatologic examinations, and 26 of them were given patch tests with various substances, including tungstic oxide, titanium oxide, cobalt chloride, and finished hard-metal powder.

The examinations resulted in the following diagnoses: contact eczema, 16; pruritus without skin lesions, 8; folliculitis, 6; and neurodermatitis, 5 [24]. The eczema and itching were localized on the areas of the body with high dust contact, namely on the face and extremities. Of the observed skin disorders, only eczema and itching were attributed to the occupational exposures.

Patch tests on 14 workers with contact eczema revealed that 3 of them were sensitive to cobalt chloride and 2 of them were sensitive to finished, hard-metal powder as well. Seven of the eight workers with pruritus and the five with neurodermatitis who were patch-tested showed no reaction. Although an allergic reaction to cobalt was noted in a few workers, the author attributed both eczema and itching to the combined irritant effect of hard-metal dust and intensive cleaning of the skin.

### Carcinogenicity Reports

The following two studies are the only ones dealing with the incidence of cancer in cemented tungsten carbide workers. No human studies are available that indicate the carcinogenic potential of either soluble or other insoluble tungsten compounds.

Bech et al [25] reported bronchial carcinoma in a worker suffering

from hard-metal disease. The 63-year-old man began working as a core maker when he was 13 years old and held this job in various iron foundries for 32 years. He subsequently worked in the hard-metal industry for 17 years. His smoking history was not reported. During the latter employment period, he worked in all of the operations of the hard-metal industry, including powder mixing. No information was provided on the level of his exposure and the nature of the metal components to which he was exposed. After 13 years of working in the hard-metal tool industry, the worker reported to the hospital with a 3-year history of persistent dry cough, shortness of breath, and pain and tightness in the chest. The incipient fibrosis was detected by radiographic examination. The fibrosis increased during the next 5 years, and a mass in the lower lobe of the right lung was diagnosed as a neoplasm. The workman died 3 years after this diagnosis. At autopsy, most of the right lung was found to be invaded by anaplastic adenocarcinoma. There was a general appearance of nonspecific fibrosis which the authors considered to be unrelated to the carcinoma. Some neoplastic invasion of the capsule of the right kidney was also observed. The worker had been exposed to a number of industrial dusts of unknown compositions and concentrations. Therefore, the tumor cannot be attributed definitely to exposure to tungsten.

In 1963, Collet and associates [26] described a case of pulmonary fibroadenomatosis in a 57-year-old man who worked in the manufacture of sharp-edged tools. The study presented the results of physical examination, bronchoscopic examination, pulmonary function tests, and chest radiographs. During the 14 years before the manifestation of the disease, the man had been exposed to unspecified amounts of dusts of tungsten

carbide powder, cobalt, tantalum, titanium, and cobalt oxalate, and to trichloroethylene vapor. After the man had worked in such an environment for 8 years, chest roentgenographs showed reticulation of the bases of both lungs and of the central portion of the left lung. After 2 more years, fever and breathing difficulties were reported; a year later, exertional dyspnea had become progressively worse. These symptoms persisted during the next three years, and the patient also developed an increased heart rate and pulmonary rates. In addition, his vital capacity was only 65% of the theoretical value, while the carbon monoxide diffusion capacity measured 19% of the theoretical value. At the end of this period, he died of respiratory failure and cardiovascular collapse. Seven months before the man's death, a sample of lung was taken for microscopic study and for spectrographic analysis for tungsten, tantalum, titanium, cobalt, and nickel.

Microscopic study of the lung sample taken 7 months before the worker's death led to a diagnosis of pulmonary fibroadenomatosis with alteration and obliteration of capillaries resulting in an endarteritis [26]. Proliferations of smooth muscle, elastic fibers, mucous-producing cells, and macrophages were also evident. The epithelial cells of the alveoli and septa were altered by stratification metaplasia, fibrous tissue, and collagen deposits. The small alveolar cells were completely absent. Electron microscopy confirmed the previously described findings and revealed that the most common changes were mitochondrial and nuclear. The lung tissue was stated to contain significant amounts (no values given) of tungsten, nickel, and titanium. The other elements, presumably tantalum and cobalt, were reported to be present only in traces. On the basis of

the microscopic findings, the authors concluded that the lesion was not malignant, although it had some questionable features. They believed that the fibroadenomatosis observed in their patient was the result of occupational exposures to dusts arising in the tungsten carbide industry. While this is a possibility, the unexplained spectrographic findings of significant amounts of nickel in the lung and the worker's exposure to trichloroethylene vapor make the basis for this conclusion equivocal.

#### Epidemiologic Studies

Studies of workers exposed to dusts of tungsten and its products in the cemented tungsten carbide industry show that the effects are chiefly respiratory. Most of the reports do not distinguish the effects of tungsten products from those due to cobalt. However, one study [27] found that the effects of exposure to mixtures containing cobalt are more severe than the effects of exposure to tungsten compounds alone.

In 1967, Mezentseva [28] reported a study of the effects on workers of exposure to airborne dusts of tungsten trioxide, tungsten dioxide, metallic tungsten, and tungsten carbide. The author determined the air levels of dusts present in a workshop where malleable tungsten was prepared and at the following stages of hard-metal production: grinding, loading and unloading, reduction of tungsten, carbonization, and sifting. Dust particle sizes, determined by what was described as the shadow method, were reported for unspecified processes in the production of hard metal; apparently, particle sizes were not determined in the malleable-tungsten workshop. Total airborne dust levels for hard-metal production were 8.3-83 mg/cu m. The diameters of 72-82% of the particles were less than 4  $\mu$ m. In

the manufacture of malleable tungsten, the airborne dust concentrations were 1.3-60 mg/cu m in various stages of processing.

The author [28] described the results of physical and radiographic examinations of 54 workers engaged in processes associated with the formation of the dust of tungsten or of its compounds, but it was not clear from the report whether these workers were employed in the hard-metal industry or in the manufacture of malleable tungsten. The physical and radiographic examinations were not described in detail. The workers examined were 29-45 years old, but other details such as smoking history and sex, which might have had an impact on the results, were not presented. No control group was mentioned. The author did not mention the average number of years these workers were employed in operations that might generate significant air levels of tungsten dust. Of the 54 workers examined, 5 showed early radiologic signs of diffuse pulmonary fibrosis; one of these had been employed for 19 years, another for 24 years, and the rest for no more than 2-3 years. Where such wide variation in exposure durations exists, it is possible that other preexisting conditions which were not described may have contributed to the cause of the signs and symptoms.

Kaplun and Mezentseva [27], in 1959, reported the effects on worker health of exposure to dusts generated in the production of hard metal. The dust concentrations in various operations of tungsten carbide manufacture and in various stages in the production of tungsten carbide-cobalt hard metal were determined gravimetrically. The concentrations of cobalt dust generated in the production of hard metal from the tungsten carbide-cobalt mixture were also monitored. Records of periodic medical examinations of

36 tungsten carbide workers who came into contact only with tungsten and its compounds were analyzed separately from those of 247 workers exposed to mixed dusts of cobalt and tungsten carbide. No control group was mentioned. Details of medical examinations and the age, sex, duration of exposure, and medical histories of the workers were not reported.

In the various processing operations in the production of tungsten carbide, the dust concentrations were 8.6-107 mg/cu m [27]. The dust concentrations in the production of tungsten carbide-cobalt hard metal were 3-186 mg/cu m, and the cobalt concentrations were 0.27-1.75 mg/cu m. The authors noted that 4 of the 36 workers who came into contact only with tungsten compounds showed radiographic evidence of early diffuse interstitial fibrosis. No other changes were reported. Analysis of medical examinations of 247 workers exposed to mixed dusts of tungsten and cobalt showed that 117 workers had some damage to the upper respiratory tract. Of these, 33 had indications of incipient diffuse interstitial fibrosis, and chronic bronchitis was diagnosed in 35. It was noted that a significant fraction (no values given) of the workers had hypotension, unspecified changes in the blood, or an impaired sense of smell. This group of 117 workers also complained of loss of appetite, nausea, and coughing. The authors concluded that the harmful health effects in the manufacture of hard metal were produced by mixed dusts of tungsten, titanium, and cobalt. They also suggested that evaluation of the biological action of such mixed dusts should be based on the content of the most toxic component, cobalt.

Basing their recommendations on the percentage of cobalt present in the mixed dusts at the plants studied, the authors [27] advised that the

mixed dust concentrations in the air should not exceed 2 mg/cu m. Although this is the first report of an attempt to distinguish the health effects of tungsten and its compounds from those produced by a mixture of tungsten carbide and cobalt, the derivation of the limit of 2 mg/cu m for mixed dusts is not clear. In the absence of details on the duration of exposure and preexisting conditions for each group, no meaningful distinction can be made between the results from the exposures to the two types of dust. The higher incidence of pulmonary disorders in the group exposed to mixed dusts of tungsten carbide and cobalt may be related to total dust concentrations that were somewhat higher than those found for the group with pure tungsten exposures.

Lichtenstein et al [29], in 1975, reported the results of a study of the effects of airborne tungsten carbide and cobalt on the health of workers in an operation that involved grinding tool bits and inserts made of two commercial grades of cemented tungsten carbide. One grade contained 72% tungsten carbide, 8% titanium carbide, 11.5% tantalum carbide, and 8.5% cobalt; and the other contained 94% tungsten carbide and 6% cobalt. About 70% of the tool-grinding activity involved the latter grade. Approximately 75% of the tool work involved regrinding old carbide tips, and 25% involved grinding new carbide tips. The air was sampled with filters in the workers' breathing zones, and the filter contents were analyzed for tungsten and cobalt by atomic absorption spectrometry. The concentrations of tungsten ranged between 0.2 and 12.8 mg/cu m, while those of cobalt were 0.04-0.93 mg/cu m. Mean concentrations were 5.16 mg/cu m for tungsten and 0.28 mg/cu m for cobalt. Of the 25 samples taken, 40% exceeded 5 mg/cu m for tungsten and 60% exceeded 0.1 mg/cu m for cobalt.



To evaluate the employees' health status, the authors [29] examined 22 tungsten carbide grinders, 31-60 years old, including 6 nonsmokers, 10 smokers, and 6 ex-smokers who had ground tungsten carbide tools for 1-30 years, for a mean duration of 11 years.

Radiographic examinations revealed no evidence of pulmonary fibrosis in any of the workers. For all tool grinders, the mean FVC and FEV<sub>1</sub>, expressed as percentages of the predicted values (based on normal values from persons of the same sex, age, and physical stature), were 88.7 and 95.1, respectively, and the mean FEV<sub>1</sub>/FVC was 86.8%. The small number of workers tested, especially when subdivided into smokers and nonsmokers, did not permit a statistical evaluation of the pulmonary function test data. However, the authors suggested that the reduced FVC, the near-normal FEV<sub>1</sub>, and the elevated FEV<sub>1</sub>/FVC ratio may be indicative of an early stage of restrictive ventilatory impairment.

The mean red blood cell counts of all 22 grinders were within the normal range [29]. Exertional dyspnea was recorded for 1 smoker and 2 ex-smokers, while 3 of 6 nonsmokers and 5 of 10 smokers complained of productive coughs. The authors concluded that, in this study, cobalt exposure provided a good index of the total dust exposure, since concentrations of the tungsten dust above its TLV were recorded only when the concentration of cobalt dust exceeded its TLV. They did not observe increases in red blood cell counts or indices of pulmonary fibrosis. The authors noted that exposures to cobalt at levels above the TLV might occur in the cemented tungsten carbide tool-grinding industry during wet process grinding in the absence of local exhaust ventilation. Although the TLV's of both tungsten and cobalt were exceeded in the cemented tungsten carbide

tool grinding operations, the authors concluded that cobalt rather than tungsten exposures caused the observed changes. However, the data presented do not clearly distinguish the effects of the two metals.

In a medical surveillance program, developed as a consequence of the above study, Bartl and Lichtenstein [30] found one case of pulmonary fibrosis in the same population of cemented tungsten carbide tool grinders. The 34-year-old tool grinder had worked in a variety of jobs for 15 years. During this period, he had ground tools or drills for a total of 7 years, 42 months of which had involved work with tungsten carbide alloys. Approximately 9 years elapsed between the time he began working with tungsten carbide alloys and the examination at which the diagnosis of pulmonary fibrosis was made.

