III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

Vanadium is a chemical element that occurs in ores at about 0.02% of the earth's crust. It may occur in oxidation states of O, II, III, IV, and V in such compounds as those that appear in Table XII-1 [1]. After refining, it is a light gray, malleable, ductile metal that is hardened and embrittled after reaction with oxygen, nitrogen, or hydrogen. Chemical and physical properties of vanadium and its industrially important compounds, primarily pentavalent, are presented in Table XII-1. It is found in air, food, plants, and animals. While some evidence suggests that vanadium may be an essential trace element for mammals, the issue has not been resolved.

Occupational exposure to vanadium-containing dusts is encountered in the mining of vanadium-bearing ores. Most of the vanadium-bearing ores in the United States come from Arkansas, Colorado, and Idaho while foreign sources include South Africa, Chile, and the USSR [2]. In milling, exposure to vanadium-containing dust can occur near the production sites of numerous vanadium compounds, particularly vanadium pentoxide and, to a lesser extent, the vanadates. Numerous exposures to vanadium compounds have occurred during the cleaning of oil-fired burners, where the dust is generated from the residual oil ash of high-vanadium content oil. Occupations with potential exposure to vanadium and its compounds as presented by Gafafer [3] are listed in Table XII-2.

Vanadium production in the world and US production, consumption, exports, and imports are shown in Table III-1 [4], expressed in short tons (1 short ton=2,000 lb).

18

TABLE III-1

VANADIUM PRODUCTION IN WORLD AND US PRODUCTION, CONSUMPTION,
EXPORTS, AND IMPORTS (SHORT TONS)

Variable	1971	1972	1973	1974	1975
World production	20,502	20,239	21,653	21,112	23,831
United States					
Production					
Recoverable vanadium*, ore and concentrate	5,252	4,887	4,377	4,870	4,743
Vanadium oxides recovered**, ore and concentrate	5,293	5,248	4,864	5,368	4,859
Consumption	4,802	5,227	6,393	7,200	5,501
Exports					
Ferrovanadium and other vanadium alloying materials, gross weight	676	269	1,416	1,335	1,018
Vanadium ores, concentrates, oxides, and vanadates	260	176	232	203	215
General imports					
Ferrovanadium, gross weight	89	578	303	225	179
Ores, slags, and residues	2,350	1,400	2,600	2,485	2,895
Vanadium pentoxide (anhydride)	30	-***	-***	533	1,275

*Recoverable vanadium contained in uranium and vanadium ores and concentrates received at mills, plus vanadium recovered from ferrophosphorus derived from domestic phosphate rock
**Produced directly from all domestic sources; includes metavanadates; figure for 1971 also includes small byproduct quantities from imported chromium ores.
***Less than 1/2 short ton

Adapted from reference 4

Consumption by type of material in the US for 1975 included 4,703 short tons as ferrovanadium, 216 short tons as vanadium oxides, 26 short tons as ammonium metavanadate, and 556 short tons as other vanadium compounds [4]. Domestic consumption of vanadium by end use was as follows: 30% in vanadium-bearing steel and iron products (as alloying agent); 30% in the transportation industry as titanium-based alloys, steel, and cast iron; 10% in construction machinery and industrial equipment; 10% in metal working machinery and tools (total for alloy use is 80%); 5% in chemical and allied products, eg, catalysts; and 15% miscellaneous use. One of the most important catalytic uses of vanadium is in the oxidation of sulfur dioxide to sulfur trioxide in the preparation of sulfuric acid. Vanadium oxytrichloride is used as a catalyst in the production of ethylene-propylene synthetic rubber. Uses of vanadium compounds are numerous, but the quantity used by the chemical and related industries has been small compared with metallurgical applications.

NIOSH estimates that approximately 174,000 employees in the United States have potential exposure to vanadium and its compounds.

Historical Reports

Vanadium was discovered by Sefstrom in 1830 and was named after Vanadis, a Scandinavian goddess [5]. The first commercial use for vanadium developed about 1860, when vanadium salts were used as coloring agents [2]. Its use as an alloying element in steels was begun about 1905 by the US automobile industry, primarily the Ford Motor Company. However, its beneficial effects in certain special steels were recognized in Europe as early as 1896. The manufacture of specialty steels has continued to be an

20

important market for vanadium. Although its catalytic properties were recognized and used as early as 1870, this application, while important, has remained small. Since 1960, the use of vanadium in nonferrous alloys, principally titanium alloys, for jet engines and airframes has become increasingly important.

Experimental studies using vanadium, begun in the 1870's, are depicted in the following paragraphs.

In 1876, Priestly [6] studied the toxicity of sodium metavanadate solution injected into the veins, alimentary canal, or subcutaneous tissue of frogs, pigeons, guinea pigs, rabbits, cats, and dogs. The lethal dose of vanadium pentoxide injected subcutaneously into rabbits ranged from 9.18 to 14.66 mg/kg. The author noted that there were two chief modes of action: a central effect on the nervous system causing drowsiness and convulsions, followed by gradual paralysis of both respiration and body motion, and an effect on the alimentary tract causing diarrhea and bloody stools. He reported a slowing and weakening of heart action accompanied by intermittent decreases in blood pressure, each decrease followed by partial recovery; this was thought to be a result of an effect on the vasomotor center of the central nervous system (CNS) and intracardiac nerve mechanisms.

In 1877, Gamgee and Larmuth [7] and Larmuth [8], from experiments with sodium metavanadate (NaVO3), pyrovanadate (Na4V2O7), and orthovanadate (Na3VO4), concluded that vanadium acted similarly to digitalis; however, they noted that the "intracardiac nervous mechanism" was affected in some way that did not exactly correspond to the effects of digitalis. In the frog, they observed that the heart ventricles became contracted from the

action of vanadium but that vagus stimulation did not cause a dilatation. During perfusion, the ventricles became permanently contracted while the atria were still beating. Experiments with white rats showed that injections of sodium pyrovanadate caused death more readily than injections of sodium orthovanadate. The authors [7,8] concluded from both experiments that orthovanadate was less harmful to frogs or rats than the metavanadate or pyrovanadate.

Dowdeswell [9], in 1878, described an extensive fatty degeneration in the livers of dogs and cats administered ammonium metavanadate orally or subcutaneously. The author stated that the lethal dose for rabbits, guinea pigs, and dogs was about 10 mg/kg of vanadium pentoxide but that it was less than 10 mg/kg for cats.

Jackson's experiments [10,11] in 1912 concerned the effects of intravenous (iv) injection of 1% sodium orthovanadate on the circulation of dogs. There was a rise in blood pressure caused by systemic vasoconstriction attributed to a direct action of the orthovanadate on arterial muscle or vasomotor endings. The heartbeat was not strengthened. The pressure in the pulmonary artery also rose as a result of systemic and pulmonary vasoconstriction. Perfused blood vessels of the lungs were constricted. There was evidence of the bronchial muscles having moderate but prolonged constriction.

In 1917, Proescher et al [12] investigated the effects of injected and orally administered vanadium on humans. Sodium tetravanadate (described as Na2V4O11) injected iv into a man at a dose of 20 mg caused constriction of the throat, salivation, lacrimation, temporary disappearance of pulse and respiration, diarrhea, vomiting, and a drop in

22

body temperature of 3 degrees. The authors estimated that 30 mg of the tetravanadate, injected iv, was a fatal dose for a 70-kg man. Vanadium pentoxide at iv or intramuscular (im) doses of 10 mg or at 20 mg (im or subcutaneous) caused few problems when injected properly. The safe dose of sodium hexavanadate (described as Na4V6O15) by an unspecified route was 60 mg for men and 40 mg for women, while the emetic dose was estimated at 100-120 mg. Sodium tetravanadate was administered orally at a daily dose of 12.5 mg for 12 days to a healthy young man and the total dose was completely recovered in the urine (12.4%) and feces (87.6%). This proved to the authors that vanadium orally administered was quickly and quantitatively eliminated, mainly through the feces.

Levaditi et al [13], in 1928, found that finely pulverized metallic vanadium, suspended in olive oil or isotonic glucose solution and injected im, had a curative effect on spontaneous spirochetosis and on experimentally induced syphilis in rabbits.

In 1939, Pereira [14] injected im a water solution containing vanadium sodium tartrate (0.15 g in 2 ml) twice weekly into patients who were in the primary stages of syphilis. He reported prompt disappearance of spirochetes, secondary lesions, and gummata, none of which was responsive to treatment by bismuth, arsenic, and the Salvarsan series. He found it also effective in yaws. The toxicity was low; only a few occurrences of oral inflammation, erythema, and hepatic reaction were observed in rabbits injected at doses of 0.02 g of the tartrate (8 total injections) over a few days.

The first description of vanadium poisoning in workers was given by Dutton [15] in 1911. The men were primarily exposed to vanadium oxide dust

and fume. The men had a dry, irritating cough, blood-stained sputum, and anemia, preceded by an increased erythrocyte count, pallor, anorexia, emaciation, albuminuria and casts, hematuria, tremors, eye irritation, vertigo, hysteria, and depression. Dutton found that tuberculosis often developed, sometimes causing death. He referred to the therapeutic use of vanadium pentoxide in diseases resulting from defective metabolism and to the poisoning that sometimes resulted from its administration. Dutton also remarked that illness was sometimes caused by wearing clothing dyed by vanadium salts.

Hamilton [16], in 1925, reported that she was unable to verify Dutton's observations [15] on a visit to a vanadium plant. Physicians interviewed at the plant, however, stated that the men always had a cough and a physician at a nearby hospital said that the dust caused an infiltration of the lungs, with moist rales throughout the chest.

Effects on Humans

Much of the information on effects of vanadium and its compounds on humans has come from accidental exposures of workers in vanadium manufacturing and processing plants and in boiler cleaning operations. Some questions posed by these studies have stimulated experimentation involving controlled exposures of humans.

Gul'ko [17], in 1956, reported on the effects of exposure to vanadium compounds on seven vanadium plant workers, 19-55 years old, with 1-8 years of employment. The plant processes included crushing, grinding, screening, loading, and boiling the unspecified technical product to yield ammonium metavanadate. Another process involved unloading, grinding, and packing of

24

sodium metavanadate. A final process involved grinding, mixing, and packing of vanadium pentoxide. Manual procedures and lack of ventilation in these areas caused very dusty conditions. Although air sampling by membrane filters was conducted at each site, the method of analysis was not described. Analysis of the urine for vanadium content in four of the workers and in four controls was performed by a phosphotungstate method. Chest roentgenograms, general examination (unspecified tests) of the blood and urine, and examination of the nose and throat were all conducted.

Mean concentrations of vanadium-bearing dusts ranged from 3.6 mg/cu m at the vanadium pentoxide site to 25.1 mg/cu m at the technical product grinding area [17]. Ninety-five percent of the dust particles of pure vanadium pentoxide, ammonium metavanadate, and sodium metavanadate were less than 5 μm in size. Vanadium contents of the dust sampled were not reported. Vanadium content in the urine of the four tested workers was 0.02-0.05 mg/100 ml of urine and was undetectable in the four controls. The complaints of the seven workers, exposed for 2-3 months at a time, were irritation of the respiratory tract and eyes that included frequent sneezing, gagging, coughing, and a feeling of scratchiness in the eyes. The mucous lining of the nose was dry, the mucosa of the posterior wall of the throat was hyperemic, and, in most workers (number unreported), minor nosebleeds were noted. After work hours, the workers felt better. The lowest concentration of dust found in the sodium metavanadate and vanadium pentoxide areas was 0.5-2.2 mg/cu m. Gul'ko concluded that the minimum concentrations in those areas caused respiratory irritation and conjunctivitis.

Because vanadium compounds caused irritation of the respiratory tract, Gul'ko [17] recommended that protective equipment be worn while processing those compounds and that workers have periodic medical examinations. He also recommended that the threshold limit value (TLV) for vanadium dust compounds [18] be lowered to less than 0.5 mg/cu m.

