III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

The chief source of chromium trioxide is from chromite ore obtained primarily from South Africa, Rhodesia, and the USSR, with minor amounts from Turkey, the Philippines, Cuba, Finland, Canada, India, and the United States. [1] Bourne and Yee [2] in 1950 reported the approximate analysis of chromite ores from Rhodesia and Transvaal, respectively, as: chromic oxide, 51.1 and 45.6%; iron oxide, 11.4 and 25.8%; aluminum oxide, 15.2 and 14.3%; silicon dioxide, 4.8 and 1.4%; and magnesium oxide, 12.7 and 11.8%.

According to Gafafer, [3] chromium trioxide is produced by roasting chromite ore with soda ash and lime to form sodium chromate, which is converted to sodium dichromate by acidification and crystallization. The sodium dichromate is then treated with sulfuric acid, and the temperature is raised above 197 C. [4] A molten reaction mixture results with the heavier chromic acid anhydride settling out. The anhydride reacts with water to form chromic acid and dichromic acid.

In 1969, approximately 25 thousand short tons of chromium trioxide were produced in the United States, of which ninety percent was used in metal treatment, such as chrome plating, copper stripping, and aluminum anodizing. [4] Other uses included catalysts, refractory purposes, organic synthesis, photography, and exports. Chromic acid is a strong oxidizing agent and concentrated solutions attack most common metals. [5] It is not combustible, but may ignite readily

oxidizable substances. [5] Significant physical properties [6] of chromium trioxide are presented in Table X-1.

NIOSH estimates that 15,000 people are potentially exposed to chromic acid mist.

Historical Reports

One of the first reports of injury to workers in this country from exposure to chromium compounds was in 1884 by MacKenzie. [7] He reported that factory workers employed in the chambers where bichromate was made invariably developed perforation of the nasal septum, generally within a few days of exposure. The characteristic development of septal perforation was described in detail. Although destruction of the cartilage was reported to be very extensive in many cases, the external appearance of the nose was said to be unchanged. Other effects reported included ulceration of the turbinates and nasal pharynx, and inflammation of the lower respiratory tract. Perforation of the tympanic membrane was also reported, due either to passage of bichromates through the Eustachian tubes or to direct external contact.

Reporting on 12 cases in two plating plants, Blair [8] in 1928 described four electroplaters who experienced symptoms of a bad cold with coryza, sneezing, watery discharge from the eyes and nose, and itching and burning of the nose, especially when they left the plant and came in contact with outdoor air. Of these four men, one had a perforated nasal septum, one a large unilateral ulcer on the septum, and two had marked congestion of the nasal mucosa with hyperemia,

swelling, mucoid discharge, and small ulcers. In the remaining 8 cases reported, workers who removed objects from the plating tanks complained little of nasal symptoms, but had ulcerative lesions of the hands and fingers. These "chrome holes" reportedly occurred only at the site of a preexisting scratch, cut, or break in the skin. No environmental levels of chromic acid were given, but the installation of an efficient ventilation system was reported to be sufficient to prevent nasal symptoms. Long sleeved rubber gloves were used to protect the hands and 5% sodium hyposulfite was reported useful to neutralize chromic acid on the hands.

Bloomfield and Blum [9] in 1928 reported a study of workers engaged in chromium plating and gave data on concentrations of chromic acid to which they were exposed. Of 19 workers exposed to chromic acid mists, 17 had symptoms including perforated septa, ulcerated septa, inflamed mucosa, nosebleed, and chrome holes.

Lehmann [10] in 1932 reported the first cases of lung cancer in workers employed in a chromate plant in Germany. The lung cancer occurred in two of "several hundred" workers. The first report in the United States on the incidence of cancer of the respiratory system among chromate workers was that by Machle and Gregorius in 1948. [11] In this mortality study of employees from seven chromate plants with mixed exposures to trivalent and hexavalent chromium compounds, the crude death rate (ie, the death rate not adjusted for age) for lung cancer was 25 times greater than normal. This investigation was

followed by others establishing an increased risk for lung cancer in workers in chromate plants. [3,12-16]