At this examination, his chest radiographs showed diffuse, bilateral, poorly delineated, parenchymatous densities distributed evenly in the upper and lower lung lobes [30]. His FVC and FEV<sub>1</sub> were 77 and 89% of normal, respectively. However, the carbon monoxide diffusion capacity was normal, and the worker did not develop shortness of breath during exercise. A sample of lung removed for biopsy was described as diffusely nodular with a slightly increased palpable density [30].

Microscopic examination of the same lung sample showed multi-focal pulmonary scarring associated with patchy interstitial fibrosis and nonspecific reactive changes in a hilar lymph node. The authors concluded that the observed interstitial fibrosis in this employee was consistent with the magnitude of his potential exposure to hard-metal dust containing cobalt.

Bech et al [25], in 1961, examined the medical histories of 255 hard-metal shapers, grinders, and powder workers who had been employed for 1 month-20 years. Chest radiographs of the 113 shapers, 120 grinders, and 22 powder workers were also examined. Their age, sex, and smoking history were not specified, and no control group was mentioned. Forced expiratory volume and airway resistance tests were performed on 19 volunteers (7 powder workers and 12 shapers) at the beginning and end of a working day. In addition, concentrations of airborne dust were measured (by gravimetric analysis) and the dust was analyzed for particle size and composition.

The breathing zone samples contained 195-1,230 particles/ml, the particles being less than 5  $\mu\text{m}$  in diameter. The dust contained 90% tungsten and 6% cobalt, the remaining 4% consisting of titanium, silica, aluminum, magnesium, and iron. An unspecified number of these workers complained of wheezing and tightness of the chest during the workday. Of the volunteers who underwent pulmonary function tests, two shapers who complained of wheezing and tightness exhibited considerably decreased (13.4-17.6%) ventilatory capacity accompanied by appreciably increased (24.3-31.8%) airway resistance. Among the 255 workers whose medical reports were examined, 1 case of hard-metal disease was diagnosed by chest radiograph; early signs of pulmonary fibrosis were noted in an unspecified number of radiographs.

Barborik [31] reported studies in 1966 on the health of 193 employees (104 men and 89 women) working in the production of hard metal. The workers, with average ages of 43 and 40 years (range 19-66 years) for men and women, respectively, were exposed to dust levels of 13-100 mg/cu m

while handling powders consisting of 70-90% tungsten carbide, 8-18% titanium carbide, and 5-25% cobalt. The composition of the airborne dust was not given. Although the particle sizes were not measured, the author concluded from data in published reports that most dust particles generated in this process were respirable. The average length of work experience was 6 years (range 1-13 years). The workers were examined for signs and symptoms of disease and for changes in chest radiographic findings.

Ninety workers (36 men and 54 women) complained of coughing, and half of this number had coughs that varied from irritant to barking [31]. Sixty-seven workers, including approximately equal numbers of men and women, complained of dyspnea. Other upper respiratory difficulties, such as burning or dryness of throat and anosmia, were less frequently reported. Moist or markedly crepitant rales were heard on auscultation in an unspecified number of workers. Of the 116 workers who were examined by spirometry, 25 showed moderate to severe disturbances in pulmonary ventilation. Roentgenologic abnormalities were reported in 31 of the workers. In 13 of the 31, the abnormalities were described as incipient, atypical, pulmonary reticulations, while in the remaining 18, they were said to be more clearcut and indicative of pronounced pulmonary fibrosis.

Barborik [31] concluded that metallic cobalt powder played a substantial role in the etiology of the disease and that its effect may have been potentiated by tungsten carbide. The author probably based his conclusion on the autopsy findings from one of the five case studies presented in the report. This worker had 12.5 and 78.6  $\mu\text{g}$  of cobalt/10 g of dry tissue in the lungs and hilar lymph nodes, respectively.

Vengerskaya and Salikhodzhaev [32] studied the effects of aerosols of tungsten, cobalt, and their compounds on workers in a hard-metal plant. The study included measurement of atmospheric concentrations of tungsten and cobalt at various operations by unspecified methods.

Of the 178 hard-metal workers (52 men and 126 women), 81% were about 30 years old [32]. About 84% of the workers had been engaged in hard-metal operations for 3 years. The concentrations of tungsten in the work atmosphere during various operations varied from 0.75 to 6.1 mg/cu m, while those of cobalt were 0.6-3.2 mg/cu m. No control group was described.

Among the 178 workers, 88 persons complained of dyspnea, coughing, pounding of the heart, headache, dizziness, nausea, loss of appetite, and impaired sense of smell [32]. The range of the mean tungsten concentrations was 0.8-1.1 mg% in the blood of 45 workers and 0.6-1.1 mg/liter in the urine of 40 workers. Tungsten was not detectable in the blood of 11 workers and in the urine of 7. Although it is not clear from the information given in the report, the workers may have been exposed to both soluble and insoluble tungsten compounds. The concentration of chlorides in the blood, measured in 30 workers, was slightly above normal in 20 and below normal in 10, while the chloride content of the urine was somewhat depressed in 32 of 39. Blood sugar levels were slightly higher than normal (no values given) in 8 of 37 workers examined, and the glucose tolerance curve in 8 of 14 workers was elevated. In 9 of 34 persons, hippuric acid elimination after loading with sodium benzoate was above 80% of the theoretical maximum conversion; it was 71-80% in 6, 61-70% in 8, and below 60% in 11 persons.

The authors [32] concluded that tungsten can be found in the blood and urine of workers exposed to aerosols of tungsten and cobalt, that the workers' blood sugars were somewhat elevated, and that there was some impairment of the detoxication of benzoic acid by the liver. They did not describe the methods used to determine tungsten concentrations either in the air or in body fluids. Therefore, the significance of the instances in which tungsten was undetectable cannot be assessed. The authors also did not elaborate on the absence of a relationship between the concentrations of tungsten in the body and the results of liver function tests or of blood changes. They did not measure cobalt concentrations in tissue and body fluid when they were aware that the exposure levels of cobalt exceeded the maximum permissible concentration (MPC) of 0.5 mg/cu m. Furthermore, they neither tried to define the causal factors involved in the study nor explained what the measured changes implied.

In 1962, Heuer [33] reported the respiratory effects in 208 workers engaged in hard-metal production, where dust levels of 277-4,064 mg/cu m were generated. Thirty-nine of the 208 employees worked in the mixing room, where the airborne dust was composed of 67.8% tungsten, 21.2% cobalt, 2.25% iron, 1.75% titanium, and 7% volatiles (not described). In the granulating room, 99 workers were exposed to dust containing 76.1% tungsten, 7.6% cobalt, 0.3% iron, and 16% volatiles. The remaining 90 workers were engaged in processing the finished hard metal. The airborne dust in this area was not analyzed for its components. The average size of 99.2-99.9% of the particles generated in various operations during hard-metal production was below 5 $\mu$ g.

During routine medical evaluations, 15 mixing room workers had complaints of cough, 14 of dyspnea, and 3 of asthma. While the physical examinations showed 5 cases of bronchitis and 14 cases of emphysema in these workers, chest radiographs revealed 3 cases of bronchitis, 10 cases of emphysema, and 23 cases of fibrosis that varied in severity. Forty of the 99 workers from the granulating room complained of coughs, and 34 reported dyspnea. Clinical signs and symptoms indicated 10 cases of bronchitis and 7 cases of emphysema among these 99 workers, while chest radiographs revealed the incidence of bronchitis in 9, emphysema in 6, and incipient or mild fibrosis in 18. Thirty-three of the 70 workers who handled the finished hard metal complained of coughs, and 16 reported dyspnea. Among these 70 workers, 10 cases of bronchitis and 2 cases of emphysema were diagnosed from clinical signs and symptoms, while chest roentgenograms showed that 7 had bronchitis, 13 had emphysema, and 14 had incipient or mild fibrosis.

On the basis of reported complaints, workers in the mixing room were the only ones to develop asthma, and they had the highest incidence of pulmonary fibrosis. The pulmonary fibroses found in these workers were more advanced or severe than those of the employees who worked in the granulating room or with the finished products. The author attributed the asthma and pulmonary fibrosis to exposure to high concentrations of dust containing the pure components of the hard metal. Analyses of the lung specimens obtained by autopsy from a mixing room worker who had severe fibrosis showed that dust particles accounted for 0.96% of the dry weight of the lung.

Chemical analyses of the dust from the lung revealed 14.4% tungsten, 9.8% calcium oxide, 9.2% phosphorus pentoxide, 5.6% silicon dioxide, 2.9% cobalt, 2.8% ferric oxide, 2.05% titanium, and 1.1% aluminum oxide, while 50.3% of the sample was lost during annealing.

The author noted that mixing room employees with mild to severe pulmonary fibrosis had worked for 4-8 years in hard-metal production. However, other employees who worked for 12 years in the same room had no adverse signs or symptoms. According to Heuer, this difference indicated that individual susceptibility was an important factor in the development of occupationally related pulmonary problems in hard-metal workers.

#### Animal Toxicity

Short- and long-term animal experiments revealed that the effects of inhalation or intratracheal introduction of insoluble tungsten compounds were limited to the respiratory system, and the effects of ingestion of soluble tungsten compounds such as sodium tungstate, were not clearly identifiable in any organs of the body. Few reports were found on the dermatologic effects of tungsten and its products in experimental animals.

Mezentseva [28] studied the effects of dusts of tungsten and its compounds on 55 white rats. Either metallic tungsten, tungsten trioxide, or tungsten carbide was injected intratracheally in single doses of 50 mg of material suspended in 0.5 ml of physiologic saline. Tungsten carbide was also administered by inhalation for 1 hour/day for 5 months to another group of animals. The tungsten carbide concentration in the exposure chambers was 600 mg/cu m, with up to 77% of the particles measuring less than 5  $\mu$ m in diameter. The age, weight, sex, strain, and number of rats



subjected to each experimental condition were not reported. Six rats served as controls. No details of their management were given. In the intratracheal studies, rats were killed 4, 6, or 8 months after administration of the suspensions and their lungs were examined microscopically. Animals exposed by inhalation were monitored for general health and body weight. At the end of the exposure period, all rats were killed and examined macroscopically for changes in unspecified internal organs.

At 4 months, the lungs of rats given metallic tungsten showed infiltration by macrophages, chiefly around the pulmonary blood vessels, and thickening of the walls between the alveoli [28]. Around the bronchi, large numbers of round cells were seen surrounding the dust particles at 6 months. Collagen fibers had overgrown these foci by 8 months; the endothelium was swollen and the walls of small vessels were thickened. Metallic tungsten did not cause macroscopic changes in the internal organs of rats at either 4, 6, or 8 months. No details of the general health and weight gain of the rats were given.

Four months after the administration of tungsten trioxide, the lungs showed considerable thickening of the walls between the alveoli and infiltration of macrophages around the vessels of the bronchi. The endothelium was swollen, with thickening of the walls of small blood vessels [28]. Eight months after the intratracheal injection, cellular proliferation persisted. Lesions surrounding the dust particles were characterized by fine, collagenous fibers and sclerosis of the vascular walls and peribronchial areas. In rats given tungsten trioxide, no macroscopic changes in the internal organs were observed either 4 or 8

months after the injection.

In rats administered tungsten carbide intratracheally, thickening of the walls between the alveoli and accumulation of macrophages around the bronchi and blood vessels were noted 4 months after treatment [28]. Lungs examined at 6 months showed cellular proliferation around the blood vessels, with overlying, collagenous fibers. At this examination, swelling of the endothelium and thickening of the walls of the small blood vessels were evident, and some hyperplasia of the tracheal lymph nodes containing free dust particles was observed. Microscopic findings in animals killed after 8 months were similar to those in animals killed at 6 months. The report did not discuss the effects of intratracheal administration of tungsten carbide on macroscopic changes of the other internal organs, on general health, or on weight.