In 1962, Zenz et al [19] studied the effects of vanadium on 18 pelletizing plant workmen, 21-55 years old, who inhaled pure vanadium pentoxide dust at concentrations greater than 0.5 mg/cu m. Purified vanadium pentoxide was received at the plant as a fine, dry powder in 55-gallon metal drums. The powder was dumped into a hopper and then conveyed on an open moving belt to a muller where the particles were reduced to a smaller size and moistened to assist in pellet formation. The material was then conveyed by an open moving belt to a pelletizing pan for conversion to pellets. All of these operations depended on open ventilation to remove atmospheric contaminants, except for two small vents along the conveyor belt. The 24-hour continuous process generated a heavy dust roughly estimated from cloud density to be 100-500 million particles/cu ft of air throughout the plant. Dust counts were not taken during this particular pelletizing operation but from previous runs of the same ores. Air concentrations of vanadium pentoxide were believed to be greater than 0.5 mg/cu m, with a mean particle size of less than 5 μm, although no measurements were made. Particle sizes ranged from 0.1 to 10 μm; however, it was later determined by the authors that the sampling filter used for this determination was of improper type and incapable of collecting all of the vanadium pentoxide particles. Vanadium fume may also have been produced from the high-temperature kiln used in the pelletizing process.

26

Felt-pad respirators were provided to men working in process areas, but other plant employees entered these work areas without respirators [19]. Ultrafine filter-type respirators were recommended and air-line respirators were provided for men working in the most dusty locations. Three of the 18 workmen had not worn their masks and complained after 1 day's work of dry cough, sore throat, and burning eyes. Medical examination of the three workers after 2 additional days' work showed conjunctivitis and inflamed throats. The three workers were sent home for 3 days. They returned to work on the 4th day and wore their respirators, only to have their symptoms recur at a greater intensity within 0.5-4 hours. Moreover, rales were observed throughout the lungs. Incessant coughing prevented the workers from using their respirators any further.

The industrial process continued for 2 weeks, and 16 of the 18 workers examined had conjunctivitis and inflammation of the nose and throat, hacking cough, rales, and wheezing [19]. The two remaining workers developed only upper respiratory irritation. Bronchospasm in an unreported number of seriously affected workers persisted for 48 hours after removal from exposure, the rales lasted 3-7 days, but the cough persisted for 2 weeks in many others. Of the 16 men with lower respiratory tract effects, 6 showed severe illness, 7 were moderately ill, and 3 had minimal illness. Four of the 18 men complained of skin itch and a sensation of heat in the face and forearms after exposure, but no objective evidence of skin irritation was found. The most severely affected men lost 4.5-11 workdays; those least affected lost no work time.

Pulmonary function tests, including forced vital capacity (FVC), forced expiratory volume, maximal expiratory flow rate, 200-1,200 cc flow

rate, maximal midexpiratory time, and forced inspiratory vital capacity, were conducted 2 and 4 weeks after exposure [19]. All the test findings were normal, except for one man who had a decreased FVC that was attributed to an unnamed preexisting pleural disease. Routine urinalysis findings were normal, while spectrographic analysis showed vanadium in the urine of 12 men. The actual vanadium content was not reported. The workers who were the most severely ill excreted vanadium for up to 2 weeks, after which no vanadium was detected in the urine in any of the men. A throat culture from one man and chest roentgenogram findings in all of the men were normal. Leukocyte counts were elevated above the normal range in nine men during exposure (range 10,000-16,000 cells/cu mm, the highest counts being found in the most severely affected workers). Five men had normal counts 3-5 days after removal from vanadium exposure, and one had elevated leukocyte counts with an elevated number (unspecified) of lymphocytes during the entire 2-week period of observation. One worker with a viral infection had a lowered leukocyte count. All others were normal by the end of the 2-week observation period. The authors suggested that the prompt return to normal leukocyte counts tended to substantiate the similarity of the vanadium intoxication aftereffects to those of zinc oxide type "metal fume fever."

After recovery, several workmen, especially those with multiple exposures, found it impossible to participate in cleanup activities because of recurrent coughing and wheezing [19]. Respirators were inadequate to prevent signs or symptoms from occurring. Although these recurrent signs or symptoms appeared to be more severe than those of the original illness, indicating possible sensitivity effects, there was no clinical evidence

28

that they were of longer duration. Four men, reexamined while experiencing recurring signs or symptoms during the cleanup operation, had normal ventilatory function. No other test results were reported. The authors believed that the vanadium intoxication was caused by the high purity of vanadium pentoxide, the small particle size, and the possible presence of vanadium pentoxide fume in the pelletizing process.

An interesting aspect of the report was the increased severity and rapid onset of the symptoms in the workers after multiple exposures, even though subsequent exposure concentrations were said to be less severe than those responsible for the initial illness. The authors [19] suggested that this sequence of events could represent a sensitivity reaction rather than an effect of accumulated vanadium. They recommended diligent engineering controls and individual protective equipment, such as air-line respirators, when handling vanadium. They also recommended a reevaluation of the acceptable TLV's for vanadium and its compounds.

In the only report of human exposure to ferrovanadium, Roberts [20], in 1965, presented a review of 15 years' experience as medical director of a ferroalloy plant. The average plant population was 2,000 people who were moved from department to department and from process to process. The employees were examined routinely every 3-5 years, and the examinations included: chest and lumbar spine roentgenograms, electrocardiograms, vital capacity studies, urine analyses, and audiograms. Concentrations of the compounds discussed were not given.

According to the author [20], ferrovanadium produced only slight irritation to the respiratory tract and eyes. Vanadium-aluminum alloy at particle sizes less than 100 mesh (about 150 μm [21]) produced irritation

of the nose and throat with coughing. The posterior of the tongue became greenish-gray after 4 hours exposure to the finer sizes. Vanadium carbide was reported to be essentially inert physiologically. No serious health hazard was noted and sizes down to 100 mesh caused little irritation of the eyes and respiratory tract.

In 1953, Tara et al [22] observed vanadium intoxication in four male dock workers, 30-40 years old, who unloaded bags of calcium vanadate from a ship for about 1.5 days. Concentrations of the calcium vanadate at which these workers were exposed were not reported. Fifty-kilogram paper bags of calcium vanadate were normally lifted out of a ship's hold by rollers and then carried to port warehouses; however, 30% of these bags had broken, so the dockers had to climb into the hold and shovel the spilled calcium vanadate, 10-15 cm thick, into other bags, thereby creating a dusty work environment. The dockers became ill after an unspecified time in the hold and had to interrupt their unloading task. The unloading was finished several days later by workers wearing filter masks.

The four dockers showed respiratory symptoms of varied intensity that forced them to leave work for periods from 0.5 day to 3 weeks [22]. Coughing occurred in three workers and wheezing, expectoration of mucus, and signs of bronchitis were noted in two workers. Also reported were "febrile movement" in one docker, expectoration of bloody mucus and a feeling of depression in another, and headache, stiffness, and vomiting in a third docker. The latter two were hospitalized for 7 and 9 days, respectively. Tara et al also reported that, prior to employment, one of the four dockers had pleurisy, another had heart disease, and a third had bronchitis.

Sjoberg [23], in 1955, examined 21 men who cleaned oil burners. Seven men cleaned very large oil burners (20-30 tons of heavy oil burned/hour), 1 man cleaned a small oil burner (1/25-1/50 the size of the ones previously mentioned), and 13 men cleaned a medium-sized oil burner (45 tons of oil burned/24 hours). Air sampling methods were not described for any of these processes. Chest radiography in one man and tests for vanadium content in the blood and urine of another man were the only examinations specified in the study.

The first seven men were exposed to vanadium pentoxide dust at concentrations of 85, 57, 10, and 2 mg/cu m with most particle sizes being between 10 and 20 μm in diameter [23]. Face masks were worn but did not appear to be effective. Of the seven men, all had irritation of the nose, six had coughing with irritation of the throat and bronchi, five had wheezing in the chest, three had irritation of the eyes, three were fatigued, two had palpitations of the heart, and one had difficulty in breathing. All of the men had one or more signs or symptoms and these were considered typical of vanadium bronchitis. On radiography, one man showed bilateral bronchopneumonia. In one man, chemical analysis of the blood failed to detect vanadium, but 5 mg/100 ml was found in his urine 16 hours after his exposure; thus, distinct excretion of vanadium was demonstrated. The signs and symptoms usually appeared 1-2 days after working in the boilers and usually disappeared a few days after removal from the cleaning area. Sjoberg noted that sulfur dioxide and sulfur trioxide were present in the boilers before they were purged with fresh air. These sulfurous gases occurred after burning the high-sulfur content oil. However, he stated that the gases could not play an important part in the causation of

31

the respiratory effects because of their volatility and the small amounts present when the boilers had been cooled prior to cleaning. Corrosion of the clothes was noted by six of the workers, but this was from the formation of sulfuric acid in the boiler after wetting the fly-ash (containing sulfur compounds).

The man who cleaned the small boiler had coughing, wheezing in the chest, and irritation of the throat and bronchi [23]. He recovered about a week after removal from the work area. No exposure concentration for vanadium pentoxide dust was given.

Of the 13 men who cleaned the medium-sized boilers, all had coughing, 12 had irritation of the eyes, nose, and throat, 10 had rashes, 9 had irritation of the bronchi, 7 had difficulty in breathing and fatigue, 3 had wheezing in the chest, and 1 had palpitations of the heart [23]. All the men had one or more of the signs or symptoms and these usually appeared on the day after cleaning; however, some signs or symptoms appeared immediately after exposure, but this was considered to be from the high concentration of sulfur dioxide and trioxide gases in the boilers. Sjoberg's explanation was that, in the 13 men, the complaints usually appeared after a few days work and, thus, were typical of vanadium exposure and not characteristic of sulfur dioxide or trioxide exposure. The corrosive effect on the clothes from the sulfuric acid-containing soot was again evident. The men were instructed to wear face masks but apparently did not always do so as indicated by the reported signs and symptoms.

Sjoberg [23] noted that exposure to vanadium pentoxide dust was mainly an acute irritation of the upper respiratory tract and conjunctiva with associated respiratory problems, including bronchitis. No greenish-

32

black discoloration of the tongue (an indicator of vanadium exposure [24-26]) was reported in any of the 21 men examined. Recommended control measures included the use of respirators and protective clothing, purging the boiler with air before entering, and burning a combination of oil and pulverized coal to decrease vanadium pentoxide deposits.

Fallentine and Frost [27], in 1954, analyzed soot from oil-fired boilers and found that it contained both vanadium and sulfuric acid.

In 1952, Williams [28] examined eight men who were exposed to vanadium pentoxide dust at concentrations ranging from 17.2 to 58.6 mg/cu m for periods of 2-5 days while cleaning the combustion chambers, fire bricks, and heating tubes of oil-fired burners. The protective equipment worn by the cleaners was not described, but photographs in the article depicted the men wearing some type of filter mask, cap, and coveralls. The primary symptoms appeared 0.5-12 hours after the workers started cleaning and consisted of sneezing in five, rhinorrhea in seven, sore throats in two, tightness of the chest in three, and chest pains in one. After 6-24 hours, secondary symptoms and signs appeared consisting of coughing in all eight, breathing difficulties in seven, depression in four, rales in three, fatigue in three, rhonchi in two, hand tremors in two, and wheezing in one. A yellow to greenish-black coating of the tongue was observed in all of the men, but the color faded within 2-3 days after removal from the work area. The coughing sometimes became spasmodic and productive and induced vomiting in one man. All of the workers had more than one sign or symptom and these continued while the men were working but became less severe 3 days after ceasing work. In one man the wheezing and breathing difficulties persisted for over a week, but no permanent effects were noted. Postexposure blood

33

pressures were lower than preexposure measurements in seven of the eight men, and in one man, there was no change. Williams suggested that the workers' familiarity with medical examination procedures when the postexposure readings were taken might have explained the measured blood pressure differences. The results of cardiac examinations, including electrocardiograms and roentgenograms of the chest, showed no abnormalities. The author entered an oil-fired burner for 1 hour during its cleaning and experienced most of the symptoms previously mentioned, as well as coughing which persisted for 2 weeks.