Effects on Humans

Chromium is a naturally occurring trace element found in human tissues. Imbus et al [17] reported normal levels of 2.65 μg/100 g of blood and 3.77 μg/liter of urine. Schroeder et al [18] reported the normal level in adult tissue in the United States to be 2.3 μg/g of ash in the kidney and 1.6 μg/g ash in the liver. Levels were higher in persons from other countries. The element was found in relatively high concentrations in all tissues of newborns (51.8 μg/g ash and 17.9 μg/g ash in the kidney and liver, respectively) but the concentration fell during the first two decades of life and was stable thereafter, except in the lungs. [18,19] In the lungs, the chromium level was reported to be 85.2 μg/g ash in infants. This decreased to a low of 6.8 μg/g ash during the second decade, after which the reported level gradually rose to 38.0 μg/g ash in the 70-80 year age group. [18] Chromium affects glucose and lipid metabolism in animals [19,20] as well as in man, [18,19] and is an essential micronutrient in mice and rats. [19]

In workers occupationally exposed to mixed chromites and chromates in the chromate producing industry, the U.S. Public Health Service [3] reported median blood chromium levels of 0.004 and 0.006 mg/100 ml blood for white and black workers, respectively. No overall mean or median was reported. Median urine levels of 0.043 and 0.071 mg/liter, respectively, were reported for white and black workers.

Among similarly exposed production and maintenance workers, Mancuso [21] reported the average urinary level was 5.1 µg/100 ml. Office workers surveyed in his study were reported to have average urinary chromium levels of 1.0 µg/100 ml. Not unexpectedly, urinary levels were higher among men exposed to soluble than those exposed to insoluble chromium compounds. Elevated levels of blood and urinary chromium were found to persist for several years after occupational exposure ceased. [21]

Chromium compounds can be allergens and are encountered in many occupations. [22,23] In one study [24] of dermatitis in an automobile assembly plant, 24.3% of those with dermatitis were found to be sensitive to chromate apparently carried over on the surface of nuts, bolts, and screws from a chromate dip. Dermatitis has been reported in the chromate producing industry [3,21] as has pulmonary sensitization. [21,23] Reports [7-9,25-27] of exposure to chromic acid, however, indicate problems not of sensitization, but rather of direct corrosive action. While there is no evidence that chromic acid workers under current conditions of industrial exposure have any appreciable risk of skin or pulmonary sensitization, these responses have been reported in workers exposed to other hexavalent chromium compounds. Though evidently rare, skin or pulmonary sensitization from exposure to chromic acid should be considered a possibility.

Careful review of the literature reveals no known cases of death caused by acute exposures. The atmospheric concentration immediately hazardous to life is not known. Acute pulmonary complications in two

workers exposed to massive amounts of chromic acid mist were reported in 1950 by Meyers. [28] The exposure levels of chromic acid were not measured by the investigator. One worker was exposed to the chromic acid mist for approximately four days while concentrating chromic acid by boiling the acid in large vats. The first symptoms were coughing and wheezing, followed by severe frontal headaches, dyspnea, pain on deep inspiration, fever, and loss of weight. After six months the worker had improved with respect to weight and cough but still had chest pains on deep inspiration. A bronchoscopic examination 6 months after exposure "revealed that the tracheal mucosa and the mucosa of the entire tracheobronchial tree was hyperemic and somewhat edematous." Eleven months after exposure, the worker still had complaints of infrequent chills, cough, and mild pains located in the anterior part of the chest.

The second worker, though working at the same operation, was exposed for only one day. He stated that he had no immediate ill effects from inhalation of the mist, but during the following three or four days hoarseness developed, with a cough productive of whitish mucoid sputum. A chest X-ray, hematologic studies, and urinalysis produced no abnormal results, but during the following three months the patient became anorexic and noted a gradual loss of 20 to 25 pounds. He was admitted to the hospital 4 1/2 months after exposure because of sharp pain at the right upper abdominal quadrant, cough, and severe, sharp chest pain, precipitated and aggravated by his chronic cough. This cough was productive of heavy, thick, greenish

mucoid sputum. He had had pneumonia on three occasions. On admission, he had a pleural friction rub. After 15 days in the hospital on a 3,500-calorie diet, he was discharged. At that time the chest was clear; the friction rub could not be palpated, nor was it heard. Approximately six months after exposure an X-ray indicated some emphysematous changes, and bronchoscopy seven months after exposure showed mucous pearl secretions. Eleven months after exposure, a persistent cough productive of greenish mucoid sputum remained.