Rats exposed to tungsten carbide dust by inhalation at 600 mg/cu m remained healthy and gained weight well during the experiment [28]. Those killed at the end of 5 months' exposure at this concentration showed no macroscopic changes in the internal organs. According to the author, the findings from microscopic examination of the lungs were essentially the same as those observed 6 months after intratracheal administration of tungsten carbide.

Mezentseva [28] concluded that metallic tungsten, tungsten trioxide, and tungsten carbide dusts did not cause severe changes. These changes were described as being more marked after the intratracheal administration of tungsten trioxide than after that of either metallic tungsten or tungsten carbide. From the experimental findings and medical data, the author concluded that these tungsten substances can cause a mild, diffuse

interstitial lung fibrosis. A permissible maximum level of exposure of 6 mg/cu m for tungsten dust was suggested.

Miller et al [16] studied the effects of intratracheally-introduced pure tungsten carbide on rat lungs. Tracheotomies were performed on 15 white rats under ether anesthesia, and 1 ml of a 10% suspension of tungsten carbide in isotonic saline was administered intratracheally. The age, sex, weight, and strain of the animals were not mentioned, the control group was not described, and the size of tungsten carbide particles in the administered suspension was not reported. An unspecified number of rats was killed at 2-week intervals for 18 weeks. The animals were examined macroscopically for exudate on the surface of the lungs, for fluid in the chest cavity, for the distribution of dust in the lungs, which were examined also for microscopic changes, and for alterations in reticulin and collagen contents.

Gross examination of the lungs 2 weeks after the tungsten carbide injections revealed that particles were present in all lobes, particularly the lower ones [16]. The lungs reportedly felt somewhat firmer than those from control animals killed at this time. The treated animals had neither exudates on the surfaces of the lungs nor fluid in the chest cavities. Microscopic examination at this time showed that, although particles were visible within the septa, most of the tungsten carbide remained free in the alveoli. Tungsten carbide was observed consistently within the alveoli throughout the experiment.

By 4 weeks, there had been some mobilization of the septal cells and engulfment of the tungsten carbide particles; these particles were found also in the perihilar lymph nodes and around the peribronchial and

perivascular connective tissue fibers [16]. Results of examinations 6-14 weeks postexposure were not reported. After 16- or 18-week examinations, findings were essentially unchanged from those at 4 weeks. Although more dust was found within the alveolar walls and lymphoid tissue of the lungs, dust was still present in the air sacs. Lung reticulin and collagen did not increase; there was no evidence of inflammation caused by bacteria.

The authors described the observed effects as responses to an inert dust and noted that tungsten carbide did not provoke a necrotizing or fibrosing response in rat lung parenchyma [16]. Commenting on these findings of Miller et al, Schepers [34] speculated that industrial cases of lung fibrosis and pneumoconiosis in tungsten carbide-tool and hard-metal industries might be caused by the coexisting exposures to cobalt.

Delahant [35] studied the effects of selected rare metals and other chemicals on guinea pig lungs in 1943 and presented the results in 1955. These experiments were undertaken to determine the particulate metallic component in cemented tungsten carbide that might provoke lung lesions. Dusts of tungsten metal or of tungsten carbide and carbon in a ratio of 94:6 were injected intratracheally into groups of six guinea pigs. The average weight of the guinea pigs was approximately 600 g. The age, sex, and strain of the animals were not given, and no control group was described. A 10% suspension of each dust in sterile isotonic saline was prepared. Although attempts were made to obtain dusts of 3  $\mu$ m in diameter or less, when this was not possible dusts were used as received. Thus, the particle size of the dusts injected in most cases was unknown. A total of 150 mg of each dust was injected intratracheally in three equal doses at weekly intervals. Animals were killed after 1, 4, 8, and 12 months, and

lung specimens were prepared for microscopic examination. None of the guinea pigs injected with either tungsten metal or tungsten carbide and carbon died during the experimental period.

Gross examinations of the lungs of animals given tungsten metal or tungsten carbide and carbon were performed [35]. Large, circumscribed pigmented lesions were found. Beneath the visceral pleura, widely distributed, small, discrete foci of pigmentation were occasionally observed. There was no appreciable temporal change in the character of the lesions. The author concluded from these findings that dusts of tungsten metal or of tungsten carbide and carbon produced relatively benign effects on lung tissue.

Schepers [36] also studied the effects of tungsten metal dust on the lungs of the guinea pigs exposed by Delahant [35]. One month after injection, microscopic examinations of the lungs showed proliferation of interstitial cells; moderate thickening of alveolar walls was most marked around massed tungsten particles. A considerable amount of macrophage infiltration into the alveoli was noted. Around the capillary blood vessels of the lung, numerous focal cellular lesions were observed. The mucosae of the bronchi and bronchioles were slightly inflamed, with some bronchioles partially or wholly closed. The investigator noted no effects on the lymphoid tissue.

Guinea pig lungs examined 1 year after the intratracheal introduction of tungsten metal dust were reported [36] to have residual lesions. These included persistent, focal, interstitial, cellular infiltration in relation to the retained particles. There were various degrees of peribronchial, peribronchiolar, and perivascular fibrocellular reactions, with

bronchiolitis obliterans and bronchial inflammation. Slight atrophic vesicular emphysema was also present. The author concluded that tungsten was probably a relatively benign substance. Commenting on the occupational significance of his findings, he remarked that exposures to the dust generated by pulverizing tungsten in the tungsten carbide industry would be relatively, though not wholly, free from risk.

Schepers [34] also microscopically examined the effects of intratracheally injected tungsten carbide and carbon (94:6) on the respiratory systems of guinea pigs. The animals used in this investigation were those described by Delahant [35]. Schepers reported that the immediate response was a diffuse hyperemia and inflammation of the bronchial mucosa. After 1 month, much of the tungsten carbide and carbon mixture had been engulfed by multinucleated macrophages. While some of these cells penetrated the alveolar walls, most were still within the alveoli. Some of the dust particles observed had aggregated in the small vascular components.

The author [34] compared these findings with those from his investigations on tantalum and cobaltic oxides and noted that the tungsten carbide and carbon mixture did not readily reach the perivascular lymphatics. Marked lymphocytic hyperplasia with infiltration of the adjoining alveolar walls and some hyperemia were observed in these areas. Such alterations in the lymphoid tissues reportedly continued for several months after the acute reactions had subsided. Confluent interstitial pneumonitis in relation to trapped dust masses or isolated foci were observed 12 months after the exposure. Most massed granules in the mixture of tungsten carbide-carbon were engulfed by multinucleated, giant cells

within the relatively atrophic alveoli. Subpleural granulomata with a minor degree of fibrocyte formation were noted occasionally. Bronchiolitis and peribronchial and perivascular fibrosis were not persistent. Schepers concluded that the mixture of tungsten carbide and carbon was less harmful to lung tissue than tungsten metal.

Delahant [35] also reported the effects of intratracheal instillations of a 91:9 mixture of tungsten carbide and cobalt dusts and of inhalation exposures to a 3:1 mixture on the lungs of guinea pigs. Six guinea pigs were injected intratracheally with a total of 150 mg of the tungsten carbide and cobalt mixture, containing particles of 3  $\mu\text{m}$  or less in diameter, in three equal doses at weekly intervals. For inhalation exposures, Delahant exposed 20 guinea pigs to particles of the mixed tungsten carbide-cobalt dust, measuring 0.5-2.0  $\mu\text{m}$  in diameter. The total exposure period was 35 days, and the dust concentration range was 8,800-10,600 particles/cu cm for the first 20 days; after a 5-day recovery period, the animals were exposed to the dust mixture for an additional 15 days at a concentration of approximately 2,800 particles/cu cm. The age, weight, sex, and strain of the guinea pigs were not given, and no control group was described.

In the group injected intratracheally, none of the guinea pigs died during the experimental period [35]. Their lungs had well-circumscribed linear and diffuse patterns of black pigmentation. The time of this observation was not given. All lungs were reported to be normally soft with no observed progressive change in the character of the lesions during the study.

Animals that died during the inhalation experiment and two animals that were killed after 181 and 585 days of recovery in normal air following the second period of exposure were examined for gross changes in their lungs [35]. Five animals died during the first period of exposure, and three more died during the 5-day inter-exposure recovery period. During the second exposure, six more animals died, two each on days 10, 13, and 15 of exposure. Post-mortem examinations showed that some of the animals had acute pneumonitic consolidations of their lungs. The lungs of guinea pigs killed 181 and 585 days after the termination of the second exposure had faint, diffuse pigmentation by dust.

From the mortality rates and the nature of the gross pulmonary reactions, Delahant [35] concluded that particulate tungsten metal and a mixture of tungsten carbide and carbon were relatively inert and that, when cobalt was mixed with tungsten carbide, the toxic and lung irritant characteristics of the cobalt component were dominant.

In another study, Schepers [37] evaluated the effects of mixtures of tungsten carbide and cobalt on guinea pig lungs. The lung tissue used in these investigations was obtained from the animals Delahant [35] exposed to the dust mixtures by both inhalation and intratracheal injection. Guinea pig lungs were examined 1 or 12 months after the intratracheal instillation of tungsten carbide and cobalt in a ratio of 91:9. Lungs of animals exposed by inhalation to the dust of a 3:1 mixture of tungsten carbide and cobalt were removed for examination at the end of the first exposure, at the end of the second exposure, and 181 and 585 days after the second exposure.



One month after the intratracheal instillation, there were areas of dense fibrosis in the lungs wherever a massive deposition of the dust had occurred [37]. Infiltration of the alveolar walls by lymphocytes had produced almost confluent pneumonitic areas, and there was infiltration of lymphocytes into the perivascular areas. There was no involvement of the hilar lymphatics. While most of the bronchial epithelium was not damaged, in areas of massive dust deposition the bronchial mucosa showed a firm fibrous reaction with some development of bronchial crypts. One year after the injection, massed dust particles were still seen in the alveolar spaces. Other residual damage included patches of pneumonitis and mild cellular and fibrous reactions around the dust deposits. The hilar lymph nodes reportedly contained some particulate matter which could be subsequently deposited in the perilymphatic zones.

The exposure to a 3:1 mixture of tungsten carbide and cobalt provoked a diffuse inflammatory reaction at an unspecified time [37]. At the end of the first exposure, the lungs were hemorrhagic. Alveoli were infiltrated with erythrocytes, plasma cells, lymphocytes, polymorphonuclear leukocytes, and a fair number of macrophages containing ingested particles. "Prominent septal cells" lined the alveolar walls at numerous points. No changes were observed in the bronchi and larger blood vessels. Examination after the first exposure showed considerable recovery with mild residual atrophic vesicular emphysema and limited infiltration of polymorphonuclear leukocytes and macrophages into the alveoli. A considerable amount of dust was still retained, mainly within the pulmonary macrophages. The author attributed a specific lesion, namely, proliferation of the cortical reticuloendothelioid cells of the hilar lymph nodes, to the mixture of

tungsten carbide and cobalt. Neither tungsten carbide nor cobalt alone was capable of provoking a similar reaction.

After the second exposure, alveolar edema and diffuse hyperemia were once again evident [37]. Six months after the second exposure, metaplastic hyperplasia of the bronchial epithelium and the formation of villous papillomas were seen. Proliferating epithelial cells and papillomas occluded the bronchi, producing regional focal emphysema. Some undefined residual effects of tungsten carbide and cobalt were still noticeable 21 months after the exposure. Epithelial hyperplasia and metaplasia of the trachea and bronchi were present at this later examination. The characteristic foci of hyperplasia of epithelioid elements of the hilar lymph nodes persisted.

Schepers [37] commented that the pronounced proliferative and metaplastic epithelial changes may have reflected a sensitizing property of cobalt. The author also cautioned that, if observations in guinea pigs have any bearing on the way in which human lungs may react, extreme care should be exercised to control inhalation exposure to metal powders. Since the 91:9 ratio of tungsten carbide and cobalt used is comparable with those to which industrial workers might be exposed, these results have direct relevance to occupational exposure.