Urine samples from the men were analyzed for vanadium content using the phosphotungstate colorimetric method of Sandell [29]. Specimens for each man were collected over a 24-hour period on the last day of boiler cleaning, precautions being taken to prevent contamination. In the most severely affected worker (5 days of exposure), concentrations of 0.07 mg (early morning specimen) and 0.4 mg (daytime specimen) of vanadium/liter of urine were found, while no vanadium or only traces of vanadium were found in the urine of five and two men, respectively. Urine specimens from all of the men showed no albumin, sugar, or blood. Electrocardiograms in all the men were normal.

Sampling was carried out during the cleaning operation by drawing dust-laden air through distilled water contained in an aspirator packed with Lessing rings [28]. Three separate samples of 3.7, 4.5, and 6.8 cu m of air were collected at a flowrate of about 7.1 cu m/hour. Vanadium was estimated both in the resultant solution and in the suspended solids. Thermal precipitator samples were used to estimate particle size and concentration. Results of the dust sampling indicated that there were

34

3,500 particles/ml (about 84 million particles/cu ft) of air. About 94% of the particles were 1 μm or less in size; particle sizes ranged up to 11 μm in diameter. Vanadium was present in the atmosphere at concentrations of 17.2 and 40.2 mg/cu m in the two superheater chambers and 58.6 mg/cu m in the combustion chambers.

Williams [28] recommended improved measures for cleaning the burners, such as cleaning them from the outside, wearing proper respirators, spraying water to reduce dust, and using a tarpaulin to protect workers from falling dust. These methods were subsequently tried and no further adverse effects were reported. Williams also suggested improvements of boiler cleaning techniques, which included reduction of exposure to petroleum soot and medical supervision of the workers throughout the cleaning process. According to the findings of Sjoberg [23], sulfates could have been present and may have caused some of the irritant effects.

Browne [30], in 1955, described vanadium poisoning in 12 men who used pneumatic chisels to cut away combustion residues from heat exchanger tubes of a gas turbine engine. Exhaust air from the chisels caused the dust (mainly vanadium pentoxide and probably vanadium silicates and vanadates), which contained about 11-20% vanadium, to become airborne. The time of onset of signs and symptoms ranged from 1 to 14 days. The average time before these signs and symptoms appeared was 4.2 days. Nosebleed was the first sign noticed in five men, followed by other respiratory signs and symptoms, such as coughing in six, tightness and pain in the chests of five, nasal congestion and wheezing in four, and difficulty in breathing in two. Alimentary signs and symptoms were reported in seven men and included black tongue in six, four with an odd taste in the mouth, two with black

teeth, and one with nausea and diarrhea. Skin problems, caused by damp conditions that yielded an irritating acid solution, were also reported by seven men and consisted of sore skin in three, one with rash, and one unspecified condition. "Smarting eyes" were reported by two workers. Analytical and sampling methods for the dust and exhaust gases were not described.

McTurk et al [31], in 1956, reported no evidence of effects on boiler cleaners working in an atmosphere containing vanadium pentoxide at an average concentration of 99.6 mg/cu m. They noted that the lack of effects was probably because of the gauze filter masks worn over the nose and mouth and because of the intermittent cleaning operation that occurred only one or two times each month. No sampling or analytical methods were presented.

In 1967, Zenz and Berg [32] placed nine healthy volunteers, 27-44 years old, in an environmental chamber and exposed them to pure vanadium pentoxide dust for periods of up to 8 hours. The environmental chamber was an enclosed room, 660 cu ft in volume, air conditioned to maintain constant temperature and humidity, and was equipped with a dust-feed mechanism to deliver the vanadium pentoxide. Air samples were drawn directly from the chamber using glass-fiber filters with a flow-calibrated vacuum pump, and they were analyzed by the spectrophotometric method of Hulcher using benzohydroxamic acid [33]. Particle size analysis showed that 98% of the collected dust was less than 5 μm in diameter. Before exposure, pulmonary function tests were conducted on the subjects on three separate occasions to obtain baseline measurements. Complete physical examinations were conducted prior to exposure and included chest roentgenograms, complete blood counts, and hematocrit measurements. Urine and feces were tested for

vanadium content by the spectrophotometric method of Hulcher [33]. Blood samples were drawn 3 weeks before and 3 weeks after exposure for determinations of serum cholesterol, total lipids, and triglycerides, but the results obtained were too varied to be used. Cystine analysis of the hair and nail clippings was performed by the Public Health Service before and after exposure, but no differences were found.

Two volunteers were exposed to vanadium pentoxide dust at a concentration of 1 mg/cu m (0.6 mg V/cu m) rather than the planned 0.5 mg/cu m (0.3 mg V/cu m) during the first 8-hour test [32]. They developed some sporadic coughing after the 5th hour, and more frequent coughing at about the 7th hour of the test. No other signs of irritation were noted. Results of postexposure chest roentgenograms, urinalyses, leukocyte and differential counts, nasal smears, and pulmonary function tests were the same as those obtained before exposure.

The same two volunteers were accidently reexposed for 5 minutes to a heavy cloud of vanadium pentoxide dust of unknown concentration 3 weeks after the original exposure [32]. Sixteen hours later, marked, productive coughing developed. The next day, rales and expiratory wheezes were present, but pulmonary function was normal. Treatment with 1:2,000 isoproterenol for 5 minutes by positive pressure inhalation relieved the coughing and wheezing; however, coughing resumed in an hour and continued for 1 week. No other signs or symptoms were reported by the authors.

Zenz and Berg [32] then exposed five volunteers for 8 hours to vanadium pentoxide dust at a concentration of 0.25 mg/cu m (0.1 mg V/cu m). Air sample findings showed an average concentration of 0.2 mg/cu m with a standard deviation of 0.06 mg/cu m, and the microscopic analysis showed

37

that 98% of the collected dust was again less than 5 μm in diameter. All of the volunteers developed a cough the next morning, but differential leukocyte counts were normal. Daily observations of the volunteers found no abnormalities. Coughing ceased after 1 week in several of the volunteers and after 10 days in the remainder. No pulmonary function changes from preexposure values were noted immediately after exposure or 2 weeks later. For vanadium analyses, postexposure blood samples were drawn every other day for 8 days and daily urine samples were collected for the same period; after 1 week, these samples were taken every other day for 14 days. Feces were collected and analyzed for vanadium content. No vanadium was found in blood samples, while the vanadium content of the urine was greatest, 0.013 mg/100 ml, at 3 days after exposure, and none was found after 1 week. Maximum fecal vanadium content was 0.3 mg/100 g; none was detected after 2 weeks.

Because of the responses at 0.2 mg/cu m, two volunteers, not previously exposed to vanadium pentoxide dust, were exposed at 0.1 mg/cu m for 8 hours [32]. No symptoms occurred until about 24 hours after exposure when considerable mucus formed that was easily cleared by slight coughing. The coughing increased after 2 days, subsided within 3 days, and disappeared completely after 4 days. There were no deviations from normal in undefined laboratory studies. The acute manifestations of pulmonary irritation observed in all volunteers demonstrated the reaction of humans to fine vanadium dust of less than 5 μm. Despite the distinct clinical picture of pulmonary irritation in all the subjects, pulmonary function tests remained unaltered [32]. No systemic complications were found.

Zenz and Berg [32] pointed out that their experiments were conducted under resting conditions, and, thus, under actual working conditions, there would be an even greater inhalation and absorption at the same concentrations of vanadium pentoxide dust. However, an experiment with volunteers engaged in physical activity was not conducted. Because of the responses at 0.1 mg/cu m, the authors recommended that the TLV of 0.5 mg/cu m for vanadium pentoxide dust be lowered. Control groups were not used and exposure experiments at lower concentrations of vanadium pentoxide dust were not performed.

In his review of vanadium toxicology in 1964, Hudson [34] reported his personal experience supervising 18 workers who were exposed intermittently to vanadium pentoxide and ammonium metavanadate in fine particles, mostly less than 1 μm in size and at an average air concentration of 0.25 mg/cu m (range 0.08-0.76 mg/cu m) as vanadium pentoxide. He observed that if the workers did not wear respirators, a discolored tongue, metallic taste in the mouth, throat irritation, and slight coughing often developed. Thus, the author concluded that the maximum permissible concentration of vanadium pentoxide dust should be lowered to 0.1 mg/cu m.

Roshchin et al [35] examined 120 workers exposed to dust containing up to 10% vanadium trioxide and up to 9% vanadium pentoxide. Three cases (two women and one man, between 33 and 40 years old) of bronchial asthma in 120 subjects had developed after contact with vanadium for 1-5 years. Removal from contact with vanadium relieved the condition somewhat, but it was not completely eliminated; if contact with the dust was renewed, the condition of the workers deteriorated. This was said to confirm that

39

vanadium could cause bronchial asthma. Similar findings, suggestive of an allergic effect, have developed in other human studies [19,26,36]; such an effect has also been demonstrated in animal studies [35].

Similar effects (respiratory tract, eye, and possible skin irritation) have been found in other studies [37-52] of industrial vanadium exposure.

Kent and McCance [53] examined the routes of excretion of sodium tetravanadate in humans. The authors did not define sodium tetravanadate but a previous study [12] described it as Na2V4O11. They injected sodium tetravanadate iv at an unspecified dose into two men daily for 6 days. The men were fed a vanadium-free diet. Analyses for vanadium content in the food, urine, and feces were performed spectrochemically. After the last injection, the total vanadium excretion by each of the two subjects by the 7th day was 93% and 89%, respectively. The authors concluded that vanadium, when present in the bloodstream, was mainly eliminated by the kidneys, since 81% of the total vanadium injected into the two subjects was excreted in the urine, and there was only 9% in the feces by the 7th day after the last injection. The authors presumed that unrecovered vanadium, about 10% of the administered dose, remained in the body.

In 1963, Dimond et al [54] administered ammonium vanadyl tartrate orally to five women and one man, 30-55 years old, to establish levels of tolerance, relationship between oral dose and urinary excretion, evidence of toxicity, and the effect on circulatory lipids. The tartrate was administered orally in 25-mg tablets, up to four times/day with meals, for 45-68 days. The amount of vanadium excreted in the urine was determined by the colorimetric method of Talvitie [55] using 8-quinolinol; urine

specimens were also examined microscopically. Total lipids, phospholipids, triglycerides, and total and free cholesterol were measured in the venous blood of all subjects; in three subjects, 17-ketosteroids and 17-hydroxycorticosteroids were also measured. Other analyses conducted were blood urea nitrogen (BUN) concentration, serum glutamic-oxaloacetic transaminase (SGOT) activity, and reticulocyte, platelet, and total and differential leukocyte counts.