Exposure to chromic acid in electroplating operations has been reported to cause a variety of adverse effects. These include lacrimation, [8,25] inflammation of the conjunctiva, [29] nasal itch and soreness, [8,25,27] epistaxis, [9,25,27] ulceration [8,9,25,27,29,30] and perforation [8,9,25,27,30] of the nasal septum, congestion of the nasal mucosa [8,9,25] and turbinates, [25] chronic asthmatic bronchitis, [29] dermatitis [30] and ulceration of the skin, [8,9,27,30] inflammation of the laryngeal mucosa, [29] cutaneous discoloration, [8] and dental erosion. [27] According to some reports, [8,9] ulceration of the skin occurs only when the plating solution comes in direct contact with the skin at the site of a pre-existing break in the skin.

Reviewing the effects of exposure to chromic acid mist from anodizing solutions, Zvaifler [26] considered the effects distinctly different from those in chrome plating operations, although others [30] report the effects are identical. Zvaifler [26] described the

cases he observed (over 100 cases) as ranging from superficial greyish ulceration of the anterior nasal mucosa with small spots of bleeding, to general involvement of all the nasal mucosa with superficial scabbing and crusting and a general dry appearance of the nose, sometimes extending to the posterior pharynx.

Pascale et al [31] in 1952 reported five cases of hepatic injury apparently due to exposure to chromic acid from plating baths. A person, who had been employed five years at a chromium plating factory, was hospitalized with jaundice and was found to be excreting significant amounts of chromium. Her lungs and cardiovascular system were normal. A liver biopsy showed histological changes resembling those found in toxic hepatitis. To investigate the possibility that the liver damage was of occupational origin, eight fellow workers were screened for urinary chromium excretion. Four of these were found to be excreting significant amounts and were examined in more detail. In three workers who had been exposed to chromic acid mists for 1 to 4 years, liver biopsies and a series of twelve hepatic tests showed mild to moderate abnormalities. No liver biopsy was taken from the fifth worker, who had been removed from further exposure because of nasal ulceration after 6 months at the plating bath. Only one of his liver function tests indicated a borderline abnormality. The urinary excretion of chromium (2.8 and 2.9 mg/24 hours) by the two workers employed four years was greater than the excretion (1.48 mg/24 hours) by the worker employed five years who suffered the greatest liver damage. The lowest urinary chromium excretion (0.184 mg/24 hours) was

measured in the fifth worker, the individual with least exposure. All five exhibited some signs of damage to the nasal mucosa. This plus the levels of urinary excretion suggests that exposures were significant, but no environmental data were reported.

Epidemiologic Studies

No epidemiologic data are available on the incidence of pulmonary cancer in workers exposed only to chromic acid. The epidemiologic data that are available pertain to workers in the chromate-producing industry. These workers were subject to mixed exposures, and these data have only indirect and limited application to chromic acid exposures.

The first report of lung cancer from exposure to chromium was given in 1932 by Lehmann. [10] He reported two cases of workers with lung cancer out of several hundred workers who had been employed in a chromate plant in Germany. No information was given on the length of exposure or on the nature and airborne concentration of the exposure to chromium compounds. Lehmann did not consider these two cases to be occupationally related.

Machle and Gregorius [11] gave the first report on the incidence of cancer of the respiratory system in the chromate industry in the United States. The workers had been exposed to chromite ore and a mixture of trivalent and hexavalent chromium compounds. Available records from seven chromate plants for the preceding 10-15 years (1933-1948) were studied. Of the 193 deaths in all plants, 66 (34.2%) were due to cancer of any type or at any site, a rate over twice that

for a control industrial group. This increase was attributable to an excessive proportion of deaths from cancer of the respiratory system. Lung cancers comprised 60% of all cancers as compared to an expected rate of 9%. In five of the seven plants, (no deaths due to lung cancer were recorded in two plants) lung cancer rates varied from 13 to 31 times normal. The mean duration of exposure prior to onset was 14.5 years.

One plant (plant C in Machle and Gregorius [11]) with no cancer deaths was small and no deaths from any cause were seen among its workers during the period covered. The second was one of two plants (D1 and D2 [11]) in the study owned by a single company. In plant D2 there were 33 deaths in 1,853 male-years (a term used by the authors to indicate that only males were included in the group studied) of exposure. Four of the 33 deaths (12.1%) were cancer deaths; none were cancer of the respiratory system. In contrast, in plant D1 there were 29 deaths in 2,491 male-years of exposure, of which five were due to lung cancer. These five deaths represented 17.4% of all deaths, or 71.4% (5 of 7) of all cancer deaths.