Kaplun and Mezentseva [38] conducted experiments on white rats in an attempt to establish the etiologic roles of tungsten, cobalt, and their mixtures in affecting workers' health in the hard-metal industry. In 4 series of experiments, 100 white rats of unspecified age, weight, sex, and strain were used. Groups of rats were given intratracheal injections of 10, 15, 25, or 50 mg of one of the following mixtures: (1) 8% cobalt and

92% tungsten, (2) 15% cobalt and 85% tungsten, and (3) 8% cobalt, 14% titanium, and 78% tungsten. The particle sizes of the dusts and the vehicle of administration were not reported, and no control group was described. Each dust mixture was administered to eight rats in the 50-mg series and to five rats in the 25-mg series; the number of rats used in the 15- and 10-mg series were not specified.

Injection of 50 mg of any of the three dust mixtures caused 100% mortality within 2 days after administration [38]. Within 5-7 days the rats that received 25 mg doses had 40, 100, and 60% mortalities in dust mixture groups 1, 2, and 3, respectively. At dosages of 15 mg, all the rats in group 2 died, and two each died in groups 1 and 3. At the 10-mg dose level, there were no deaths in groups 1 and 3, but 5 of 13 rats died within 2-3 days in group 2. The absolute lethal dose for the dust mixture of 15% cobalt and 85% tungsten was 15 mg (2.25 mg cobalt), while that of the other two groups was 50 mg (4 mg cobalt). The minimum lethal dose was 10 mg (1.5 mg cobalt) for the 15:85 mixture and 15 mg (1.2 mg cobalt) for the mixtures containing 8% cobalt. The authors, without presenting details, noted that the minimum and absolute lethal doses of pure metallic cobalt were 5 and 10 mg, respectively; however, the absolute lethal dose of the 15% cobalt dust mixture contained only 2.25 mg of cobalt. They concluded that the dust mixtures were more toxic than the separate dust components and that the toxicity of cobalt was increased in the presence of tungsten and titanium carbides. However, since the absolute lethal doses of the dust mixtures containing cobalt were 50-400% greater (15 and 50 mg) than that alleged for metallic cobalt alone (10 mg), it is probable that the dust mixture itself exerted some toxic effects.

Without making distinctions among the three dust groups, the authors [38] reported that animals dying after receiving doses of 25 mg or 50 mg of the dusts had thickened interalveolar septa that sometimes fused together to form solid areas of airless, homogeneous tissue containing many free-lying dust particles. The thickening of the septa was attributed to severe hyperemia and cellular infiltration by lymphocytes and macrophages. Large amounts of dust and secretions were observed in the bronchial lumina. In addition, marked hyperemia and cellular granulo-nodular degeneration were seen in the livers; and the kidneys of these animals showed granulomatous degeneration of the cells of the convoluted and descending tubules and obstruction in the glomeruli and proximal tubules.

Single doses of the three dust mixtures were administered intratracheally in the following amounts: 10 mg for the first mixture, 15 mg for the second mixture, and 10 mg for the third mixture [38]. The lungs, liver, and kidneys of animals given the first, second, and third mixtures were examined after 6, 4, and 6 months, respectively. The lungs of rats exposed to the first dust mixture showed extensive areas of dense tissue around the dust particles resulting from infiltration by lymphoid elements. Massive lymphocytic accumulations were observed around the small and medium-sized bronchi, and the mucosae of the bronchi were hypertrophic, with adenomatous proliferation and formation of papillomata. Changes in the walls of the blood vessels caused exudation of plasma, and there was excessive connective tissue around the small and medium-sized vessels. The liver and kidneys showed marked hyperemia. The lungs of rats exposed to the second dust mixture were similarly affected, but the adenomatous proliferation was more marked. Some hypertrophic adenomatous tissue was

overgrown by fine strands of connective tissue. In the third group, in addition to the lung changes seen with the first two dust mixtures, diffuse sclerosis of the lung tissue was observed. The effects of the second and third dust mixtures on the liver and kidneys were not described. The authors [38] concluded that the changes produced by the three dusts were similar and that they were more marked than those produced by metallic cobalt. These investigations indicated that the activity of cobalt is enhanced when tungsten and cobalt act together. The authors hypothesized that the solubility of cobalt might be increased in the presence of tungsten.

To test their hypothesis, Kaplun and Mezentseva [38] determined the solubilities of 100 mg of powdered metallic cobalt and of (the first two) dust mixtures containing 100 mg cobalt in unstated volumes of 0.3% hydrochloric acid, which has a pH equivalent to that of gastric juice. During a period of 24 hours, only 3 mg of cobalt dust was dissolved, while 12 and 15 mg of cobalt were dissolved from the 8:92 and 5:85 dust mixtures. Although the universality of this solubility behavior was not tested in other solvents, the authors believed that their hypothesis on the enhanced toxicity of cobalt in the presence of tungsten might still be acceptable. Although this conclusion was based on the cobalt content of the mixtures and on the assumption that dust mixtures containing tungsten or tungsten and titanium are more toxic than is pure cobalt, the data do not show clearly that the toxicity of cobalt was enhanced by the presence of tungsten or titanium.

Schepers [39] also assessed the biologic actions of a number of industrial chemicals that pose potential occupational hazards. Among these

were manganese tungstate, tungsten, and tungsten carbide. An unspecified number of guinea pigs were injected intratracheally with either a suspension or a solution of each of the above compounds, and the animals were examined after 12 months for pulmonary lesions, including epithelialization (proliferation of epithelial cells) and neoplasia. The experimental design was not described, and the nature of lung evaluation and rating was not stated.

Manganese tungstate was rated as slightly reactive in producing pulmonary lesions and moderately reactive in inducing epithelialization [39]. In comparison, both tungsten and tungsten carbide were graded as slightly reactive in inducing both pulmonary lesions and epithelialization. According to Schepers, none of the three materials induced tumors. Although the assessment of the reactivity of these substances included the number of animals affected, there was no report of the incidence rate of pulmonary lesions and the nature of their distribution.

Brakhnova and Samsonov [40] compared the toxicities of silicides of three transition metals, titanium, molybdenum, and tungsten. Albino rats of unspecified age, weight, sex, and strain were given tungsten silicide by inhalation or intratracheal injection for 1-6 months. The control group was not described, and the concentrations of tungsten silicide and the precise durations of exposure to it were not given. The toxicities of the silicides were evaluated (time not specified) qualitatively from microscopic examination of the lungs; the quantitative effects on the concentrations of collagen and ascorbic acid in the lungs served as estimates of the fibrogenic activity. The authors did not distinguish the effects of tungsten silicide administered by inhalation from those caused

by its intratracheal injection.

Pulmonary tissue obtained from rats exposed to tungsten silicide for 1-6 months exhibited hyperplastic lymph nodes, localized thickening of alveolar walls, perivascular infiltration by lymphocytes, and nodules composed of fibroblasts, lymphocytes, and macrophages [40]. Compared with the other silicides studied, tungsten silicide produced degenerative changes in various organs, including the liver, kidneys, and heart, that were considerably less pronounced. Vascular permeability was not affected by tungsten silicide. The concentrations of collagen in the lung were increased to 51.6 and 56.9% above the control levels at 1 and 6 months, respectively, after the exposure. Ascorbic acid synthesis in the lungs of animals exposed to tungsten silicide was elevated from 50 to 60% above that in the controls. The authors concluded that the results supported the maximum permissible concentration (MPC) of 6 mg/cu m for tungsten silicide established at that time in the USSR. However, it is not clear how the authors reached this conclusion.

Spiridonova and Suvorov [41] conducted several studies to assess the biologic effects of tungsten hexachloride and the products of its hydrolysis on rats and mice. In the authors' short-term experiments, rats were either given 1,800 mg/kg of tungsten hexachloride intragastrically or exposed to 0.043-0.14 mg of tungsten hexachloride/liter of air for an unspecified period. The age, weight, sex, and strain of the animals were not mentioned, and no control group seems to have been used.

The orally dosed animals had necrotic foci in the mucosa and submucosa of stomach and intestines and in the liver and kidneys [41]. Rats exposed to tungsten hexachloride at 0.043-0.14 mg/liter of air

lacrimated, had profuse blood-stained oral and nasal discharges followed by necrosis of the skin and mucosa, and died of pulmonary edema. No data were presented on the number of deaths. The authors, comparing the LD50's in mice of tungsten hexachloride (1,086.5 mg/kg of body weight by gavage) and of tungstic oxide (4,786 mg/kg of body weight by ip injection), suggested that the chloride form was more toxic than the oxide because the former probably was hydrolyzed in vivo, releasing a sufficient number of chloride ions to be toxic. Since the total buffer capacity of the blood is approximately 45-50 meq/liter and the stated LD50 dose of tungsten hexachloride corresponds to about 213 meq of HCl/liter of blood, this hypothesis seems tenable.

In a second series of experiments, the authors [41] used male white mice weighing 18-22 g to compare the toxicities of tungsten chloride in various stages of hydrolysis. Groups of 10 mice were given ip injections of 1 of 5 aqueous solutions made by starting with a sufficient dose of tungsten hexachloride to yield 3.3 meq/kg of Cl (216 mg/kg of tungsten hexachloride). This was administered immediately after preparation, after neutralization with sodium hydroxide, 30 minutes after preparation, on the following day, and on the following day after filtration. If the tungsten hexachloride were completely hydrolyzed, this dose would release about 44 meq of HCl/liter of blood. This would be sufficient to neutralize completely, or almost completely, the total buffer capacity of the blood. Neutralization reduced the mortality by 50%, while hydrolysis more than doubled the mortality. The toxic hydrolysis product was filterable. The investigators concluded that toxicity of the tungsten hexachloride was produced by its chloride ions and that the toxic effect of free ions in the



thoroughly dissociated hydrochloric acid was greater (100% mortality after 1 day) than that of the rare metal chlorides. They concluded further that the chloride ion plays a major role in the production of the acute toxic effects of tungsten hexachloride.

While these conclusions may be valid, it is not clear how the data relate to industrial exposure, since the route of administration in most studies was ip injection. Although inhalation exposures were conducted and deaths of animals from pulmonary edema were reported, the authors did not indicate the percentage of the experimental animals affected. They concluded that the chloride form of tungsten was more toxic than the oxide. However, their conclusion is not necessarily a valid one, because the LD50 comparisons cited were for different routes of exposure.

Gol'dman et al [42] reported the results of a study on the effects of a charge of calcium-magnesium-tungstate phosphor and finished calcium-magnesium-tungstate phosphor in rats. The chemical composition of the charge was: tungstic oxide, 75%; calcium oxide, 18%; magnesium oxide, 5%; and lead dioxide, up to 3%. The charge and the finished product (after heating of the charge) differed in physical structures (not specified). The particle size of neither product was described. Rats in 2 groups of 10 were given intratracheally single doses of 50 mg suspensions of either the charge or the finished calcium-magnesium-tungstate material brought to 0.5 ml in a sterile physiologic solution. The age, weight, sex, and strain of the rats were not presented, and no control group was described. Six months after dosing, rats from each group were killed and their liver, kidneys, spleen, and heart were examined for macroscopic changes. Changes in the lungs were evaluated by microscopic examination.

No gross changes were observed in the internal organs of either group, but the lungs, 6 months after the administration of the charge of calcium-magnesium-tungstate, showed evidence of cellular proliferation, mainly of lymphocytes and macrophages, with considerable thickening of the interalveolar septa [42]. Cellular infiltration was noted around the bronchi and vessels, and most dust particles had been engulfed by the infiltrated cells. In some areas, accumulations of the dust, with marked cellular proliferation around them, were seen. Some cellular foci were rich in collagen fibers. In the lungs from rats given the finished product, some interalveolar walls were thickened; in other places, the walls of the alveoli were thin, smooth, and torn. The dust was lying free, mostly as separate granules. The lungs showed some emphysematous areas and cellular proliferation around the bronchi and vessels. It was noted that, although the charge of calcium-magnesium-tungstate and the finished product caused similar lung changes, the former had the more severe effect.

Referring to the study of Mezentseva [28], Gol'dman and associates [42] commented that the changes in the lungs produced by the charge of calcium-magnesium-tungstate and those produced by tungsten trioxide were similar but that those caused by the former were the more marked. Since the phosphor contained other potentially toxic substances, such as lead dioxide, the comparison may not be a valid one.