The vanadium content of urine was determined in four subjects during the 24-hour period after administration of the tartrate at varying doses of 25-125 mg [54]. In all cases, wide fluctuations in urinary excretion suggested unpredictable absorption of the tartrate. No laboratory findings indicative of toxicity occurred. Reticulocytes, platelets, and total and differential leukocyte counts were within normal limits. BUN and SGOT values were unchanged. Three of the women excreted 11.8-18.2 mg of 17-ketosteroids/24 hours (normal, 5-15 mg/24 hours' volume, excreted as dehydroisoandrosterone) and 6.1-9.5 mg of 17-hydroxcorticosteroids/24 hours (normal, 5-10 mg/14 hours' volume). All subjects reported gastrointestinal difficulties manifested by black, loose stools and increased intestinal activity accompanied by cramps. On a daily dose of 50 mg or more, a purple-green tint developed on the tongue but disappeared promptly. Two subjects said they experienced greater fatigue and lethargy than usual while taking vanadium. A cholinergic-blocking drug (triglyclamol chloride) given with each dose of ammonium vanadyl tartrate seemed to lessen the intestinal symptoms and to permit administration of a larger dose of the tartrate. The total daily dose tolerated varied from 50 to 125 mg. No statistically significant changes occurred in blood lipids, phospholipids,

41

triglycerides, or cholesterol. There were no measurable toxic effects of ammonium vanadyl tartrate on the bone marrow, liver, kidneys, or adrenal glands.

In 1962, Somerville and Davies [56] treated 12 patients, 23-64 years old, with oral doses of diammonium vanado-tartrate for 6 months to test its effect on serum cholesterol concentrations. All of the patients were on a diet restricted in fat. Nine of these had hypercholesterolemia (seven also had ischemic heart disease) and three had ischemic heart disease with normal serum cholesterol concentrations. The tartrate was given in doses of 25 mg three times daily for 2 weeks, 125 mg for the next 2 weeks, and this dosage was maintained further for 5 months in 10 patients; during the 5th month, administration of the drug was stopped in 2 patients because of toxic gastrointestinal effects. Blood samples were drawn and analyzed for serum cholesterol by paper electrophoresis [57] three times before diammonium vanado-tartrate administration, monthly during administration, and for 2 months after administration stopped. Vanadium content in the urine was detected by the colorimetric method of Rockhold and Talvitie in which vanadium forms a magenta color with p-aminodiethylaniline [58]. Blood urea, hemoglobin, lipoprotein, and urine albumin were determined before and during administration of the tartrate.

Statistical analysis indicated that there was no significant effect on serum cholesterol values [56]. Lipoprotein, blood urea, hemoglobin, and urine albumin were unchanged. Five patients had upper abdominal pain, nausea, and losses in appetite and weight. Symptoms in three of these patients improved after the doses were reduced, and, in the other two patients, the drug was stopped after 4 months. Green tongue appeared in

five patients and a sixth developed pharyngitis with marginal ulceration of the tongue. Vanadium was found in the urine of nine patients; however, no quantitative measurements were made.

Effects on serum cholesterol levels have been investigated and can be found in reviews elsewhere [59-61].

The most common route of entry for vanadium in industrial situations reported above was via the respiratory tract, although entry by the oral route could occur and lead to greenish-black discoloration of the tongue. Stokinger [62], however, noted that sodium metavanadate was absorbed through the skin of animals (unspecified) when applied as a 20% solution and acted as a primary irritant to human skin at a concentration of 10%. Ammonium metavanadate and vanadium pentoxide in 0.5 and 0.8% solutions, respectively, did not irritate the skin. His conclusions, however, were not supported by any data. No other reports of skin absorption have been found in the available literature.

Thus, in summary, the most commonly described and best documented effects of short-term exposure to vanadium, primarily to vanadium pentoxide dust, in the previous studies were respiratory tract, eye, and possible skin irritation. Major signs and symptoms demonstrated were coughing, wheezing, difficulty in breathing, bronchitis, and chest pains. A greenish-black discoloration of the tongue was reported in some of the studies, but was considered an indicator of exposure rather than a sign of intoxication. Symptoms usually ceased shortly after removal from the exposure area. No systemic, carcinogenic, mutagenic, teratogenic, or reproductive effects from vanadium exposure were indicated by the limited, often short-term, studies. Some of these studies suffered from a lack of

pertinent data, ie, on duration of exposure, on concentration of airborne vanadium, on sampling and analytical methods, and on specific forms of airborne vanadium found. Interestingly, in the boiler-cleaner studies, sulfur trioxide and dioxide were implicated as a possible cause of some of the signs or symptoms attributed to vanadium. However, since these effects have been seen in the absence of exposure to sulfur oxides, eg, in bagging operations, in crushing operations, and in experimental exposures, it seems correct to attribute the effects in the boiler studies to exposure to vanadium compounds. Possibly sulfur oxides enhanced the effects of vanadium in the boiler studies.

Epidemiologic Studies

The following studies of workers exposed for a long time indicated that exposures to vanadium caused signs and symptoms similar to those of the short-term studies described above. Again, the irritant effects were reversible on cessation of exposure. There were, however, more severe conditions reported, ie, emphysema and pneumonia, but the available data make these reports less than certain.

In 1939, Symanski [63] described vanadium poisoning in 19 vanadium plant workers exposed to vanadium pentoxide dust at unknown concentrations over a period of a few months to several years. The technical processes of producing vanadium pentoxide, pure vanadium, and ferrovanadium were described. Those parts of the production processes involving mixing, scraping, leaching, and shoveling of material produced clouds of dust. Medical procedures used by the author included medical and work histories and subjective complaints, examination of the chest, heart, and abdominal

44

organs, neurologic and radiologic examinations, routine blood and urine analyses, and sputum tests.

The medical examination showed no evidence of gastrointestinal disturbances or evidence of disease in the blood, kidneys, or nervous system, and sputum test results were negative for evidence of tuberculosis. Of the 19 workers, 18 had coughs, 13 showed reddening of the nasal mucosa (rhinitis) and surrounding tissue, 12 had wheezing, humming, or whistling sounds in the lungs, 10 had burning eyes, 9 expectorated mucus or had rhinorrhea, 7 had tightness or pain in the chest, 5 had excessive eye secretions, 4 sore throats were evident, 3 demonstrated sneezing and had radiologic expression of chronic bronchitis (only 1 worker had both simultaneously), and 2 had rhonchi, bronchitic cough, or colds. All of the workers had more than one sign or symptom. Symanski pointed out that severe chronic bronchitis might occur, perhaps progressing to bronchiectasis, with continued exposure.

Symanski [63] recommended the mechanization and enclosure of all work processes that were dusty in nature, use of dust masks, and proper training of a large number of workers so that work with vanadium would be intermittent rather than continuous. The author concluded that vanadium pentoxide dust had primarily an irritant effect on the respiratory system and conjunctiva and that there was no reason to suspect that vanadium had any adverse systemic effects on the body. There were no data presented on the concentrations of vanadium pentoxide dust produced throughout the plant.

In a later (1954) report, Symanski [64] described 17 occurrences of vanadium intoxication at the same vanadium plant, 10 of which he observed

in 1952 and 7 followups from his 1939 study [63], described above.

Technical changes had been made at the vanadium plant since 1939, including a wetting process to reduce airborne dust, which reduced the number and severity of disorders caused by vanadium pentoxide [64]. A majority (number not given) of the 10 vanadium plant workers observed in 1952 and employed for 2-3 years complained of rhinorrhea, coughing, and occasional lacrimation. Although bronchitis was diagnosed in several of the workers, all examinations, including roentgenograms, showed no irregularities and the general health of the subjects was not impaired. The seven followup workers, men 38-60 years old employed for 2-13 years at the plant, were examined for residual signs and symptoms and chronic disorders caused by vanadium pentoxide dust exposure. All seven workers had the characteristic disorders of vanadium intoxication while working in the vanadium plant, ie, irritated mucous membranes of the eyes and upper respiratory tract, discharge from the mucous membranes, head colds, sneezing and nosebleeds, sensation of pain in the pharynx, coughing with some expectoration, chest pains, and difficulty in breathing. Two workmen who had been employed for the longest periods, 9 and 13 years, were diagnosed as having emphysema, but Symanski stated that it was impossible to definitely implicate vanadic acid (vanadium pentoxide) because of the age of the men involved and "other factors" that could have contributed to this disease. However, because chronic bronchitis can lead to emphysema, the author was inclined to attribute a substantial amount of the damage to repeated inhalation of vanadium dust.

The author [64] concluded that the reduction of adverse effects on the 10 workers was because of the modification of technical procedures used

46

in the vanadium plant, and that the effects of long-term exposure in the form of emphysema on 2 of the 7 followup workers were partially from the greater amount of vanadium exposure in the early years of the plant operation. The concentrations of vanadic acid (vanadium pentoxide) to which the 17 workers were exposed were not given.

Wyers [24], in 1946, described 10 occurrences of vanadium pentoxide dust exposure observed over a 9-year period in 50-90 vanadium plant workers. Length of exposure to the vanadium pentoxide dust (10-15% vanadium pentoxide; other components unspecified) for the 10 men, 30-63 years old, ranged from 5 months to 16 years (mean of 6 years) The dusty conditions were caused by the crushing and grinding of the raw materials (all containing vanadium pentoxide) used in the plant, that is, soot from oil-burning ships, furnace residues from oil refineries, and slags from the production of ferrovanadium.

The workers' complaints included coughing in eight, difficulty in breathing in six, pain and tightness in the chests of four, sputum in three (one bloodstained), salty taste in the mouths of two, heart palpitations on exertion in one, exhaustion in one, and attacks of pleurisy in two [24]. Medical examination of the workers showed four with rales and four with rhonchi, four with lung reticulations in roentgenograms, three with accentuated pulmonary second sound, two with linear striations in lung roentgenograms, tremors in the hands of two men, emphysematous-type chest in two (one had emphysema), and two with greenish-black tongues (an indicator of exposure rather than intoxication, according to Wyers). Medical examination also showed one instance each of left ventricle enlargement, pale skin, bronchitis in a worker who had had the condition

47

prior to working in the vanadium plant, and prolonged expiratory sounds. Three workers developed pneumonia and one died. All the workers had more than one sign or symptom. While the author believed that increased blood pressure was an effect of vanadium intoxication, it could not be ascertained that blood pressure was truly elevated in the 10 workers because of the lack of preexposure blood pressure data.

Wyers [24] suggested that colds and pneumonia were more frequent in vanadium workers than in the general public; however, no data were provided to substantiate this. He also did not report concentrations of vanadium pentoxide dust at which the 10 workers were exposed or provide any quantitative data correlating exposure and effect.

In 1950, Sjoberg [26] published the findings of his 2-year observations of 36 vanadium production workers, ages 20-59 years, who had inhaled 0.03-5.58 mg/cu m of vanadium pentoxide dust. Only 9 of the 36 men had any previous exposure to vanadium. The plant received slag containing what was stated to be FeV204 and vanadium trioxide, which was then crushed, pulverized, and mixed with soda, probably soda ash. These steps were followed by warm water extraction, precipitation, and drying of the vanadium pentoxide to yield a brownish-red powder containing 85-90% vanadium pentoxide. The bulk of vanadium pentoxide was packaged in paper bags and delivered to manufacturers of ferrovanadium. Some of the vanadium pentoxide was used as a catalyst in a sulfuric acid production plant. When the vanadium production plant was first opened, all workers were constantly exposed to the dusts at high concentrations; however, better engineering controls were installed during the following years, and, consequently, dust concentrations were greatly reduced. The exception to

this was at the catalyst plant where there still were dust problems. Dust masks and pressure-air masks were distributed to all employees handling vanadium-containing material at about the same time engineering controls were installed in the plant.

Dust was measured with a konimeter, and particles were counted using a microscope [26]. Detailed medical examinations were conducted at the beginning and at the end of the observation period (most of the clinical reports covered a 1-year period). The tests included chest roentgenograms; spirometric, laryngoscopic, and bronchoscopic examinations of the respiratory tract (the same otolaryngologist examined the men throughout the observation period); hemoglobin measurements, erythrocyte, leukocyte, and eosinophil counts; erythrocyte sedimentation rate; serum bilirubin content; serum alkaline phosphatase value; thymol turbidity values; formol-gel test; Takata's serum test (for liver function); vanadium content of the blood and urine (by optical spectral analysis); and urine analyses for albumin, specific gravity, urobilin, and sediment. Electrocardiographic examinations were conducted at the beginning of the observation period, once after that, and after exertion (running up four flights of stairs) in 31 of the men. Patch tests using a 2% sodium metavanadate solution and a skin biopsy from the test site were performed. A group of 703 workers from mines and sawmills, who had presumably only been exposed to inert dust, were used as controls. Statistical analyses were performed with the use of the Student's t-test.