The worker populations of plants D1 and D2 were comparable with respect to age distribution, exposure history, color, and geographic location. The two plants differed significantly in the incidence of nasal irritation and septal perforation. These complaints occurred in 53.4% of the workers in plant D1, but only in 29.6% of workers in D2. The authors considered this a difference in degree only and stated that perforations may occur without associated high rates for lung

cancer. There was a distinct difference in the compounds processed by the two plants. Plant D1 produced sodium bichromate from chromite ore. Plant D2, in which there was no lung cancer, produced chromic acid and basic chromic sulfate from the sodium bichromate. The authors concluded that the experience in these plants suggested the monochromates may be responsible for the lung cancer.

Baetjer [32] in 1950 reviewed the literature reporting lung cancer cases attributable to chromate exposure. At that time, 122 cases of respiratory cancer had been reported. Of these, 109 worked in the chromate-producing industry, 11 in the chrome pigment industry, and 2 in other industries. Sixty-three cases occurred in Germany, 57 in the United States, and 1 each in Switzerland and England. The average duration of employment in the German chromate-producing group was 22 years. The average for the United States cases was 16 years, and the average in the German pigment cases was 12 years.

Although the best available data had been used, the Machle and Gregorius report [11] had been limited since in it the cause of death often was based on clinical findings alone. Furthermore, it did not include any workers who left the industry prior to developing lung cancer, and the control groups were not comparable in all respects to the chromate group. To overcome these objections, Baetjer [16] in 1950 reported an investigation of the records of two hospitals in Baltimore, where a chromate-producing plant was located. In the records from 1925 to 1946 of one hospital, there were 198 cases of men with lung cancer which was histopathologically confirmed with biopsy

or autopsy material. In the second hospital's records, from 1930 to 1948, there were 92 such cases. Two control groups were chosen from the records of the first hospital. One of these (226 cases) was selected from all men admitted for 10 days or more, excluding those admitted for traumatic injuries or psychiatric illness. This group, like the lung cancer group, chose to come or was referred to the hospital for more or less serious illness. The second control group (177 cases) consisted of males with cholelithiasis, chosen because this disease, like lung cancer, presents diagnostic problems. From the records of the second hospital, only the first control group was selected (499 cases). All control groups were selected to have the same age and yearly distribution as the cancer cases, and no case was included in more than one group.

The number of chromate workers among the lung cancer patients was compared to the number in the control groups. None of the patients in the control groups had a reported exposure to chromium compounds. Seven (3.5%) of the 198 lung cancer victims at the first hospital and 3 (3.3%) of the 92 at the second hospital were or had been chromate workers. Statistical analysis indicated that the percentage of lung cancer patients who had been chromate workers was significantly higher than expected on the basis of the control groups. The percentage of lung cancer patients who were employed at the chromate-producing plant was compared with the percentage of the employed male population of Baltimore who were employed at the plant. Statistical analysis again indicated that the percentage of chromate

workers in the lung cancer series was significantly higher than the percentage of chromate workers in the employed male population of Baltimore. This study therefore confirmed the earlier conclusions of Machle and Gregorius [11] that the number of deaths due to cancer of the lungs and bronchi was greater in the chromate-producing industry than was normally expected.

Mancuso and Hueper in 1951 [12] reported on a study of occupational cancer in workers in a chromate plant. The workers were exposed to a mixture of trivalent and hexavalent chromium compounds including chromic acid. Of 33 deaths from all causes, nine (27.2%) were from all types of cancers. Six of these (18.2% of all deaths) were from cancer of the respiratory system. The mean latent period was 10.6 years. In comparison, out of 2,931 deaths in Lake County, Ohio, in which the plant was located, 34 were due to lung cancer. The ratio of lung cancer to total deaths in the chromate plant was 17 times that of Lake County.

This was followed with a report by Mancuso [21] on the clinical and toxicologic aspects of 97 workers examined in a chromate-production plant: 63% showed perforations of the nasal septum or ulcers of the mucosa, 87% had chronic rhinitis, 42% had chronic pharyngitis, 10% had hoarseness, and 12% had polyps or cysts. Thirty-seven percent of the 97 examined had some involvement of the nose, throat, and sinuses.