Lauring and Wergeland [43] investigated the ocular toxicity of 12 industrial metals, including tungsten, in rabbits. Two rabbits with body weights of 1.5 and 2.0 kg were used in the experiments with tungsten. In one rabbit, the left eye, which was sham-operated, served as a control, while a particle of tungsten metal less than 1 mm in diameter was

introduced under general anesthesia into the midvitreous region of the right eye through a stab incision. In the second rabbit, one eye was left intact and untreated while the other received the metal in the midvitreous region by the same method. The age and sex of the rabbits were not mentioned. The rabbits were examined at weekly intervals for the first 4 postoperative weeks and then at monthly intervals for 1 year. The evaluated parameters included the size and shape of the pupils, the degree of anterior segment inflammation, the presence of cataracts, and the degree of vitreous inflammation. From these pathologic evaluations, the authors classified tungsten as "completely inert." No changes were noted in either the control or the untreated eyes of these rabbits.

Kinard and Van de Erve [44], in 1943, reported the effects of tungsten metal powder on the growth of rats. They used 38-day-old animals from mixed Wistar albino and Minnesota piebald strains. Groups of 10 rats, 5 of each sex, were caged separately and fed ad libitum with ground dog chow containing 2, 5, or 10% tungsten metal powder; controls were given the ground dog chow without tungsten. Food consumption was determined from the food remaining in the containers after each feeding. The weight gains of rats were recorded at 10-day intervals for 70 days. Animals were killed after 70 days, and their gastrointestinal tracts were examined grossly.

During the 70-day period, the weight gains of male rats fed diets containing 2, 5, or 10% tungsten were 94, 113, and 108% of those of male rats fed the control diet, while the weight gains of female rats fed the three experimental diets were 104, 97, and 85% of control weight gains [44]. During the dosing period, each male rat fed the 2% tungsten diet consumed an average of 21 g of tungsten, while those on 5 and 10% consumed

54.5 and 104 g, respectively. Female rats, in the same period, consumed an average of 14.8, 41.0, and 75.0 g of tungsten when fed the diets containing 2, 5, and 10% tungsten metal powder, respectively. The authors attributed the different weight gains by male and female rats fed diets containing 10% tungsten to the reduced food consumption of the female rats. They did not find any exudation of blood into the mucous membranes of the small or large intestines in rats fed tungsten for 70 days. They concluded that tungsten metal powder did not show marked toxic action at the levels used in their experiment.

In 1924, Karantassis [45] reported the toxic effects of sodium tungstate ( $\text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O}$ ) on guinea pigs. In one study, three guinea pigs with an average body weight of 616 g were each given a single dose of either 0.50 or 0.75 g of sodium tungstate by gastric intubation. In another study, five guinea pigs, weighing an average of 635 g, were given subcutaneous injections of sodium tungstate. Three guinea pigs received single doses of 0.50 g each, and the remaining two received daily doses of 0.10 g until their deaths at 16 and 17 days. The age, sex, and strain of the guinea pigs used were not reported. No control group was mentioned. In both studies, the author monitored the general visible signs before death, the time at which death occurred, the results of gross examination at autopsy, and the presence of tungsten in the gastrointestinal tract, lungs, liver, kidneys, bones, blood, and urine.

Guinea pigs from both experiments had anorexia, colic, uncoordinated movements, sudden jumps, trembling, and breathlessness [45]. Although the signs were similar in both groups, they were more pronounced and prolonged in the guinea pigs given sodium tungstate subcutaneously. Dose-related

differences were not reported.

In both studies, guinea pigs given 0.50 g of sodium tungstate died 16-23 hours later [45]. In the guinea pigs given sodium tungstate orally, autopsy revealed that the stomach contained a bloody, greenish substance, and the large intestine contained bloody, diarrheic fecal matter. The liver showed small, discolored lesions and the lungs contained small, hemorrhagic spots. The peritoneum and all other organs, including the small intestine, spleen, testes, brain, kidneys, and suprarenal capsules, appeared normal. In subcutaneously dosed animals, post mortem examination showed an intense congestion of the liver, large infarcts in both lungs, dark blood in the heart, bloody diarrhea, and an appearance of asphyxiation. The condition of the brain, testes, peritoneum, gastrointestinal tract, and suprarenal capsules was not reported. No distinction was made between the effects of 0.75- and 0.50-g doses in the orally dosed group. Subcutaneous injections of 0.10 g of sodium tungstate/day for 16-17 days caused necrotic and indurated patches in unspecified tissues and a 23% loss in body weight; detachment of a small portion of abdominal skin and yellow patches of degeneration in the liver and kidneys were also noted.

Analysis of the tissues of animals from both experiments showed that tungsten was present in the stomach, intestines, liver, kidneys, lungs, blood, and urine [45]. In the orally dosed group, tungsten was also present in the walls and in the contents of the gastrointestinal tract. In the subcutaneously injected group, tungsten was present in bones and in necrotic and indurated patches in unspecified tissues.

At the lower subcutaneous dose-level (0.10 g/day), the total lethal dose of sodium tungstate for each guinea pig was 1.65 g, while the lethal dose for a single administration was about 0.50 g [45]. Expressed as elemental tungsten, the single lethal doses for intragastric and subcutaneous administrations were estimated to be 0.55 and 0.45 g/kg, respectively. Because of the small sample size and lack of statistical analyses, the significance of these values is difficult to assess. However, this is the first published study attempting to distinguish between the oral and subcutaneous toxicities of sodium tungstate.

In a 1942 abstract, Selle [46] presented the results of a study of the effects of sodium tungstate on rats. Male and female rats were given 5 ml/kg daily of a 0.1 M aqueous solution of sodium tungstate (0.164 g/kg body weight) either subcutaneously or orally. The age, weight, and strain of the rats were not reported. Although controls were indicated, the treatment of the controls and their number were not described. The number of doses and the duration of sodium tungstate administration were not given. At an unspecified time after the administration of sodium tungstate, body weights were recorded, the rats were killed, and the weights of the kidneys and adrenal glands were determined. At an unspecified time, tungsten excretion in feces and urine was measured, and rectal temperature was monitored.

The subcutaneous injection of sodium tungstate resulted in body weights of male and female rats that were 26 and 11%, respectively, below those of controls [46]. The kidneys of these animals were 45 and 42% heavier in male and female rats, respectively, than in the controls, and the adrenal glands of the males were 43% heavier than those of controls.

The subcutaneous injection of sodium tungstate produced a severe drop in rectal temperature, about 8 F in 2 hours, with a return to normal in 8 hours. Most of the subcutaneously administered tungsten was eliminated in the urine within 12 hours, while that administered orally was excreted in urine and feces within 12-24 hours. When sodium tungstate was administered orally, no changes in kidney, adrenal, or body weights resulted; this may be a significant finding, since sodium tungstate administered subcutaneously was slightly more toxic than that given orally.

In 1940, Kinard and Van de Erve [47] compared the influence of age, sex, and postprandial conditions on the effects of subcutaneously injected sodium tungstate in rats. Rats, in equal numbers of each sex, were fed dog chow during the experiment. In the first experiment, aimed at determining the influence of postprandial conditions on the toxicity of sodium tungstate, 2 groups each containing 27 rats were fasted for 24 hours. One group was weighed after food had been withheld for a day, injected with a calculated dose of sodium tungstate, and then fed. A second group was weighed after fasting, fed, and then injected 1-3 hours later with sodium tungstate at a dose based on body weight before feeding. The age and weight of the rats and the amount of sodium tungstate administered were not reported. Mortality was recorded in both groups for an unspecified period.

Mortality was 40.7% in the first group and 14.8% in the second [47]. The authors concluded that rats were less susceptible to sodium tungstate administered during the periods of active absorption and metabolism that follow a meal than to administration following fasting. They conceded, however, that the data presented did not reveal whether the observed effect was caused by impairment in the direct absorption and utilization of

nutrients or by changes in the absorption of tungsten.

The second part of the study [47] was designed to evaluate the effects of age on the toxicity of subcutaneously injected sodium tungstate. Five groups of rats, ranging in age from 30 to 365 days, with an average of 23 rats per group, were fasted for 24 hours and weighed individually. Sodium tungstate was injected subcutaneously at a dose of 150 mg of tungsten/kg body weight. Mortality was recorded for an unspecified period. For rats 30, 44, 66, 170, 195, and 365 days of age, mortalities were 0, 30, 59, 100, 89.5, and 100%, respectively, ie, there was an increase in mortality with increased age. Analysis of deaths in the groups with 10-80% mortality revealed a 15:13 ratio of males to females, indicating that the male rats are slightly more susceptible to injected sodium tungstate than females.

In the third experiment, the dose-response relationship of sodium tungstate in 66-day-old rats was studied [47]. The sex and weight of the rats were not given. Rats were fasted for 24 hours, weighed, injected with sodium tungstate, and then fed. Nine groups of rats, with an average of 25 in a group, were given subcutaneous injections of sodium tungstate in doses equivalent to 100-250 mg of tungsten/kg of body weight. Mortality data were obtained during the 5 days after injection. The authors reported that the LD50 of subcutaneously injected sodium tungstate for 66-day-old rats was 223-255 mg/kg (140-160 mg/kg of tungsten). Their data did not indicate the times after the injection when the first and the most deaths occurred.

Kinard and Van de Erve [48] evaluated the comparative toxicities of tungstic oxide, sodium tungstate, and ammonium-p-tungstate. They used equal numbers of 37-day-old male and female rats, caged separately in



groups of five or six animals. Diets for experimental animals were prepared by incorporating 0.1, 0.5, or 2.0% tungsten equivalents of sodium tungstate, 0.1, 0.5, or 3.96% tungsten equivalents of tungsten trioxide, and 0.5, 2.0, or 5.0% tungsten equivalents of ammonium-p-tungstate into ground dog chow. Control animals were fed the dog chow only. The experiment continued for 70 days.

Rats had 100% mortality when fed diets containing ammonium-p-tungstate equivalent to 5.0% tungsten, tungstic oxide equivalent to 3.96% tungsten, or sodium tungstate equivalent to 2.0% tungsten [48]. However, ammonium-p-tungstate caused 80% mortality at a level equivalent to 2% tungsten. Tungstic oxide given at a level equivalent to 0.5% tungsten caused 80 and 66% mortalities in male and female rats, respectively, while sodium tungstate at the same level caused 50 and 66% mortalities. In comparison, 0.5% tungsten in the diet as ammonium-p-tungstate caused no deaths. Diets containing either sodium tungstate or tungstic oxide in a concentration equivalent to 0.1% tungsten caused no fatalities.

After 70 days, the male and female rats fed ammonium-p-tungstate equivalent to 0.5% tungsten weighed 3.9 and 5.3% less, respectively, than the controls [48]. Male and female rats receiving tungstic oxide at a tungsten equivalent of 0.1% weighed, respectively, 6.3 and 7.4% less than controls; for male and female rats given the same concentration of sodium tungstate, the weight decreases were 8.8 and 10.6%. Corresponding to the decreased weight gains in various groups, there were moderate-to-sharp declines in food intake which appeared to be dose-related. Thus, in male rats fed sodium tungstate at levels of 0.1, 0.5, and 2.0% of tungsten equivalents, the food intakes were 83, 47, and 20% of that of controls,

respectively, while in females they were 96, 72, and 31%. Similarly, the food intakes of tungstic oxide groups at levels of tungsten equivalent to 0.1, 0.5, and 3.96% were 91, 33, and 20% of control values for males and 100, 72, and 51% for females. With diets containing 0.5, 2.0, and 5.0% tungsten as ammonium-p-tungstate, the food intakes of male rats were 102, 27, and 46% of control values. Females fed ammonium-p-tungstate at levels of tungsten equivalent to 0.5 and 2.0% had food intakes 96 and 82% of that of the controls.