Dust concentrations in the air of the plant ranged from 0.6 to 87 mg/cu m, with the vanadium pentoxide concentrations in three areas of the plant calculated at 0.03-5.58 mg/cu m [26]. The particle count varied from

49

6 to 140/ml, of which 22% were less than 8 μm and 39% less than 12 μm. Six men had slight conjunctivitis. Nasal mucous membrane inflammation incidence was high at the first examination. Dryness or smarting of the nose, blocking of nasal passages, or sores in the nostrils were observed. All of the incidences were generally moderate, and no perforations of the nose were noted. The proportion of vanadium workers with normal nasal conditions was less than that in the controls (61% versus 80%). Complaints of dry, irritated, or painful throat were reported by the vanadium workers. Normal conditions of the throat were observed in 42% of the vanadium workers versus 64% of the controls. The larynx was normal in 42% of the vanadium workers versus 88% of the controls. Hoarseness was an occasional complaint, but no severe changes of the throat were observed. Laryngoscopic examinations of the trachea showed that both controls and vanadium workers had about the same percent of normal conditions.

At the last examination of the upper respiratory tract, the incidence of normal conditions was less than at the first examination for the nose (50% versus 61%), throat (10% versus 42%), and larynx (27% versus 42%). Of the noses examined, a majority showed chronic increased thickness and edema of the nasal mucosa, several of which were described as allergic in type. There was only slight irritation to the larynx and throat with some atrophic changes.

Bronchitis was common during the period of exposure and was far more common in the exposed men than in the control group; the average length of incapacity from bronchitis was 13 days [26]. Of the 36 men examined, 31 had wheezing in the chest, 27 had shortness of breath, 22 had dry coughing, and 14 had productive coughing. Some complained of a violent choking

50

cough, especially at night. There was no blood-stained sputum. Rales were frequently heard on auscultation, but bronchoscopy performed on four workers showed three with no more than slight inflammatory changes and one with intensely reddened tracheal mucosa.

Acute changes occurred in the lungs of five men, pneumonia in one and bronchopneumonia in four; three of these men had been heavily exposed to dust at work [26]. Two other men who had left the plant also had bronchopneumonia. These were considered as probable incidences of pneumonitis caused by vanadium pentoxide dust and bacteria. An allergic factor also may have been involved, as one of the five workers had eczematous lesions and reacted positively to a vanadium patch test. No signs of emphysema or fibrosis of the lungs were demonstrated either on radiographic or spirometric examination. Because of the short observation period, Sjoberg didn't rule out possible lung changes, and he recommended followup examinations to answer that question.

Skin lesions were found on several workers during the observation period, particularly during the 1st year of plant operation; these included eruptions primarily on the face and hands [26]. Only one man demonstrated allergy by reacting positively to patch tests given at the beginning and end of the observation period. Microscopic examination of a biopsy specimen from the site of this worker's allergic lesions verified an eczematous reaction. The alkaline soda used in the factory may have been responsible for some of the skin lesions.

The number of positive urobilin reactions in the vanadium workers was no higher than in the controls [26]. Serum bilirubin and alkaline phosphatase values were normal. Takata's serum test and the formol-gel

51

test were negative. The thymol turbidity test mean values were slightly higher than normal both at the beginning and end of the observation period. In the absence of further evidence of liver lesions, a causal relationship with exposure to vanadium seems unlikely.

Greenish-black, discolored tongues were absent, as were intestinal symptoms [26]. No severe weight loss was observed; on the contrary, most workers gained weight. Fever was present only in the five men with bronchopneumonia or pneumonia.

Electrocardiographic examinations showed extra systoles in three workers and transient coronary insufficiency in one man [26]. Palpitations of the heart on exertion and sometimes at rest were present in some cases. According to Sjoberg, it could neither be ruled out nor established that the observed abnormal changes in the heart might have been associated with exposure to vanadium. Accentuated pulmonary second sound and raised blood pressures were not found during the observation period. Hemoglobin values and erythrocyte counts decreased slightly, especially in "regular" employees of the plant, but these findings were considered to be within normal limits. No tendency toward decreased leukocyte counts was present, and increased eosinophil counts were observed only in one man who showed a positive allergy to vanadium. No erythrocytes containing basophilic granules (stippled cells) were observed. The erythrocyte sedimentation rate was slightly increased, probably caused by an increased tendency toward infection in the respiratory tract.

Weakness and fatigue were common symptoms after heavy exposure to dust [26]. Giddiness was observed in a few workers, but this was vague and unspecific and was not attributed to vanadium, since work histories and

medical findings in these men indicated other functional causes. Tremors of the right hand and foot were found in one man, appearing 1 month after he had had pneumonia; the trembling disappeared in 2 weeks. Pupillary and patellar reflexes and smell and taste senses were normal. Symptoms of a neurasthenic character, such as tiredness, anxiety, and sleeplessness, were found but were attributed to aggravated respiratory symptoms or shift work.

The urine tests showed no signs of disease of the urinary tract that could have been caused by vanadium [26]. Vanadium content in the ash of the urine from workers ranged from less than 0.0003% to 0.002%. Controls had 0.0003% or less vanadium in the ash of the urine. Vanadium content in the ash of the blood ranged from less than 0.0003% to 0.001% in the workers. Controls had less than 0.0003% vanadium in the ash of the blood. The tests showed a greater amount of vanadium in the ash of the blood and urine of the exposed workers as compared with the controls and showed that vanadium was absorbed and then excreted. However, no relationship was found between the vanadium content of the urine or blood and occupational exposure to dust.

In 1956, Sjoberg [65] described a followup investigation from his 1950 report [26] on 6 of the 36 workers with the most marked respiratory symptoms. All six of the men continued to work full time in the vanadium mills. The examination of the six men was conducted 8 years after the beginning of the initial observation period and 5 years after their last spirometric tests. Subjective complaints of bronchitis with rhonchi, resembling asthma, and bouts of labored breathing and fatigue were reported. Two men were found to have slight-to-moderate bronchitis, verified on bronchoscopy. No evidence of pneumoconiosis, emphysema, or

other chronic disease related to employment was found. The mucous membranes of the respiratory tract showed no abnormalities; minor changes in electrocardiograms and poor performances on muscular tests were attributed to increasing age.

In 1968, Tebrock and Machle [36] described the exposure of plant workers during a 5-year period to europium-activated yttrium orthovanadate, a vanadium-bearing phosphor used in color television picture tubes. Exposures were studied in three factories, one engaged in the manufacture of the phosphor and its reclamation, and two involved with the finished dry phosphor and its application to the inside of the color television tubes, in addition to some reclamation processes. The population at risk averaged 3,000 people with 18,000 man-years of exposure since operations began in 1963. The most frequent exposure was to the finished product, with weekly brief exposures to the raw materials, the most important being vanadium pentoxide. No effects were observed that could be attributed to yttrium or europium, so all environmental data were based on vanadium (expressed as vanadium pentoxide) alone.

Seventy-five air samples, taken over 102 weeks in the worst exposure areas of the three factories, were collected on membrane filters and then analyzed for vanadium using an undescribed method. Analysis of the urine and blood for vanadium content, blood pressure measurements, pulmonary function tests, and 2,000 chest roentgenograms on 250 workers with the highest exposure possibilities, taken over an 8-year span from 1960 to 1968, were completed. Concentrations of vanadium in the air ranged from 0.02 to 3.2 mg V205/cu m with a mean value of 0.844 mg/cu m; particle sizes ranged from less than 1 to 10 μm with 90% being less than 1.5 μm in size.

The vanadium content of the urine was never more than 0.05 mg/liter, and no blood abnormalities, elevated blood pressures, or changes in pulmonary function were noted. However, men working with vanadium pentoxide and not using proper respiratory protection occasionally had increased blood pressures that returned to normal quickly when exposure was reduced. The chest roentgenograms showed no changes that could be related to dust exposure, except for those in six men who had varying degrees of reticulation or increased bronchovascular markings at times. However, these varied from year to year, so no trend was discernible.

Clinical observations by Tebrock and Machle [36] showed that the most common effects in those exposed were conjunctivitis, tracheobronchitis, and contact dermatitis. Other signs and symptoms reported were greenish-colored tongue, irritated nasal passage with mucous discharge, irritated respiratory tract with bronchitis and bronchospasm (often enhanced on repeated exposure), chest pain, difficulty in breathing, coughing spasm, and occasional palpitations. Allergy was also a factor as some of the workers reacted positively to patch tests with a sodium metavanadate solution. No permanent damage or systemic effects were found. The authors concluded that the effects of exposure to the vanadium phosphor were mainly of an acute nature and reversible on cessation of exposure, but that some chronic changes in the mucous membranes were found, and that the incorporation of vanadium as the orthovanadate into the crystalline lattice of the phosphor apparently resulted in the formation of a compound of much lower toxicity than that of vanadium pentoxide alone. No data were presented to compare the toxicity of the phosphor to that of vanadium pentoxide alone. The authors recommended studying the exposed workers for

possible delayed effects and also described engineering control measures to be used to lower the exposure concentration below the existing TLV [66] of 0.5 mg/cu m for vanadium.

Since only 67 of 75 air samples were reported, it is not possible to verify the mean value for vanadium of 0.844 mg/cu m quoted by the authors [36]. Methods of sampling and analysis were not given in detail.

Lewis [25], in 1959, studied the effects of vanadium exposure on 24 men, 38-60 years old, who had worked with vanadium at two locations (Colorado and Ohio) for at least 6 months (average employment 2.5 years) and presumably had not been exposed to any other metals. All but one vanadium concentration were less than 0.38 mg/cu m. Forty-five men of the same age range, economic status, and job-related activities as the vanadium workers were selected at random as controls from an area near the two plants (22 in one location, 23 in the other). Each of the men received a complete physical examination, which included medical and work histories, electrocardiogram, urinalyses (routine and for vanadium content), hematocrit determination, and serum cholesterol analysis. A standardized history form was used, and all histories and physical examinations were completed by one observer. Air samples were taken in both plants by collecting dusts on millipore filters using calibrated air pumps. Analysis for vanadium in both the dust and urine was carried out by the colorimetric method of Talvitie [55] using 8-quinolinol. Particle size measurements were also performed on each dust sample.

Significant differences were found by Lewis [25] in the symptoms and physical findings of the exposed workers and controls. Eye, nose, and throat irritation, productive cough, and wheezing were the most significant

56

symptoms, while congestion of the pharynx, green tongue, rales, and rhonchi were the most significant physical findings. In almost one-half of the workers who had a cough, it was of a productive nature. The author stated that the signs of bronchospasm from inhalation of vanadium could persist for 2-3 days after cessation of exposure and could mean that particulate vanadium was present in the respiratory tract during the same time period. Another possibility was that the smooth muscle contraction was maintained by mechanisms other than direct chemical irritation. The color of the tongue, of no toxicologic importance but a sign of vanadium exposure, varied from pale green to dark greenish-black depending on the atmospheric concentrations of the vanadium compounds (vanadates and vanadium pentoxide). The mean concentrations of vanadium found in the urine of the controls and of the exposed workers were 11.6 and 46.7 μg/liter, respectively. Air analyses showed that the maximum air concentration was 0.925 mg/cu m of vanadium (as vanadium pentoxide), and the remaining concentrations were less than 0.38 mg/cu m (range 0.38-0.018 mg/cu m) with 97% of the particles less than 5 μm in size. There were no significant differences in the results of the electrocardiograms, hematocrits, and clinical urinalyses of the exposed and control groups.