A total of 17.5% of those given gastrointestinal X-ray examinations had evidence or ulcers, gastritis, or gastrointestinal tumor.

In comparison, X-ray examinations of a group of cement workers showed that 4 of 41 (9.8%) had similar evidence. The author stated "workers of a chromate factory seem to have an excess liability to inflammatory and ulcerative conditions of the gastrointestinal tract.caused by the ingestion of chromates." Any relevance of these data to workers exposed only to chromic acid would, however, be speculative. Neither the sex of the workers nor the years of work in the industry by departments was defined. In the nine production departments of this plant, air concentrations of total chromium expressed as chromium trioxide, based on weighted average 8-hour exposures, ranged from 0.17 to 3.12 with a median value of 1.0 mg/cu m. [2]

Baetjer et al [33] in 1959 reported on the analysis for soluble and insoluble chromium of lung tissue from 16 men who had worked 1.5 to 42 years in a chromate plant. Eleven of these were lung cancer victims. The range of concentrations for exposures to both soluble and insoluble chromium for the workers was stated to be great. The concentrations of soluble (water soluble and acid soluble) chromium in the lungs ranged from 0.54 to 42.4 mg/10 g lung tissue ash. For acid insoluble chromium the concentrations ranged from 0.0 to 148.2 mg/10 g lung tissue ash. One worker who had been out of the industry for 23 years (whose exposure to chromium compounds was estimated as "heavy" during his two years in the industry) had 3.3 mg soluble chromium/10 g lung tissue ash. In this same worker, the urine contained no chromium; in 100 g of blood, analysis showed 5.4 µg in the cells and 2.0 µg in the plasma. No correlation was found between the presence

or absence of lung cancer and the concentration either of soluble or of insoluble chromium. The concentration varied greatly from one lobe to another and even in different areas of the same lobe. The bronchogenic cancers often contained little or no chromium.

The Division of Occupational Health, Public Health Service, published a report in 1953 of a study on the health of 897 workers in the chromate-producing industry. [3] Approximately 1,800 samples were collected throughout the industry for the purpose of defining the atmospheric environment. The great majority of these were air samples, but material and settled dust samples were also collected.

It was found that the milling, roasting, and leaching processes generated dusts containing chromite ore, soda ash, roast, residue, and sodium chromate. Sodium bichromate and sodium sulfate were usually found associated only with the neutralizing, treating, and concentrating operations. An appreciable portion of the total chromium was present in an acid soluble-water insoluble state, indicating the presence of a form or forms of chromium which were dissimilar from either insoluble chromite ore or water soluble, hexavalent chromium. Roasting, leaching, neutralizing, and treating operations had the largest proportion of acid soluble-water insoluble chromium. However, settled dust samples from many areas not associated with roast or residue processes had high percentages of acid soluble-water insoluble chromium.

From the six chromate-producing plants, employing about 935 persons, 897 males were medically examined. [3] The study produced no

data to show that exposure to the chrome compounds affected the rate of dental caries. Some of the workers, however, developed a yellowish discoloration of the teeth and tongue. A higher percentage of the chromate workers experienced gingivitis and periodontitis. Pulmonary markings suggestive of fibrosis were not significant among chromate workers but bilateral hilar enlargements were observed. No correlation could be established between prevalence of heart disease and years in the chromate industry. White and red blood cells and casts in urine appeared more frequently than is usually observed in the average industrial population. These findings tended to increase with increasing years of exposure in the chromate-producing industry.

Perforation of the nasal septum was found in 509, or 56.7% of these chromate workers. It was reported that septal perforation sometimes occurred after less than six months of exposure. Other workers with years of heavy exposure did not experience perforation, apparently because of prophylactic measures. The use in combination of a mask, petrolatum in the nostrils, and nasal douching was judged to be the most effective protection. [3] The authors concluded that the prevalence of nasal perforation was not a valid index of the prevalence of pulmonary carcinoma.

Ten of the 897 chromate workers examined were diagnosed as having bronchogenic carcinoma (3 of the 10 had been diagnosed before the survey). [3] The mean age of these 10 workers was 54.5 years and the mean exposure to chromate 22.8 years. A survey of a comparison group from a chest X-ray survey in Boston showed 20.8 lung cancer

cases per 100,000 people, whereas the rate for bronchogenic cancer among chromate workers was 1,115 per 100,000 or 54 times that of the control group. Comparing the morbidity and mortality experience of male members of sick benefit associations in seven chromate producing plants, cancer of the respiratory system was found to be 29 times the rate for all males in the United States.