It is noteworthy that the proportional decreases in body weight in female rats were greater than those of males, although the tungsten compounds had a smaller effect on the intake of food by the females than on that by the males. This suggests that tungsten exerted some effect that was specific, or at least relatively specific, for females on either digestion and absorption of food stuffs or metabolic utilization of foodstuffs. Balance studies, especially of nitrogen, might be useful in deciding between these two possibilities. Johnson et al [49] found that tungsten could be incorporated into such enzymes as xanthine oxidase and sulfite oxidase in place of molybdeum to yield inactive proteins. This suggests that the second of the two general possibilities mentioned above may be the correct one. Johnson et al used only male rats and fairly high doses of tungsten (25 ppm in the drinking water) to obtain their results. If females were more sensitive to tungsten in this regard than were male rats, the effect on their metabolic activities catalyzed by these important enzymes would be much greater than those of males. Knowledge of the role of sex in this regard seems to be of some importance.

From the mortality and body weight data, the authors [48] concluded that ammonium-p-tungstate was the least toxic of the three compounds. Although the data were not analyzed statistically, this is the first report which reveals that tungstic oxide and ammonium-p-tungstate are less toxic than the soluble sodium tungstate.

Nadeenko [50] compared the acute toxicities of sodium phosphotungstate, sodium tungstate, and tungstic oxide by determining their oral lethal doses in 300 mice and 40 albino rats. The author did not present the experimental details. After brief excitation, all mice and rats given the three tungstate compounds sat with backs arched; their muscle tone was decreased; and the hind legs of some of the mice became slightly paralyzed. From these observations, Nadeenko concluded that the animals exhibited inhibited motor functions. The durations and doses at which these symptoms occurred were not reported. These experiments were evaluated statistically by probit analysis, with the results expressed as elemental tungsten.

The oral LD50 of sodium phosphotungstate was  $700 \pm 79$  mg/kg for mice and  $1,600 \pm 201$  mg/kg for rats [50]. The oral LD50 of sodium tungstate was  $240 \pm 13.5$  mg/kg for mice and  $1,190 \pm 129.5$  mg/kg for rats. Administration of tungstic oxide at 840 mg/kg killed half of the animals (species not stated); however, there was no further increase in the percentage of deaths with doses up to 2,500 mg/kg body. Nadeenko concluded that this compound was less toxic than either sodium tungstate or sodium phosphotungstate. He suggested that the lower toxicity of tungstic oxide was a result of its lower solubility.

Nadeenko [50] also studied the toxic effects of sodium tungstate on rabbits, guinea pigs, and rats. As in the above study, the experimental design was not presented. The oral LD0, LD50, and LD100 were reported as 500, 875, and 1,500 mg/kg respectively, for rabbits, 500, 1,152, and 2,000 mg/kg for guinea pigs, and 700, 1,190, and 2,000 mg/kg for rats. The author concluded that rabbits were more susceptible to the toxic action of sodium tungstate than were either rats or guinea pigs.

To study the selective effect of tungsten on individual physiologic functions and systems of animals, Nadeenko [50] conducted a set of subacute experiments for an unspecified period of time on albino rats and rabbits. The animals were given sodium tungstate orally at presumably daily doses of 100, 50, 25, or 10 mg/kg. The number, age, sex, weight, and strain of the animals were not reported, and no control group was described.

Nadeenko [50] reported that, at all doses, the growth of the rats was retarded and their blood cholinesterase activities were lowered; in rabbits, the sulfhydryl (SH) concentrations of whole blood and serum were decreased and synthesis of glycogen in the liver was disturbed. Stained sections of the gastrointestinal tract and kidneys showed signs of increased vascular permeability, hemorrhages, degenerative dystrophic changes, and moderate proliferative cellular reactions.

Nadeenko [50] also attempted to determine the noneffective and threshold chronic oral doses of tungsten in rats and rabbits. Sodium tungstate was administered to rabbits in doses of 5, 0.5, 0.05, or 0.005 mg/kg daily for 8 months and to rats in doses of 0.5, 0.05, or 0.005 mg/kg daily for 7 months. There were seven animals in each dosage group. Their sex, age, weight, and strain were not presented. Control groups of the

same size were used, but it was not clear how they were treated. Throughout the exposures, the general behavior and body weight of the animals were monitored. The blood SH content and cholinesterase and alkaline phosphatase activities were measured in the rabbits. Blood cholinesterase and alkaline phosphatase activities were determined at monthly intervals. The glycogen-forming function of the liver was measured in rabbits after loading them with galactose. In rats, the conditioned reflexes were monitored on animals trained to respond to the sound of a bell and to a light, and this test was used as a measure of the functional state of the CNS. The intervals at which such measurements were made were not given. At the end of the experimental period, the SH contents of brain and liver tissues of rats were determined. The author reported, without identifying the species, that, after the termination of chronic poisoning, he determined the tungsten concentrations in blood, liver, femur, intestines, and kidneys; he also conducted macroscopic and microscopic examinations of the gastrointestinal tract, lungs, liver, spleen, and brain of both species.

In rabbits, sodium tungstate at doses of 5 and 0.5 mg/kg of body weight decreased the availability of SH groups in serum during months 5-8 of the experiment and produced decreases of about 23 and 16%, respectively, in blood cholinesterase activity at the end of 8 months [50]. Sodium tungstate at doses of 0.05 and 0.005 mg/kg caused no changes in either the SH content or the blood cholinesterase activity of rabbits. Blood alkaline phosphatase activity was inhibited by as much as 18% ( $P < 0.01$ ) by sodium tungstate at a dose of 5.0 mg/kg during months 4-8 of the experiment. However, in the 0.5-mg/kg and 0.05-mg/kg groups, changes were sporadic and

inconsistent and, in the 0.005-mg/kg group, the blood alkaline phosphatase activity was not inhibited. Rabbits receiving sodium tungstate doses of 5.0 and 0.5 mg/kg of body weight had concentrations of glucose in their blood 20-25% higher than control levels 1 hour after iv loading with galactose. Nadeenko noted this change at months 6 and 7 of the experiment and interpreted it as an indication that the glycogen-forming function of the liver had decreased. No changes in the glycogen-forming function of the liver were observed in the 0.05 and 0.005 mg/kg groups. None of the rabbits showed pathologic changes in the esophagus, large intestines, lungs, liver, or spleen. In rabbits given tungsten at 5 mg/kg, some areas of the intestinal mucosae showed an increase in lymphoid infiltration of the villi and necrosis of their terminal portions.

In rats, sodium tungstate at doses of 0.5 and 0.05 mg/kg caused pronounced disturbances in conditioned reflexes [50]. The latent periods of sodium tungstate-treated animals were 1.6-1.7 seconds for the bell and 2.4-2.7 seconds for the light, compared to 0.9 and 2.0 seconds, respectively, for controls. Animals given the maximum doses of sodium tungstate exhibited a larger number of extinctions of the conditioned reflexes. Disturbances of conditioned reflexes were indicated by a statistically significant increase in the number of equalizing and paradoxical phase states (For explanation of terminology, see reference [51]). No data were presented on the statistical analyses. Nadeenko noted that study of extinction and recovery of the conditioned response to a bell revealed a pronounced decrease in the lability of nervous processes in the cerebral cortices of the 0.5 and 0.05 mg/kg dose-groups. No changes were noted in the conditioned reflex with a dose of 0.005 mg/kg. Necrotic

lesions and destruction of the apical portions of the intestinal villi were also evident in rats given sodium tungstate at 0.5 mg/kg. No animal had pathologic changes in the esophagus, large intestine, lungs, liver, or spleen.

Although he gave no values, Nadeenko [50] reported that analyses of the concentrations of tungsten in various tissues of experimental animals (species unspecified) revealed that the highest concentrations existed in groups receiving 5 and 0.5 mg/kg of sodium tungstate. A less pronounced but significant accumulation of tungsten was found in tissues of animals given sodium tungstate at 0.05 mg/kg, while a dose of 0.005 mg/kg produced increases only in the concentration of tungsten in the blood and intestines. From these findings, the investigator concluded that tungsten has cumulative toxicity. Nadeenko believed that the daily dose of 0.05 mg/kg was below the threshold level, since it did not cause appreciable biochemical changes in the animals, although it did affect the conditioned reflexes of rats.

In 1945, Kinard and Aull [52] described the distribution of tungsten in rat tissues after dietary feeding of tungsten or its compounds. Rats of an unspecified strain, 37 days old, were caged in groups of two males and two females. During the 100-day experimental period, the control group received ground dog chow, while the experimental groups were fed this basal diet with the incorporation of tungsten or tungsten compounds at one of the following levels: tungstic oxide and sodium tungstate at levels equivalent to 0.1% tungsten; ammonium-p-tungstate at 0.5% tungsten; tungsten metal at 2 and 10% tungsten; and purified tungsten metal (purified to remove any trace of oxide from the metal) at 10% tungsten. Diet and water were given

ad libitum to each group of rats.

Analysis of the tissues removed at the end of the 100-day period revealed that bone and spleen were the major sites of tungsten deposition [52]. The concentrations of tungsten ranged from 8 to 18 mg% in bone and from 2 to 14 mg% in the spleen, with averages of 11.5 and 7.5 mg%, respectively. Only traces of tungsten (less than 1 mg%) were present in skin, kidneys, and liver. The blood, lungs, testes, and muscles showed traces of tungsten only in some cases. Except for a single instance for each organ, the brain, heart, and uterus were free of tungsten. The investigators concluded that there were no marked differences among the distribution patterns of the various tungsten compounds tested. Since the doses of tungsten administered as various tungsten compounds were not comparable and since quantitative results were not presented for all the tissues that were analyzed, this conclusion may not be entirely valid.

Aamodt [53] measured the metabolism of inhaled tungstic oxide in dogs. Six purebred beagles, of unspecified sex and age, were anesthetized with pentobarbital at 27 mg/kg. They then inhaled a mist of radiolabeled  $^{181}\text{W}$ -tungstic oxide of 98 microcuries/ml specific activity through a face-mask for 6 hours. The dogs were killed 165 days after exposure, and tissue samples were collected from all dogs.

Measurements of the radioactivity in inhaled and expired air showed that 1.9-8.0 microcuries of tungstic oxide were deposited in the respiratory tract [53]. Sixty percent of the inhaled activity was deposited in the lower part of the respiratory tract. In the partial body measurements made over the lung area, about 69% of the activity was lost with a biologic half life ( $t_{1/2}$ ) of 4 hours, the next 23% with a  $t_{1/2}$  of 20



hours, 4.6% more with a  $t_{1/2}$  of 6.3 days, and 3% with a  $t_{1/2}$  of 100 days. In contrast, measurements taken for the lower half of the body showed 94% with a  $t_{1/2}$  of 9 hours, whereas 4.1% had a  $t_{1/2}$  of 6.3 days. The remaining 1.6% of the radioactivity was removed with a  $t_{1/2}$  of 139 days. Without giving any actual experimental values, Aamodt indicated that the activity was lost rapidly from the blood, although there were some variations in the measured activity which, he explained, were caused by biologic variation in the clearance patterns in individual dogs. Of the organs tested, the lungs and kidneys were found to retain maximum radioactivity, 47.7 millionths and 41.3 millionths of the inhaled activity/g of tissue, respectively. Other tissues contained only about 10% as much activity as did the lungs and kidneys. In terms of total burden of radioactivity, most of the activity was found in the skeleton (37%), lungs (31%), kidneys (15%), liver (9.7%), and skeletal muscle (5.7%).

The reported effects of insoluble tungsten or cemented tungsten carbide administered intratracheally or by inhalation were chiefly respiratory in nature. No studies are available of the effects of soluble tungsten compounds given by similar routes of exposure. Moreover, the oral administration studies did not clearly distinguish the principal organs affected by soluble tungsten. Few reports are available on the dermal effects of tungsten compounds or cemented tungsten carbide in experimental animals.

#### Correlation of Exposure and Effect

Effects of both short-term and long-term occupational exposures to tungsten and its compounds have been identified among employees in the

cemented tungsten carbide industry (Table III-1). The only work areas in this industry that permit specific evaluation of the effects of tungsten and its compounds are those processing stages that precede the incorporation of other toxic metals into the final products. Only two human studies meeting this criterion were obtainable [27,28]. These studies showed that the effects of inhaled tungsten and tungsten compounds are exerted chiefly on the respiratory system. Radiologic signs of pulmonary fibrosis were reported by Mezentseva [28] and by Kaplun and Mezentseva [27] in 9-11% of the hard-metal workers who were exposed to dusts of tungsten and its compounds.