Lewis [25], comparing his study with four others [24,26,63,67], considered the reasons for the differences noted, and concluded that there was no evidence of chronic intoxication or injury attributable to vanadium exposure. However, in view of vanadium's known respiratory effects, he suggested it was important to exclude persons with arrested tuberculosis or chronic lung diseases from exposure to vanadium dust.

In 1955, Vintinner et al [67] conducted environmental and medical studies of 78 workers engaged in the processing of vanadium-bearing ore and of 37 control workers. The controls (median age 25 years) were employed by the same company in occupations where there was no exposure to vanadium. Half of the 78 workers (median age 27 years) were exposed to dust from the ore before roasting (inactive ore), and the other half (median age 32 years) were exposed to vanadium ore after roasting (active ore) and to the final product of vanadium pentoxide. All dust particles were less than 5 μm in diameter. About two-thirds of the men in the exposed and control groups had been employed less than 3 years. In all three work areas, a total of 105 air samples and 15 material- and settled-dust samples were collected and analyzed for vanadium concentration; 20 air samples also were taken to determine the sulfur dioxide content of the air. Air was sampled at each work location at random times on different days in each plant over a period of 3 weeks. Duration of sampling was 20-40 minutes in vanadium exposure areas and about 2 hours in control group workplaces. Occupational, personal, and medical histories, as well as chest roentgenograms and analyses of urine and blood samples, were conducted. The vanadium content of all air, blood, and urine samples was determined by the method of Talvitie [55] using 8-quinolinol.

Sulfur dioxide concentrations ranged from nondetectable to 2.0 ppm, an insufficient amount to cause irritation according to the author [67]. Air concentrations of vanadium were 0.01-2.12 mg/cu m in the inactive ore area, and 0.77-58.8 mg/cu m (average 12.77 mg/cu m) and 0.02-1.10 mg/cu m in the active ore areas.

Exposed workers compared to controls had significantly higher incidences of several signs and symptoms indicative of irritation to the upper respiratory tract and eyes. Numerous other signs and symptoms were reported in the exposed group, such as palpitations on exertion, night sweats, pneumonia, tiredness, and increased corneal vascularization. The authors indicated that these Peruvian workers had an "elevated" use of alcohol, tobacco, and coca. In addition, the mines were located at altitudes of about 14,000 and 15,000 feet, so it is conceivable that drug use and hypoxia contributed to the observed effects; however, drug use and working and living altitudes did not differ significantly between workers and controls. The exposed workers showed no significant differences from the controls in the laboratory tests, except for the vanadium content of the urine. The highest values in the urine of the control group, inactive ore group, and active ore group were 0.060, 0.110, and 0.298 mg/liter, respectively.

Animal Toxicity

The animal experiments described in the following discussion were selected to reduce repetition of the effects described in the previous sections. Included in this section are studies that offer evidence as to the mode of toxicity of vanadium and its compounds and other effects that have not been demonstrated in humans.

Roshchin [41,68] carried out three series of experiments on the long-term effects of vanadium aerosol on white rats of unreported age, sex, and weight. In the first series, 20 white rats were enclosed in a chamber (not described) where they inhaled a condensation aerosol of vanadium pentoxide at a concentration of 3-5 mg/cu m for 2 hours every other day for 3 months.

The aerosol was obtained by heating vanadium pentoxide in the flame of a Volta arc. In the second series, 15 white rats inhaled an aerosol of vanadium pentoxide (generated by grinding) at a concentration of 10-30 mg/cu m for 1 hour/day for 4 months. In the third series, 15 white rats inhaled ferrovanadium dust at a concentration of 1,000-2,000 mg/cu m of air for 1 hour every other day for 2 months.

On extended inhalation of vanadium pentoxide, apparently in the first two series, the rats became emaciated and passive, and there was a discharge from the nose, said to be hemorrhagic, but probably a porphyrin from the Harderian gland [41,68]. The rats exposed to ferrovanadium dust had no outward signs of poisoning during the 2-month period. The body weights and behavior of these animals did not differ from those of the controls. Microscopic examination of tissues of all the rats killed after the termination of the experiment showed only changes in the lungs, which were signs of marked irritation of the respiratory mucosa and injury to the lining of the blood vessels, resulting in stasis and increased permeability of the capillaries, producing perivascular edema and hemorrhages. The investigator did not report whether these lung changes were from ferrovanadium, vanadium pentoxide, or both. Also a spastic effect on the smooth muscle of the bronchi (bronchospasm) was evident, which may explain the development of an asthmatic type of bronchitis and of expiratory difficulty observed in the case of short-term poisoning. Roshchin mentioned the effects of absorption of vanadium, ie, high concentrations led to focal hemorrhages or congestion of the vessels of the internal organs and the brain, and that these effects may also have explained the neurologic signs, toxic nephritis, and the disorders (unspecified) of

60

protein metabolism encountered in his previously performed short-term studies [41,68]. There were several weaknesses in this report. The number of rats that had lung changes was not given, and although controls were mentioned, no other facts about them were presented. No statistical data were available and the analytical method for determining the air concentrations of vanadium was not given. Some of the changes observed, such as hemorrhages, may have been agonal rather than a reflection of vanadium toxicity.

Roshchin et al [35], in 1965, studied the toxic effects of vanadium trioxide dust inhaled 2 hours/day for 8-12 months on 18 male rabbits weighing between 2.7 and 3.3 kg. There were nine control animals. Of the 18 experimental rabbits, 13 were exposed for 2 hours daily in a chamber in which the vanadium trioxide dust concentration was 40-75 mg/cu m, and 5 received vanadium metal at a dose of 5 mg/kg daily by mouth for 5.5 months. After 1.5 months, attacks of difficult and rapid breathing with nasal discharge were observed in five rabbits that inhaled vanadium trioxide, but the animals usually returned to normal within 4-5 hours after their removal from the chamber. However, these rabbits died at the height of one of the attacks. At the end of the testing period, the surviving experimental rabbits showed reductions in body weight (4.6% loss; controls gained 12.3%), leukocyte count (in spite of normal erythrocyte count), hemoglobin value (fell from 75 to 67.8%), vitamin C content of the blood, serum protein sulfhydryl group value, and tissue respiration activity in liver and brain tissue. Blood cholinesterase activity increased by an average of 25%. No changes were noted in the rabbits' behavior, erythrocyte count, total protein content, ratio of protein fractions of blood serum, or

respiratory quotient. The author stated that an allergic effect of vanadium trioxide must be considered, especially with the occurrence of increased cholinesterase activity in animals; however, he did not elaborate on the connection between blood cholinesterase changes and allergy.

A characteristic feature of vanadium trioxide dust inhalation was the irritant effect [35]. Attacks of bronchial asthma from vanadium trioxide were said to have occurred in experimental animals, and the authors believed this showed that vanadium trioxide had an allergenic effect.

In 1966, Roshchin et al [69] studied the effects of ferrovanadium and vanadium carbide dusts inhaled at concentrations of 40-80 mg/cu m by white rats and rabbits of unstated age, sex and weight. Twelve rats inhaled ferrovanadium dust every day for 2 months, while 12 rats and 8 rabbits inhaled vanadium carbide every day for 9 months. The duration of each day's exposure was not given. Particle sizes ranged from 69 to 74% of less than 2 μm, and from 85 to 93% of less than 5 μm. Biochemical studies of the blood were conducted during the two experimental periods. At the end of the experiment, the animals were killed and their organs were examined for abnormalities. One group of 10 rats and 10 rabbits was used as controls, apparently for all experiments.

The rats and rabbits showed what the authors interpreted to be only chronic conditions, such as catarrhal bronchitis, and moderate but widespread proliferative interstitial changes resulting in sclerosis and perivascular edema [69]. Roshchin et al noted that biochemical changes from chronic exposure to dusts of vanadium (unspecified form) and ferrovanadium were similar in nature, but they added that these were unstable, less clearly expressed, and statistically unreliable. The

interstitial proliferative process in the lungs was more evident in rats than in rabbits. However, the degree of difference or the compounds involved were not presented. The authors concluded that the effect of vanadium on animals was the same, whether bound to carbon (vanadium carbide) or to iron (ferrovanadium and alloys). Overall, the paper is unsatisfactory from the standpoint of lack of data and clarity about details.

There appeared to be no statistically significant changes in the rats after inhalation of ferrovanadium, based on the data and statements as reported by Roshchin et al [69]. Roshchin et al did not give any indication of alveolar damage from ferrovanadium. They stated that sclerosis occurred, but not to any great extent. The impression is that the effects of ferrovanadium are reversible on cessation of exposure.

In 1966, Pazynich [70] performed two experiments to study the responses of rats to inhaled vanadium pentoxide at several concentrations. In the first experiment, lasting 70 days, 33 white male rats weighing 110-130 g were divided into 2 experimental groups and 1 control group; 11 rats were in each group. Groups 1 and 2 were exposed continuously for 24 hours/day, 7 days/week, to vanadium pentoxide at concentrations, determined colorimetrically, of 0.027 and 0.002 mg/cu m, respectively; the controls were free from exposure.

All groups of rats were active and gained body weight [70]. In group 1, during the experiment, the motor chronaxy of the extensor muscles decreased, the chronaxy of the flexor muscles increased so that the normal ratio was altered, which the author interpreted as a change in the CNS caused by the highest concentration (0.027 mg/cu m). The percentage of

63

leukocytes with altered nuclei increased, and the oxyhemoglobin content in the venous blood was reduced. Measurements taken 20 days after the experiment ended were the same as the initial values. Blood cholinesterase activity in group 1 decreased during the experimental period and 90 days thereafter, but there were no changes in groups 2 and 3. The total protein of the blood serum increased in groups 2 and 3; however, it was reduced in group 1. Protein fractions of blood serum showed increased gamma globulins and decreased beta globulins in group 1. The author reported that, 20 days after the experiment, no significant differences were noted in protein fractions of groups 2 and 3, although no initial values or experimental values were reported for these groups. Liver tissue of group 1 placed in a Warburg apparatus absorbed 24% more oxygen than controls (P<0.05). There were no reliable differences in groups 2 and 3. Microscopic study of tissues showed that only group 1 had abnormal changes. The lungs showed vascular congestion, focal hemorrhages, and indications of bronchitis. The liver displayed acute vascular congestion in the central veins, accumulation of leukocytes in portal areas, and granular dystrophy of the hepatic cells. The kidneys showed granular dystrophy and some necrosis of the epithelium of the convoluted tubules, and the myocardium had congested blood vessels surrounded by focal hemorrhages. Rats that inhaled vanadium pentoxide at a concentration of 0.002 mg/cu m (0.001 mg/cu m as vanadium) for 70 days showed no toxicologic changes.

In the second experiment, lasting 40 days, a group of 10 young male white rats of unspecified weight was exposed continuously for 24 hours/day, 7 days/week, to vanadium pentoxide at 0.006 mg/cu m, and an identical control group was unexposed [70]. Chronaxy of the antagonist muscles in

the rear leg, leukocytes with altered nuclei, plus the general condition and weight changes of the rats were all evaluated using the same techniques as in the first experiment.

After 30 days, reliable changes ($P < 0.05$) occurred in the ratio of the chronaxy of antagonist muscles in the experimental rat group versus those of controls [70]. On the 6th week of exposure, all rats were given water alone. After both groups were not fed for 3.5 days, rats in the experimental group showed significant ($P < 0.001$) changes in the relationship of chronaxy of extensors to flexors in the rear leg; it was the reverse of the normal (index--0.92). There was a reliable increase by a factor of 4.83 in abnormal nuclei of leukocytes ($P < 0.005$) in exposed rats in comparison with the controls. The animals' weights and general conditions were not reported.