Taylor in 1966 [13] reported on a study of a group of chromate workers followed over a period of 24 years (1937-1960) using Old-Age and Survivors Disability Insurance records. The workers were exposed to multiple trivalent and hexavalent chromium compounds. A total of 1212 chromate workers were included in the study. For respiratory cancer 8.344 deaths were expected, 71 deaths were observed; for all other cancers 23.894 deaths were expected, 32 observed; for respiratory diseases 7.843 deaths were expected, 19 observed. Expected deaths from the selected causes were determined from the age-cause specific mortality rates for the U.S. civilian male population. No data were presented on levels of worker exposure to chromates.

All of the preceding reports [3,11-13,16,32] of lung cancer in the United States chromate-producing industry have varying degrees of overlap. At the time of the earliest report, [11] there were seven chromate plants in the United States, all of which were included in that study. The later reports used different methods, but included all or some of the same plant populations and cases reported by the other studies. Therefore, these reports do not all represent different worker populations.

Bidstrup [14] in 1949 interviewed and X-rayed 724 chromate workers in Great Britain and discovered one case of lung cancer. Bidstrup and Case [15] reported a follow-up study of the remaining 723 workers, conducted almost six years after the first study. In the follow-up, it was found that 217 workers had left the industry and were lost to the follow-up. A total of 59 men were known to have died, 12 of these by lung cancer. This compared to 3.3 expected lung cancer deaths, or an incidence of 360% of expected. The difference was statistically significant, but as the authors pointed out, by the time all the men at risk have lived their life span, the lung cancer increase probably will be found to be very much higher. The possibility that the increase was due to nonoccupational factors such as diagnostic bias, place of residence, social class, or smoking habits was examined and discarded. It was not possible to form an opinion about the identity of the occupational carcinogen.

The chromate workers in the above studies [3,11-16,32] had exposures to a mixture of trivalent and hexavalent chromium compounds of which chromic acid was only a minor part. The workers were exposed to chromite ore, chromite-chromate intermediates and chromates as well as trace metals and minerals associated with the processing of the chromite ore. These studies suggest that exposure to the roasted chromite ore complex may be important as a causative agent of the lung cancer observed in chromate workers.

In the literature, there is no direct evidence that exposure to chromic acid per se at the measured concentrations and under the

conditions of industrial exposure has led to cancer. However, no study of this nature has been undertaken. More definitive data are needed on this subject.

Bloomfield and Blum [9] in 1928 reported on a study of health hazards in chromium plating. In the study 19 workers were examined who had worked from one week to three years with exposure to chromic acid in the chromium plating room. Of the 19 workers examined, 17 had inflamed mucosa, 11 nosebleed, 6 chrome holes, 4 ulcerated septa, and 3 had perforated septa.

In 1930 the Inspectorate of Factories, London, issued a report on the examination of 223 workers engaged in chromium plating. [30] Ninety-five (42.6%) had dermatitis or scars of old ulcers, 116 (52%) had either perforation or ulceration of the septum or devitalization of the mucous membrane. Ulceration of the nasal mucous membrane was seen as early as two weeks after exposure. No data were given on the atmospheric concentration of chromic acid to which the examined workers were exposed.

In 1944 Zvaifler [26] reported on the study of over 100 cases of workers exposed to chromic acid mists from a 5.0% chromic acid solution used in anodizing operations. Atmospheric concentrations of chromic acid were not given. Neither the length of time of exposure nor the sex of the workers was given in the cases discussed. The author stated that cases of chromic acid poisoning from anodizing operations (using a 5% solution of chromic acid) are quite different

from those resulting from chromium plating and are largely limited to the nasal mucosa though skin rashes are common.

Vigliani and Zurlo in 1954 [29] reported on a study of exposures to a variety of agents in the working environment and their effects on the workers for validating safe exposure levels. In a group of 150 workers exposed to chromates and chromic acid from electrolysis baths and during the production of chromic acid anhydride and alkali chromates, the investigators reported an ulcer of the nasal septum, inflammation of the larynx and ocular conjunctiva and chronic asthmatic bronchitis among the workers, one cancer of the nasal septum and one lung cancer. The average concentration of chromates at the time of the investigation was stated to range from 0.11 to 0.15 mg/cu m.