In both short- and long-term animal experiments, the major effects of inhalational or intratracheal exposure to tungsten and its compounds were similarly limited to the respiratory system, while the effects of ingestion were not so clearly apparent in any organs (Table III-2). As in the reports of the human studies, no dermatologic effects were described in these animal reports. Mezentseva [28] reported that lungs of rats exposed by inhalation to tungsten carbide at 600 mg/cu m, 1 hour/day, for 5 months showed proliferative reactions of the lymphoid histiocytic elements and uniform thickening of the alveolar walls followed by mild fibrosis. Mezentseva [28] also stated that rats given single intratracheal doses of 50 mg of either metallic tungsten, tungsten carbide, or tungsten trioxide showed no severe pulmonary changes upon microscopic examination.

Dusts of metallic tungsten or tungsten carbide, given intratracheally to guinea pigs by Delahant [35] as a total dose of 150 mg in three equal weekly doses, did not irritate the lung tissue. Similarly, 1 ml of a 10% suspension of tungsten was given intratracheally to rats by Miller et al

[16], who found that the only changes in the animals' lungs, such as mobilization of septal cells, engulfment of pigment, and accumulation of particles in the air sacs, lymphoid tissue, and alveolar walls, were those typically produced by an inert dust.

However, Schepers [34] found that the intratracheal injection of 3 weekly doses of 50 mg of a 94:6 mixture of tungsten carbide and carbon caused acute hyperemia and bronchial inflammation in guinea pigs. Minor residual changes, such as the development of subpleural fibrocellular granulomata, were also noted in their lungs. Brakhnova and Samsonov [40] reported that inhalational and intratracheal exposure of rats to tungsten silicide for 1-6 months caused hyperplasia of the lymph nodes, sporadic thickening of the alveolar walls, and increased collagen in the lungs. These results suggest that tungsten and some of its compounds, such as those most frequently encountered in the cemented tungsten carbide industry, have distinct toxicities.

While opportunities for occupational exposures to soluble tungsten compounds are limited, a number of animal studies are available delineating their toxicities. In 1924, Karantassis [45] administered single intragastric and subcutaneous doses of sodium tungstate to guinea pigs and observed anorexia, colic, incoordination of movement, trembling, dyspnea, and loss of weight prior to death. Rats injected subcutaneously with sodium tungstate also had congested livers and large infarcts in both lungs. Smaller subcutaneous doses of sodium tungstate also produced degenerative patches in liver and kidneys. Selle [46] also noticed that rats given subcutaneous doses of sodium tungstate had increased kidney weights.

Two studies attempted to differentiate between the toxicities of the soluble and the insoluble tungsten compounds. Kinard and Van de Erve [48] fed young male and female rats diets containing 0.1-5% tungsten equivalents of tungstic oxide, sodium tungstate, and ammonium-p-tungstate. At these levels, 100% mortality was caused by a 2% tungsten equivalent of sodium tungstate, by a 3.96% tungsten equivalent of tungstic oxide, and by a 5% tungsten equivalent of ammonium-p-tungstate. Tungsten equivalents of 0.5% in the diet caused no deaths in the ammonium-p-tungstate group; tungstic oxide, at the same concentration of the metal caused 88 and 66% deaths in males and females, respectively, and sodium tungstate caused 50 and 60% deaths. Sodium tungstate was concluded to be the most toxic of the three compounds.

Nadeenko [50] compared the oral toxicities of tungstic oxide, sodium tungstate, and sodium phosphotungstate in rats and mice. After brief periods of excitability, all mice and rats given the three tungsten compounds sat with backs arched; their muscle tone was decreased, and the hind legs of some mice became slightly paralyzed. In mice, the oral LD50 of tungstic oxide was 840 mg/kg, while those for sodium phosphotungstate and sodium tungstate were 700 and 240 mg/kg, respectively. Nadeenko concluded that tungstic oxide was the least toxic of the three and suggested that its lower solubility, compared with those of the other two compounds, was the cause. Thus, soluble tungsten compounds were considerably more acutely toxic in experimental animals than the insoluble compounds.

Most reports of occupational exposure to tungsten and its compounds, with the exception of the two studies already described, deal with the

effects of mixed dusts containing cobalt [27,28]. The effects of such mixed dusts were chiefly respiratory in nature, although some dermal effects were evident. The pulmonary involvement reported in a number of these studies was characterized by exertional dyspnea, coughing, and weight loss [15,17-19,25]. These clinical signs sometimes progressed to extrinsic asthma [23], diffuse interstitial pneumonitis [18], or fibrosis [17,20,22]. The type of pneumoconiosis seen in the cemented tungsten carbide industry is referred to as "hard-metal disease." While the total dust levels and cobalt concentrations were reported in most studies, tungsten concentrations were documented in only a few cases. Most dust particles generated in various operations in which tungsten is processed and used are less than 5  $\mu\text{m}$  in diameter and hence are in the respirable size range [17,25,28,42,54].

Some authors described the pulmonary responses of cemented tungsten carbide workers as hypersensitivity [17,20]. This response was so described because of the reversibility of some clinical symptoms, the occasional radiologic improvement on withdrawal from exposure, and the recurrence of symptoms on reexposure. Bruckner [23] diagnosed extrinsic asthma in a cemented tungsten carbide worker and attributed it to a hypersensitivity mechanism. This worker experienced asthmatic symptoms 1-3 minutes after beginning work, even though he wore a respirator designed to remove particles of 0.6  $\mu\text{m}$  diameter or larger.

Two studies [14,24] described the dermatologic effects of occupational exposures to unspecified levels of dusts in cemented tungsten carbide industries. Schwartz et al [14] stated that 20 workers employed 1 month or more in this industry developed erythematous, papular dermatitis,

mainly on the sides of the neck, the eyelids, and the forearms. While the abrasiveness of the dust reportedly contributed to the sensitization process, cobalt sensitization was concluded to be the cause of the dermatitis. Skog [24] reported skin effects including contact eczema, pruritus, folliculitis, and neurodermatitis, in 34 (9.4%) of the 361 workers in the cemented tungsten carbide industry. Cobalt sensitization was detected by patch tests in 3 of the 14 workers with contact eczema, found mainly on the eyelids and between the fingers. This author [24] concluded that the primary irritant effect of the combined metal dusts produced most of the contact eczema.

Although these studies are well documented in terms of the observed effects, it is difficult to distinguish the effects of tungsten and its compounds from those produced by cobalt and perhaps other metals and compounds. However, most of the authors attributed the effects of these mixed exposures primarily to the presence of cobalt.

The effects of exposures of experimental animals to tungsten-cobalt mixtures on the respiratory system are well documented, but dermatologic effects were not described in laboratory animals. In a collaborative experiment with Delahant [35], Schepers [37] noted that guinea pigs, exposed by inhalation to a 3:1 mixture of tungsten carbide and cobalt for 20 days at 8,800-10,000 particles/cu cm and then at 2,800 particles/cu cm for 15 days developed acute inflammation of the respiratory tract, followed by focal pneumonitis and residual bronchial epithelial hyperplasia and metaplasia. He emphasized that the unusual epithelial reaction was the characteristic feature of exposure to a mixture of tungsten carbide and cobalt. Delahant [35] noted that five animals died during the 20-day

exposure and that an additional six died during the following 15-day exposure. Delahant [35] and Schepers [37] also examined the responses of guinea pigs to intratracheal administration of 3 weekly 50-mg doses of a 91:9 mixture of tungsten carbide and cobalt. They reported pneumonitis and mild cellular and fibrotic reactions around the dust deposits in the lungs of these guinea pigs. Delahant [35] and Schepers [37] concluded that the intense irritant property of cobalt was dominant when cobalt was combined with tungsten carbide. Kaplun and Mezentseva [38] injected rats intratracheally with the following dust mixtures: (1) 15% cobalt and 85% tungsten, (2) 8% cobalt and 92% tungsten, or (3) 8% cobalt, 14% titanium, and 78% tungsten. The rats that received 25 mg of dust had 100, 40, and 60% mortalities in groups 1, 2, and 3, respectively, within 5-7 days. At the 10 mg-dose level, 5 of the 13 rats in group 1 died within 2-3 days, but none of the rats in groups 2 and 3 died.

The absolute lethal dose for the dust mixture containing 15% cobalt was 15 mg (2.25 mg cobalt)/rat, while that for the other two mixtures was 50 mg (4 mg cobalt) [38]. Comparing these values with the absolute lethal dose of metallic cobalt alone (10 mg), the authors suggested that the toxicity of cobalt was enhanced in the presence of tungsten because the latter increased the solubility of the former. However, as the absolute lethal doses of the three dust mixtures were 50-400% greater than that of metallic cobalt, the results do not necessarily support the hypothesis of enhanced toxicity of cobalt; cobalt and tungsten may, however, have synergic actions that are additive to some degree.

## Carcinogenicity, Mutagenicity, Teratogenicity, and Effects on Reproduction

In 1961, Bech et al [25] reported a case of cancer in a 63-year-old man who had been exposed to hard-metal dusts containing tungsten for 17 years and who had previously worked as a core maker in various iron foundries for 32 years. Ten years after beginning employment in the hard-metal industry, he developed a persistent dry cough, dyspnea, and pain and tightness in the chest. Radiologic chest examinations revealed hilar shadows, linear markings, and micro-nodular opacities. Four years later, there were signs of progressive deterioration with increased shadows above the right portion of the diaphragm. The subject died 3 years later with an anaplastic adenocarcinoma of the right lower lobe of the bronchus. The hilar and paraaortic glands were also invaded by the tumor, and a neoplastic invasion of the right renal capsule was noted at autopsy. Since the worker had been exposed to a number of industrial dusts of unknown composition and amounts, the tumor cannot be attributed specifically to exposure to tungsten.

Collet and coworkers [26], in 1963, described a case of pulmonary fibroadenomatosis in a 57-year-old worker employed for 14 years in the manufacture of hard-metal tools. During this period, he was known to have been exposed to dusts of tungsten carbide, metallic cobalt, tantalum, titanium, and cobalt oxalate, and to trichloroethylene vapor. After he had worked in this environment for 8 years, radiologic examination of his chest revealed reticulation at the bases and in the left central portion of the lungs. After 2 more years, fever and breathing difficulties were reported; a year later, exertional dyspnea had become more severe. During the next three years, clinical observations and pulmonary function tests indicated



that his condition had deteriorated further. At the end of this period, he died of respiratory failure and cardiovascular collapse. A biopsy of lung tissue performed 7 months before his death led to the diagnosis of pulmonary fibroadenomatosis; spectrographic analysis of the tissue taken for biopsy demonstrated what were described as large amounts of tungsten, nickel, and titanium in his lungs, although he had no known occupational exposure to nickel. In this case, as in the case reported by Bech et al [25], the worker had been exposed to a mixture of metal dusts and to the vapor of trichloroethylene at unknown concentrations [26], The precise role of tungsten in the development of the fibroadenoma cannot therefore be determined.

The aforementioned reports indicate that tungsten and its compounds are neither confirmed nor suspected as carcinogens, mutagens, or teratogens.