Pazynich [70] concluded from the two experiments that vanadium pentoxide inhaled continuously at a concentration of 0.027 mg/cu m for 70 days significantly affected the rats and produced morphologic lesions in the liver, kidneys, and lungs; that a concentration of 0.006 mg/cu m vanadium pentoxide inhaled for 40 days influenced the rats only after the animals had been starved for 3.5 days; that vanadium pentoxide inhaled continuously for 70 days at a concentration of 0.002 mg/cu m had no effect on the rats, and that, based on these findings, the daily mean maximum permissible concentration of vanadium pentoxide in the atmosphere (probably for community air) should be set at 0.002 mg/cu m. He did not present his reasons for assuming that rats and humans were equally susceptible to vanadium poisoning.

In 1967, Kanisawa and Schroeder [71] studied the incidences of tumors in mice of both sexes given vanadyl sulfate during their lifetimes. Random-bred white Swiss mice, of the Charles River strain, were given from 20-22 days of age until death, doubly deionized water containing essential trace metals: manganese (10 μg/ml), chromium (1 μg/ml), cobalt (1 μg/ml), copper (5 μg/ml), zinc (50 μg/ml), and molybdenum (1 μg/ml) as the acetate, citrate, or molybdate. Groups of 23-71 of each sex, randomly selected from the litters, were given additional elements at 5 μg of metal/ml of water, eg, vanadyl sulfate. The diet contained 3.2 μg of vanadium/g of feed. Dead mice were weighed and 542 were necropsied. Tissues of 433, considered abnormal, were fixed in Bouin's solution, sectioned, and stained with hematoxylin and eosin. Microscopic examinations were made on the heart, lungs, kidneys, liver, spleen, and any other organs that appeared abnormal or had a visible tumor. The data presented only represented tumors visible under a magnifying lens. Numerical data were treated by chi-square analysis and by Student's t-test. Pretumorous lesions of the liver and lungs were designated as growths of atypical parenchymal cells lacking in proper stroma, which replaced normal epithelial cells in the bronchi, alveoli, or hepatic sinusoids. Benign tumors were considered to be autonomous growths of well-differentiated cells that might be slightly atypical, but which did not metastasize to other organs or in the organ of origin. Sections of tissue were analyzed microscopically depending on the presence of cell clusters in the lungs and liver appearing pretumorous; of circumscribed benign adenomas, carcinomas, sarcomas, or lymphomas; leukemias; and other tumors benign and malignant in lungs, liver, mammary glands, and other locations. As no significant differences appeared

66

between incidences of tumors in the two sexes, they were grouped together.

Of 170 controls that died within a 33-month period, 40 had benign tumors and 15 had malignant tumors, at a total tumor incidence of 32.4% [71]. No autopsies were performed on 28 of the 170 controls. Twenty-nine of the 40 benign tumors were adenomas, 20 of the lungs, 7 of the liver, and 2 of the mammary glands; the remaining 11 benign tumors included 3 lymphomas and 8 specified as "other." Of the 15 malignant tumors, 6 were found in the lungs and 5 in the mammary glands, and 2 were classified as leukemia and lymphoma. Of 47 vanadium-fed mice that died, 6 had benign tumors and 9 had malignant tumors, at a total tumor incidence of 32%; 5 of the 47 were not autopsied. Five of the six benign tumors were adenomas, four of the lungs, and one of the liver, and the remaining one being specified as "other." Of the nine malignant tumors, four were of the lungs, one of the mammary glands, three were classified as leukemia, and one as "other." The mice receiving vanadyl sulfate did not exhibit a significantly different incidence of tumors based on the total number of animals autopsied at the end of 33 months. The highest death rates for the autopsied mice occurred during 15-24 months of age, and, at this time, 113 controls and 34 vanadium-fed mice were autopsied and showed 39 (34.5%) and 11 tumors (32.4%), respectively. Examined sections of 141 controls showed 62 with pretumorous lesions and 55 with tumors, 15 of the 55 being malignant. Of 38 examined sections in the vanadium group, 16 had pretumorous lesions and 15 had tumors, 9 of these malignant. There was no weight difference between vanadium-fed mice and controls at all ages.

No evidence was presented in this study which suggested that vanadium influenced the incidence of tumors [71]. The diet, however, was

67

unavoidably high in vanadium, although fairly low in other metals studied, causing the investigators to question the significance of the data. If the dietary vanadium was introduced mostly from milling machinery containing steel, it seems probable that the resultant vanadium would not be readily absorbed. The intake of water was calculated roughly at 7 ml/100 g of body weight/day, which means about 35 μg of vanadium/100 g/day or about 13 mg/100 g/year were consumed. The ingestion of 6 g of food/100 g of body weight/day would supply an additional 19.2 μg of vanadium/100 g of body weight/day. The yearly total for both food and water, then, would amount to 19.8 mg of vanadium/100 g of body weight. Kanisawa and Schroeder [71] estimated that this dietary intake was about 17-29 times that measured for a 70-kg man in normal vanadium consumption.

Other studies by Schroeder and coworkers [72-74] using essentially the same procedures involving mice and rats showed the same results as the above study [71], ie, vanadium was not found to be carcinogenic at a level of 5 ppm (5 μg/ml), as vanadyl sulfate, in drinking water after lifetime ingestion.

Franke and Moxon [75], in 1937, studied the toxic responses and hemoglobin values in rats fed vanadium as sodium metavanadate. Two groups of 10 young male and female albino rats (Wistar Institute strain), each appearing to be about 30-40 g by the authors' growth curves, were given 25 or 50 ppm, respectively, of vanadium as sodium metavanadate in special wheat diets for 100 days. Two control groups of 10 rats each were given the same diet without vanadium. The rats were kept in individual draw cages and weighed at 5-day intervals throughout the experiment. Hemoglobin determinations were made on each rat on the 1st day and 6-10 times during

68

the course of the experiment. Blood was drawn from the tip of the tail and hemoglobin values were determined by the method of Franke and Potter [76]. On the 100th day, the rats were killed and examined for gross lesions.

Franke and Moxon [75] found vanadium to be slightly toxic when fed to rats at 25 ppm, in that the growth rate was less than that of controls, although the treated rats ate more. Vanadium was distinctly toxic at 50 ppm, at which level diarrhea occurred. However, the ingestion of sodium metavanadate had no definite effect on the hemoglobin values of the rats. Macroscopic necropsies were performed but not reported. Longer periods of feeding would have increased the value of this study, as would more information about the possible toxic effects observed.

Romoser et al [77], in 1961, studied the toxicity of vanadium as calcium vanadate in growing chicks. Phosphate supplements containing vanadium can be found in rocks and colloidal clays and could possibly be used as animal feed; thus, three experiments were used to determine the effects of vanadium on the performance of the growing chick. In the first experiment, four replicate groups of 13 male chicks, housed in brooders, were fed a basal ration (already containing 3 ppm of vanadium) with 40-600 ppm of vanadium added for 11-32 days. In the second and third experiments, the authors used three replicate groups of 25 male Vantress x Arbor Acre crossbred broilers housed in floor pens. The second experiment entailed the use of a commercial broiler starter ration with 10-40 ppm of vanadium added for 7-28 days. In the third experiment, the authors fed chicks the same basal diet as in the first experiment but with 21-42 ppm of vanadium added to the diet for 9-30 days. All experiments had control groups containing the same number of chicks as the vanadium group that were fed

diets without added vanadium. The rations and water were consumed at will and body weight gains and feed-conversion measurements were made at the end of each experiment period.

In the first experiment, 40 ppm of vanadium (lowest concentration added) depressed the rate of weight gain and efficiency of feed utilization of the chicks [77]. All vanadium concentrations less than 200 ppm depressed growth rates and efficiency of feed utilization, while at greater than 200 ppm, all of the chicks died by the end of the experimental period (11-32 days). In the second and third experiments, the authors found that vanadium at concentrations up to 20 ppm could be tolerated, but, at 30-42 ppm, progressively greater effects were obtained (lowered rate of weight gain and efficiency in the feed utilization). Growth was significantly (P=0.05) depressed from the addition of 30 ppm of vanadium to the basal ration, and, at 40 ppm, vanadium feed conversion was also significantly depressed.

Romoser et al [77] suggested that the endogenous vanadium content of rock phosphate supplements be below a concentration that would supply less than 30 ppm to a practical diet designed for broiler strain chickens; also, that the vanadium concentration in the rations should be below 3 ppm to protect the health of chicks, based on the three experiments.

In 1936, Franke and Moxon [78] determined the minimum fatal doses of vanadium as sodium metavanadate in 46 young Wistar strain rats of unspecified sex weighing 125-175 g. The vanadium was injected intraperitoneally (ip) and a wide range of doses (4.0-40.0 mg/kg) was used to determine the minimum fatal dose, defined as the dose that would kill at least 75% of the animals within 48 hours. The rats which were administered

70

vanadium at large doses usually died of asphyxiation, while rats receiving smaller doses became comatose prior to death. The minimum fatal dose range was 4.0-5.0 mg/kg.

In 1953, Dalhamn et al [79] described the toxic effects of vanadium (as ammonium metavanadate) on 16 white mice, its effect on the blood pressure and respiration of 12 rabbits and 4 cats, and the use of dimercaprol (BAL) as an antidote for vanadium intoxication. Sex, age, strain, or weight information were not given for the experimental animals. Groups of 16 mice were injected subcutaneously with vanadium and 8 of these were immediately injected ip with BAL at 40 mg/kg. Small unspecified doses of ammonium metavanadate were given at first, then increased until the groups in the two series showed 100% mortality at 10 days after dosing.

A second experiment was conducted to test the effects of vanadium on blood pressure and respiration, both alone and in combination with BAL in the 12 rabbits and 4 cats [79].

In mice, the LD50 for vanadium alone was 20.4 mg/kg and 21.9 mg/kg with BAL. All eight mice survived when only BAL was injected by vein at a dose of 40 mg/kg. Intravenous injections of vanadium at doses of 0.2 or 0.4 mg/kg reduced the arterial blood pressure and increased the respiratory frequency, while reducing the amplitude, in the rabbits and cats. When BAL at doses of 25-40 mg/kg was injected before vanadium at doses of 0.2 or 0.4 mg/kg, there was a rise in arterial blood pressure instead of a fall. The respiratory effects on rabbits appeared to have been unchanged by BAL, while in cats, similar results or just a slight change in respiration were seen. There were no controls and no details were given as to what other toxic effects the injections of vanadium and BAL produced.

71

Biochemical and pharmacologic effects of vanadium, to the extent now understood, seem not to contribute to the derivation of an occupational health standard, and are not reviewed here.

Other reviews [59-61] have suggested that vanadium can inhibit synthesis of cholesterol and other lipids, activities of coenzymes A and Q, and several enzymes.

Correlation of Exposure and Effect

Exposure to vanadium and its compounds occurs primarily by inhalation or by contact with the skin or eyes. Human response to inhalation of vanadium compounds has been well documented and includes acute upper respiratory irritation with mucous discharge, and lower respiratory tract irritation with bronchitis [22,23,36,63,65], bronchospasm [19,25,36], and chest pain [24,30,36,63,64]. Other effects include discoloration of the tongue [20,24,25,28,30,34,36,56], contact dermatitis [19,23,26,30,36], and conjunctivitis [17,19,20,23,25,26,36,63,64,67]. Acute respiratory irritation has resulted from inhalation of vanadium-containing dusts and fumes at reported concentrations of 0.1-85 mg/cu m. At the higher concentrations in this range, irritation has been more severe and has almost always included the eyes, nose, throat, and bronchi.