In 1965 Kleinfeld and Rosso [25] reported on a study of nine cases of workers with injury to the nasal septa from exposure to chromic acid while engaged at chromium plating. Atmospheric concentrations of chromic acid ranged from 0.18 to 1.4 mg/cu m. The plating tanks were not provided with local exhaust ventilation. General room ventilation was provided through the use of room fans and opened windows. Four of the nine workers examined with exposure times ranging from 2 to 12 months had perforated nasal septa, three workers with exposure times ranging from 1 to 10 months had ulcerated nasal septa, and two workers with exposure times of 0.5 and 9 months, respectively, had moderate injection of the nasal septa. The air

sampling was done at the breathing zone level near where the worker stood.

In 1972 Gomes [27] made a study of the incidence of cutaneous-mucous lesions in workers exposed to chromic acid in the State of Sao Paulo, Brazil. He found that only 50% of the industries used exhaust protection and that the threshold limit for workers in electroplating with hot chromic acid was frequently surpassed. Clinical examination of the 303 workers exposed to chromic acid revealed that 24% had perforated nasal septa and 38.4% ulceration of the same. Together, these lesions of the nasal septum affected more than 50% of the workers. More than 50% of the workers examined showed ulcerous scars not only on the hands, but also on forearms, arms, and feet. Ulcerous scars on the feet were due to working without boots and the wearing of Japanese type sandals.

Animal Toxicity

In order to study in animals the reported cancer hazard due to chromium, Hueper [34] attempted to identify a species and tissue sensitive to the carcinogenic action of chromium or its compounds. Chromium and chromite ore were introduced in a powdered form suspended in two different vehicles (lanolin, gelatin) by various routes (in the femur, intrapleural, intraperitoneal, intravenous, intramuscular, intranasal sinus) into mice, rats, guinea pigs, rabbits, and dogs. Results were equivocal at best as to evidence supporting a carcinogenic action of metallic chromium and chromite ore. Only in

rats were tumors observed which might have been causally related to the chromium deposits.

Subsequently, Hueper [35] implanted chromite ore roast mixed with sheep fat into the thigh muscle tissue and into the pleural cavity of male rats. Of the 25 rats with pleural implants 2 developed squamous-cell carcinomas coexisting with sarcomas of the lung and 2 developed tumors (one of which was benign) remote from the site of implantation. Of the 31 rats receiving implants in the thigh muscle, 3 had fibrosarcomas of the thigh and ten developed tumors (four of which were benign) remote from the site of implantation. Two series of 15 female rats each were implanted with sheep fat only into the pleural cavity and into the thigh, respectively, as controls. Of those with pleural implants, one developed a benign tumor at the site and three developed tumors (2 benign) remote from the site of implant. In the series with thigh implants, three developed tumors (one benign) remote from the implant. This suggested to the investigator that the chromite ore roast contained carcinogenic material, possibly the water insoluble-acid soluble chromium compounds present.

Hueper and Payne [36] implanted finely pulverized calcium chromate, sintered calcium chromate, sintered chromium trioxide and barium chromate mixed with sheep fat into the pleural cavity and into the thigh muscle of rats. Of 20 male and 15 female rats in each series, rats implanted with calcium chromate developed 8 thigh tumors and 21 pleural tumors; rats implanted with sintered calcium chromate developed 8 thigh tumors and 17 pleural tumors; rats implanted with

sintered chromium trioxide (some of which had been changed to lower valency during sintering at 2000 F for one hour) developed 15 thigh tumors and 14 pleural tumors. The rats implanted with the barium chromate (low degree of solubility) did not develop any tumors either in the thigh muscle or the pleural cavity. With one exception, all tumors were sarcomas, usually of the spindle cell- or fibro-sarcomatous type. Two groups of 20 male and 15 female rats were implanted with pellets of sheep fat only into the plural cavity and into the thigh, respectively. No tumors were observed in any of these control animals. The data suggested to the investigators that several chromates with medium solubility produce cancer when introduced into the tissues of rats in the form of a depot assuring prolonged exposure to chromium in rather small amounts.