TABLE III-1

EFFECTS OF OCCUPATIONAL EXPOSURE  
TO TUNGSTEN-CONTAINING SUBSTANCES

| Composition of Substances  | Exposure Concentration and Duration                             | Number of Workers | Effects   | Reference |
|--|---|-------------------|---|-----------|
| Tungsten carbide   | 8.6-106.6 mg/cu m   | 36                | Diffuse pulmonary fibrosis in 4   | 27        |
| "  | 8.3-83 mg/cu m<br>7-10 yr                                       | 54                | Diffuse pulmonary fibrosis in 5   | 28        |
| Cemented tungsten carbide<br>90% tungsten,<br>6% cobalt,<br>4% titanium, silica,<br>aluminum, mag-<br>nesium, iron, etc                          | 195-1,230 particles/<br>ml                                      | 255               | Hard-metal disease in 1; in 12 given pulmonary function tests, reduced ventilatory capacity and rise in airway resistance in 2, rise in respiratory airway resistance in 2, wheezing in 4; slight change in chest X-rays of several                                       | 25        |
| Cemented tungsten carbide<br>70-90% tungsten carbide,<br>8-78% titanium carbide,<br>5-25% cobalt   | 13-100 mg/cu m  | 193               | Coughing in 47%, dyspnea in 35%, disturbance of pulmonary ventilation in 21.5% of 116 examined by spirometry; reticulation in chest X-rays in 16% of 93 workers   | 31        |
| Cemented tungsten carbide<br>0.27-1.75 mg/cu m of cobalt   | 3-186 mg/cu m   | 247               | Damage to upper respiratory tract in 117; chronic bronchitis in 35; incipient pulmonary fibrosis in 33  | 27        |
| Cemented tungsten carbide<br>2.4-4.1% cobalt   | 2.1-3.5 mg/cu m<br>6 yr   | 1,802             | Inflammation of conjunctivae, upper respiratory tract, and mucous membranes; chest X-ray abnormalities in 36; cobalt sensitivity  | 15        |
| Cemented tungsten carbide<br>0.6-3.2 mg/cu m of cobalt   | 0.75-6.1 mg/cu m<br>up to 3 yr                                  | 178               | Dyspnea, coughing, impaired sense of smell in 88; some impairment of liver function   | 32        |
| Cemented tungsten carbide<br>0.04-0.93 mg/cu m of cobalt<br>0.28 mg/cu m mean  | 0.2-12.8 mg/cu m<br>as tungsten;<br>5.1 mg/cu m mean<br>1-30 yr | 22                | Reduced FVC and elevated FEV <sub>1</sub> /FVC ratio; exertional dyspnea in 3; productive cough in 8  | 29        |
| Cemented tungsten carbide<br>80-90% tungsten carbide,<br>8-18% titanium carbide,<br>5-25% cobalt   | -   | 375               | Allergic asthma and exertional dyspnea in 1, reversed on removal from work environment; coughing; dyspnea, restrictive ventilatory defect, and micronodular or linear opacities on chest X-rays in 12, with death of 8 from bronchopneumonia or cardiorespiratory failure | 19        |
| Cemented tungsten carbide  | 2.3-62.3 mg/cu m<br>up to 17 yr                                 | 29                | Dry cough, exertional dyspnea in 9; allergic asthma in 3; pulmonary fibrosis in 1   | 17        |
| Cemented tungsten carbide<br>pure metals, car-<br>bides, and oxides<br>of tungsten, ti-<br>tanium, tantalum,<br>and niobium, and<br>cobalt metal | -   | 100               | Irritation of upper respiratory tract in 15, diminishing on removal and recurring on reexposure; exertional dyspnea (not reversible), rapid weight loss in 5  | 20        |
| Cemented tungsten carbide  | -   | 5                 | Episodic wheezing and coughing, relieved by removal from work environment and recurring upon return; no chest X-ray abnormalities   | 18        |

TABLE III-1 (CONTINUED)

EFFECTS OF OCCUPATIONAL EXPOSURE  
TO TUNGSTEN-CONTAINING SUBSTANCES

| Composition of Substances  | Exposure Concentration and Duration | Number of Workers | Effects   | Reference |
|--|-------------------------------------|-------------------|---|-----------|
| Cemented tungsten carbide<br>75% tungsten carbide,<br>3-25% cobalt, small amounts of titanium carbide, chromium carbide, and nickel            | -<br>12-28 yr                       | 12                | Cough, exertional dyspnea, progressive interstitial fibrosis; cor pulmonale leading to cardio-respiratory arrest in 8   | 18        |
| Cemented tungsten carbide<br>67.8%-76.1% tungsten,<br>7.6-21.2% cobalt,<br>0-1.7% titanium,<br>0.3-2.3% iron,<br>7.0%-16% volatiles (paraffin) | 277-4,064 particles/<br>cu m        | 208               | Asthmatic symptoms, bronchitis, emphysema, pulmonary fibrosis   | 33        |
| Cemented tungsten carbide<br>tungsten, cobalt, titanium, tantalum, niobium, or their oxides and carbides                                       | -<br>-                              | 1                 | Coughing, expectoration, exertional dyspnea, diffuse bilateral clouding, nonresonant wet rales; restrictive ventilatory impairment; improved on removal from work environment   | 21        |
| Cemented tungsten carbide<br>tungsten, cobalt, or tantalum   | -<br>1 yr                           | 1                 | Exertional dyspnea, dry irritated cough, fever, cyanosis, rales, restrictive ventilatory, impairment of lung function; small lungs with striated or honeycomb pattern; no improvement on removal from work environment      | 21        |
| Cemented tungsten carbide<br>tungsten carbide, cobalt, sometimes titanium and tantalum carbide   | -<br>7 yr                           | 1                 | Diffuse bilateral densities from chest X-rays; reduced vital capacity; lung biopsy showed multifocal pulmonary scarring with patchy, interstitial fibrosis  | 30<br>29  |
| High speed steel containing cobalt   |                                     |                   |   |           |
| Cemented tungsten carbide<br>tungsten, tantalum, and titanium carbides, cobalt   | -<br>1 mon or more                  | 20<br>of<br>1,200 | Erythematous, papular eruptions on neck, eyelids, forearms, backs of hands and ankles; patch tests on 6 showed sensitivity to cobalt powder   | 14        |
| Cemented tungsten carbide<br>0-95% tungsten carbide,<br>0-40% titanium carbide,<br>0-20% tantalum-niobium carbide,<br>5-25% cobalt             | -<br>-                              | 34<br>of<br>361   | Contact eczema in 16; pruritus without skin lesions in 8; folliculitis in 6; neurodermatitis in 4; patch testing in 14 who had contact eczema revealed that 3 reacted to cobalt chloride and 2 to hard-metal powder as well | 24        |
| Cemented tungsten carbide<br>tungsten carbide, metallic cobalt, tantalum, cobalt oxalate   | -<br>14 yr                          | 1                 | Fever, exertional dyspnea, reticulonodular opacities on chest X-rays; reduced vital capacity; death from respiratory failure and cardiovascular collapse; diagnosis of pulmonary fibroadenomatosis                          | 26        |
| Vapors of trichloroethylene  |                                     |                   |   |           |

TABLE III-1 (CONTINUED)  
EFFECTS OF OCCUPATIONAL EXPOSURE  
TO TUNGSTEN-CONTAINING SUBSTANCES

| Composition<br>of<br>Substances   | Exposure<br>Concentration<br>and Duration | Number<br>of<br>Workers | Effects   | Ref-<br>erence |
|---|---|-------------------------|---|----------------|
| Cemented tungsten carbide<br>90% tungsten,<br>6% cobalt,<br>4% titanium, alumi-<br>num, magnesium,<br>iron, etc | 195-505 particles/ml<br><br>22 mon-22 yr  | 6                       | Persistent dry cough; dyspnea, and<br>pain and tightness in chest; hilar<br>shadows, linear markings, and micro-<br>nodular opacities in chest X-rays;<br>one died from anaplastic adenoma of<br>lower lobe of bronchus | 25             |
| Cemented tungsten carbide<br>primarily tung-<br>sten carbide  | 34 mon -                                  | 1                       | Wheezing, respiratory distress, 2<br>asthma attacks requiring hospital-<br>ization; asthmatic symptoms re-<br>curred on reexposure to work en-<br>vironment; diagnosis of extrinsic<br>asthma                           | 23             |

TABLE III-2

EFFECTS ON ANIMALS OF INHALATION EXPOSURE AND INTRATRACHEAL INJECTION OF  
TUNGSTEN-CONTAINING SUBSTANCES

| Composition of Substance       | Route of Exposure | Species     | Exposure Concentration, Duration                                       | Effects  | Reference |
|--------------------------------|-------------------|-------------|--|--|-----------|
| Tungsten hexachloride          | Inhalation        | Rats        | 43 - 140 mg/cu m   | Lacrimation, profuse blood-stained oral and nasal discharges; death  | 41        |
| Tungsten carbide: cobalt 75:25 | "                 | Guinea pigs | 8,800 - 10,600 particles/cu m x 20 d, then 2,900 particles/cu m x 15 d | Lung inflammation, dilation of alveolar-wall capillaries, infiltration by lymphocytes and plasma cells   | 37        |
| Tungsten carbide: cobalt 10:1  | Intratracheal     | "           | 50 mg/dose 1 dose/wk x 3 wk  | Pneumonitic areas in lungs, lymphocytic infiltration of perivascular areas, bronchial crypts   | 37        |
| Tungsten carbide: cobalt 94:6  | "                 | "           | 50 mg/dose 1 dose/wk x 3 wk  | Hyperemia and bronchial catarrh, minor interstitial pneumonitis, lymphoid hyperplasia, trapped dust masses in lungs, pleural fibrocellular granulomata | 34        |
| Tungsten dust                  | "                 | "           | 50 mg/dose 1 dose/wk x 3 wk  | Interstitial pneumonitis and bronchiolitis   | 36        |

TABLE III-3

## EFFECTS ON ANIMALS OF ORAL DOSES OF TUNGSTEN-CONTAINING SUBSTANCES

| Composition       | Route of Exposure | Species     | Exposure Concentration<br>Duration | Effects   | Reference |
|-------------------|-------------------|-------------|------------------------------------|---|-----------|
| Powdered tungsten | Oral              | Rats        | 10% in diet                        | Weight loss in females 15.4%; no effects in males                               | 44        |
| Sodium tungstate  | "                 | Guinea pigs | 2,000 mg/kg                        | LD50  | 50        |
| "                 | "                 | "           | 1,152 mg/kg                        | "   | 50        |
| "                 | "                 | "           | 500 mg/kg                          | LD0   | 50        |
| "                 | "                 | Mice        | 240 mg/kg                          | LD50; arched backs, decreased muscle tone, slight paralysis of hindlegs         | 50        |
| "                 | "                 | Rats        | 2,000 mg/kg                        | LD100   | 50        |
| "                 | "                 | "           | 1,190 mg/kg                        | LD50  | 50        |
| "                 | "                 | "           | 700 mg/kg                          | LD0   | 50        |
| "                 | "                 | "           | 2%<br>in diet for<br>70 d          | Death of 100%   | 48        |
| "                 | "                 | "           | 0.5%<br>in diet for<br>70 d        | Death of 80%  | 48        |
| "                 | "                 | Rabbits     | 1,500 mg/kg                        | LD100   | 50        |
| "                 | "                 | "           | 875 mg/kg                          | LD50  | 50        |
| "                 | "                 | "           | 500 mg/kg                          | LD0   | 50        |
| "                 | "                 | Guinea pigs | 0.50 -<br>0.75 g/<br>600 g         | Anorexia, colic, uncoordinated movements, trembling, dyspnea; death at 16-23 hr | 45        |

TABLE III-3 (CONTINUED)

## EFFECTS ON ANIMALS OF ORAL DOSES OF TUNGSTEN-CONTAINING SUBSTANCES

| Composition              | Route of Exposure | Species     | Exposure Concentration<br>Duration | Effects   | Reference |
|--------------------------|-------------------|-------------|------------------------------------|---|-----------|
| Sodium tungstate         | Oral              | Guinea pigs | 0.55 g/kg                          | Single lethal dose  | 45        |
| Sodium phospho-tungstate | "                 | Mice        | 700 mg/kg                          | LD50; arched backs, decreased muscle tone, slight paralysis of hindlegs | 50        |
| Tungstic oxide           | "                 | "           | 840 mg/kg                          | "   | 50        |
| "                        | "                 | Rats        | 0.5%<br>in diet for<br>70 d        | LD50  | 48        |
| Ammonium-p-tungstate     | "                 | "           | 2%<br>in diet for<br>70 d          | Death of 80%  | 48        |
| "                        | "                 | "           | 0.5%<br>in diet for<br>70 d        | No deaths   |           |