Employees wearing filter masks and working at airborne vanadium pentoxide concentrations of 17.2-58.6 mg/cu m all experienced chest pains and coughing, sometimes spasmodic or productive [28]. Lower concentrations of sodium metavanadate, ammonium metavanadate, pure vanadium pentoxide, and vanadium ores, ranging from 3.6 to 25.1 mg/cu m, also produced respiratory tract irritation with coughing, sneezing, and minor nosebleeds [17]. When

72

exposed to europium-activated yttrium orthovanadate at an average concentration of 0.844 mg/cu m (range 0.2-3.2 mg/cu m), all of the well-known signs and symptoms of vanadium irritation were seen, though the most prominent respiratory effects observed were inflammation of the trachea and bronchi [36].

At concentrations of 1.0 mg/cu m or below, complaints were limited to coughing and throat irritation, again becoming less intense as air concentrations decreased [32]. Controlled exposure of humans to pure vanadium pentoxide at 1.0 mg/cu m produced persistent coughing, lasting 8 days, but no other signs of irritation [32]. In 18 workers exposed to submicron particles of vanadium pentoxide and ammonium metavanadate at an average concentration of 0.25 mg/cu m (range 0.08-0.76 mg/cu m), throat irritation and slight coughing were periodically observed [34]. Lewis [25], studying 24 workers exposed to vanadium pentoxide and vanadates at concentrations of 0.02-0.38 mg/cu m at 6 locations and 0.92 mg/cu m at one location, reported coughing, irritation of the nose and throat, and congestion of the pharynx as the most significant signs and symptoms. Interpretation of which concentrations in the range 0.08-0.76 mg/cu m [34] or in the range 0.02-0.38 mg/cu m [28] caused the irritant effects noted is not feasible because of the significant variation in concentrations found. However, the controlled human exposures performed by Zenz and Berg [32] allow such interpretation. These investigators [32] found that 8-hour exposures to vanadium pentoxide at 0.2 mg/cu m (0.1 mg V/cu m) produced, after 24 hours, a slight productive cough in five volunteers; no other irritant effects were noted. An 8-hour exposure of two volunteers at 0.1 mg of vanadium pentoxide/cu m (0.06 mg V/cu m) only caused mucus formation

within 24 hours. This mucus was easily cleared by slight coughing that lasted 3-4 days.

Most animal studies of vanadium toxicity have dealt with injected or oral doses. Of the few inhalation studies, most involved vanadium concentrations greater than 1.0 mg/cu m. Pazynich [70], however, described exposure of rats to vanadium pentoxide at concentrations of 0.002, 0.006, and 0.027 mg/cu m. Motor chronaxy measurements, biochemical indices, weight, and general condition of the animals indicated that there were some, probably slight, effects at a concentration of 0.027 mg/cu m. Whether changes in blood and motor chronaxy are reliable indicators of toxicity is questionable. At a vanadium pentoxide concentration of 0.006 mg/cu m, no changes in motor chronaxy or blood measurements were observed unless the animals were stressed by starvation for at least 3.5 days.

Other signs that often appeared after inhalation of vanadium compounds were wheezing, rales, rhonchi, and chest pains, but without signs of changes in ventilatory function. The appearance of these effects is difficult to correlate to exposure concentrations but the possibility of their presence should be recognized in cases of suspected overexposure to vanadium. Long-term exposures to vanadium compounds have resulted in signs and symptoms similar to those of short-term exposure, and the irritant effects were reversible on cessation of exposure. There have been reports of more severe changes such as emphysema and pneumonia; however, these have not been adequately correlated to occupational exposures because of the lack of data.

Whether or not chronic obstructive lung disease (emphysema) is a consequence of vanadium exposure is not so clear as is desirable for a firm

conclusion. Some cases have been observed [24,64], but data on other possible causes in the populations, such as smoking, are not available. However, cases of bronchial asthma and bronchitis have been observed with sufficient frequency to warrant concern for decreased ventilatory function, and, possibly, a progressively decreased ventilatory function, on continuous exposure.

In addition to respiratory effects, ocular and dermal effects have been reported to result from contact with airborne vanadium compounds. Manifested primarily as a burning sensation or conjunctivitis, eye irritation occurs at concentrations as low as 0.018 mg/cu m [25]. The concentration range reported by Lewis [25] was 0.02-0.92 mg/cu m with all but one concentration less than 0.38 mg/cu m. These were the lowest concentrations found to cause eye irritation. There have been no reports of permanent eye damage resulting from vanadium at any concentration.

Several authors have described irritation of the skin after exposure to vanadium dusts [19,26,30,36]. This irritation usually takes the form of a sensation of heat or itching, sometimes accompanied by rashes or eczematous lesions, and has been reported at airborne vanadium concentrations of 0.03-85 mg/cu m [23,26,36]. Allergy may also be a factor in the occurrence of skin problems, since positive patch tests have been observed in a few cases of exposure [26,36]. Other compounds, such as caustic soda, sulfuric acid, or other corrosives, are commonly found in industrial environments, and may cause similar skin irritation when present in the workplace [23,26].

Although exposures to vanadium are primarily respiratory, ocular, or dermal, some oral contact may also occur, as shown by occasional reports of

75

greenish-black discoloration of the tongue and oral mucosa of vanadium workers [24-26]. It appears that this sign is of no toxicologic importance [24-26] but is, in some cases, an indicator of the presence of vanadium compounds, and is at least cosmetically undesirable. Oral discoloration has occurred at reported concentrations as low as 0.08-0.76 mg/cu m (average 0.25 mg/cu m) [34], and it has often been accompanied by a salty or metallic taste. The discoloration disappears without further complication within 2-3 days after removal from exposure.

Many other nonspecific effects have been noted in workers exposed to vanadium compounds. Heart palpitations on exertion have been reported but have not been definitely linked to occupational exposure to vanadium. Fatigue has also been reported, but this was attributed to aggravated respiratory symptoms or shift work [26]. There were little or no effects on the gastrointestinal tract, kidneys, blood, and CNS, and there were no generalized systemic effects. No conclusive evidence of pneumonoconiosis, emphysema, or other chronic disease was found. Also, no carcinogenic, mutagenic, teratogenic, or reproductive effects of vanadium on humans or animals were found. There is conflicting evidence of whether or not there is a correlation of airborne vanadium concentrations with the vanadium content of postexposure urine samples.

Although the manufacture of ferrovanadium and vanadium-containing alloys consumes 80% of the vanadium produced yearly, there are few quantitative data to evaluate the reactions of humans exposed at low concentrations of these compounds. Roberts [20], reporting a review of 15 years' experience at a ferroalloy plant, observed that vanadium metal, ferrovanadium, vanadium-aluminum, and vanadium carbide, all at unknown

76

concentrations, resulted in only slight nose, throat, and respiratory irritation when the particle size was below 100-200 mesh (about 150 μm and 75 μm, respectively [21]). Unlike such vanadium compounds as the oxides or vanadates, ferrovanadium compounds have not caused the more severe signs and symptoms such as wheezing, rales, rhonchi, or chest pain.

Roshchin [41,68] reported no ill effects on rats exposed to ferrovanadium at 1,000-2,000 mg/cu m. However, he later reported that rabbits and rats exposed for 2 months to ferrovanadium and vanadium carbide dusts at 40-80 mg/cu m did not show signs of acute intoxication, but did show morphologic evidence of perivascular edema, bronchitis, and interstitial sclerosis.

Ferrovanadium compounds have not shown evidence of eye or skin irritation in humans or animals.

The effects of vanadium on humans and animals are summarized in Tables III-2, III-3, and III-4.

Carcinogenicity, Mutagenicity, Teratogenicity, and Effects on Reproduction

There are no data in the available literature that show whether vanadium and its compounds are mutagenic or teratogenic. However, the carcinogenic potential of vanadium was tested by administering vanadyl sulfate at 19.8 mg of vanadium/100 g of body weight/year for the lifespan of white Swiss mice of the Charles River strain [71]. There was no evidence in this study that the ingestion of vanadyl sulfate influenced the incidence of tumors in the mice. Further studies of other vanadium compounds, of other species, and using other routes of exposure are desirable.

77

Table III-2

EFFECTS OF VANADIUM COMPOUNDS ON HUMANS

Substance	Duration and Route of Exposure	Concentration (mg V/cu m)	Reported Effects	Reference
V2O5	Unknown respiratory	1-48	Respiratory irritation with bronchopneumonia, heart palpitations	23
"	2-5 d respiratory	10-32	Respiratory irritation, tremors, discolored tongue	28
"	8 hr respiratory	0.6	Coughing	32
"	5 min respiratory	0.6	Cough, rales	"
"	8 hr respiratory	0.1	Coughing	"
"	"	0.06	Cough	"
V2O5, NaVO5	Unknown respiratory	0.3-1.2	Eye, respiratory irritation	17
V2O5, NH4VO3	"	0.04-0.4	Respiratory irritation, discolored tongue	34
V2O5, V2O3	1-5 yr respiratory	Unknown	Asthma in 3 of 120 workers	35
Ca3(VO4)2	1.5 d respiratory	"	Bronchitis, fever, headache, GI distress	22
V-Al alloy	Unknown respiratory	"	Respiratory irritation, discolored tongue	20
Vanadium carbide	"	"	Little effect	25
Ferro-vanadium	"	"	Eye, respiratory irritation	"
Vanadium metal	"	"	Respiratory irritation	"
Ammonium vanadyl tartrate	45-68 d oral	25 mg, 1-4 times/d	GI discomfort, discolored tongue, increased steroid excretion	54
Diammonium vanado-tartrate	6 mon oral	25 mg/d for 2 wk, then 125 mg/d for 22 wk	GI discomfort, pharyngitis, tongue ulceration and discoloration	56

78

Table III-3

SUMMARY OF EPIDEMIOLOGIC STUDIES WITH VANADIUM

Substance	Duration and Route of Exposure	Concentration (mg V/cu m)	Reported Effects	Reference
Vanadium ore	<3 yr respiratory	0.01-2.12	Eye, respiratory irritation	67
V205, vanadates	2.5 yr (mean) respiratory	0.01-0.52	Respiratory irritation, discolored tongue	25
V205	0.5-16 yr 6 yr (mean) respiratory	-	Cough, pulmonary effects with chest pain	24
V205	2-13 yr 6.6 yr (mean) respiratory	-	Eye, respiratory irritation, chest pain, bronchitis, emphysema	63
V205	2-3 yr respiratory	-	Eye and respiratory irritation, bronchitis	"

Table III-4

EFFECTS OF VANADIUM COMPOUNDS ON ANIMALS

Substance	Species	Duration and Route of Exposure	Concentration or Dose	Reported Effects	Reference
V2O5	Rats	2 hr/every 2d for 3 mon respiratory	3-5 mg/cu m	Lung damage	68,41
"	"	70 d respiratory	0.027 mg/cu m	Lung, liver, and heart changes; blood changes	70
"	"	40 d respiratory	0.006 mg/cu m	Motor chronaxy changes	"
"	"	70 d respiratory	0.002 mg/cu m	No effects	"
V2O3	Rabbits	2 hr/d 8-12 mon respiratory	40-75 mg/cu m	Labored breathing, deaths	35
NH4VO3	Mice	Subcutaneous	20.4 mg/kg	LD50	79
NaVO3	Rats	ip	4-5 mg/kg	Deaths	78
Ca3(VO4)2	Chicks	11-32 d oral	200-600 ppm	Death	77
"	"	7-32 d oral	30-200 ppm	Reduced growth rate	"
"	"	7-28 d oral	10-20 ppm	No effects	"
NaVO3	Rats	100 d oral	25-50 ppm	Reduced growth rate, diarrhea	75
Vanadium metal	Rabbits	5.5 mon oral	5 mg/kg/d	No effects	35
Ferro-vanadium	Rats	1 hr every 2 d for 2 mon respiratory	1,000-2,000 mg/cu m	Peribronchitis, perialveolitis	41
Ferro-vanadium	"	2 mon respiratory	40-80 mg/cu m	Bronchitis, interstitial sclerosis, perivascular edema	69
Vanadium Carbide	Rats, Rabbits	"	"	"	"