Payne [37] injected calcium chromate, sintered calcium chromate, and sintered chromium trioxide in a tricaprylin vehicle subcutaneously into the nape of the necks of mice. Only one tumor was observed in 52 mice injected with calcium chromate. No tumors were seen in the groups of 52 mice each which received sintered calcium chromate, sintered chromiun trioxide, or in the control group. When calcium chromate and sintered calcium chromate in sheep fat were implanted intramuscularly in mice, nine tumors were seen in mice implanted with the sintered calcium chromate, and only one in those receiving calcium chromate. The tumors observed were of the same type as those reported earlier by Hueper and Payne. [36] The author concluded that the carcinogenic action of chromium was dependent on the solubility of the

compound and the amount present, stating that if hexavalent chromium in the form of chromate ion is available in too large a dose, acute effects result, but that a smaller dose can result in malignancy.

These results and conclusions were corroborated by Roe and Carter [38] who injected rats intramuscularly with calcium chromate in arachis oil. Twenty once-weekly injections were given. The first two injections contained 5.0 mg of calcium chromate, but signs of severe local inflammation developed, so the dosage in the last 18 injections was 0.5 mg. Of 24 test rats, 11 developed spindle cell sarcomas and seven developed pleomorphic sarcomas at the injection site. No tumors were seen in 16 controls.

Laskin et al in 1969 [39] reported studies of selected chromium compounds in a cholesterol carrier using an intrabronchial implantation technique. Compounds under investigation included chromic chromate, chromic oxide, chromium trioxide, calcium chromate, and process residue. Pellets were prepared from molten mixtures of materials dispersed in equal quantities of cholesterol carrier. These studies included materials of differing solubilities and valences, and have involved over 500 rats that were under observation for periods of up to 136 weeks.

Lung cancers that closely simulate lung cancer in man were found in these studies. With the calcium chromate, eight cancers were found in an exposed group of 100 animals. Six of these were squamous cell carcinomas. In all the experimental groups except the one exposed to chromium trioxide, there was evidence of atypical squamous metaplasia

carcinomas. In all the experimental groups except the one exposed to

of the bronchus. In the 100 rats implanted with chromium trioxide, two tumors were observed, both hepato-cell carcinomas.

Since these studies implicated calcium chromate as a lung carcinogen, inhalation studies using this compound were begun. [40] The study is not yet completed, but preliminary results suggest a carcinogenic action in rats after chronic exposure to aerosols at a concentration of 2.0 mg/cu m. These results may be significant for the human experience in the chromate-producing industry. As noted by this researcher, [40] calcium chromate exists in the residue step to the extent of 3% in no-lime roasts and at significantly higher levels when lime is used.

Correlation of Exposure and Effect

Only five studies are available which report both the effects in man of chromic acid exposure and atmospheric levels of chromic acid. [9,25-27,29,41] All these reported the atmospheric levels as measured at the time of the study. Consequently, all share a common weakness, in that effects were reported which were cumulative effects of past exposures to chromic acid concentrations which may have been different from the levels reported. Nevertheless, limited correlations can be drawn.

In the study by Bloomfield and Blum, [9] six plating plants were surveyed and the atmospheric concentration of chromic acid was determined in each, based on a total of 39 air samples. Using these data and the occupational histories of the workers, the investigators estimated the amount of chromic acid to which some workers were

exposed daily during the time employed in the plating room. When the worker had been employed only a short time, "the estimated degree of exposure was more than an approximation" in the authors' opinion, since the ventilation system in use at the time of the survey had been in use throughout the individual's employment.

Exposures were estimated for 23 workers who were given physical examinations. Four of these were controls with no known exposure to chromic acid. Estimated exposures for the remaining 19 ranged from 0.12 to 5.6 mg/cu m. Six platers were exposed to chromic acid estimated at a level of 0.12 mg/cu m. Employment had ranged from one week to seven months. All had inflamed mucosa and three had nosebleed. The exposures in the past may have been different from those observed at the time of the study, but the data do indicate that distinct injury to the nasal tissues can result after relatively short exposures. Some of these six platers were exposed such a short time that their experience strongly suggests that, assuming an accurate estimate was made, a concentration of 0.12 mg/cu m can cause inflammation of the nasal mucosa and nosebleed. This was the conclusion of the authors, [9] who stated that continuous daily exposure to concentrations greater than 0.1 mg/cu m is likely to cause definite injury to the nasal tissues.

Kleinfeld and Rosso [25] studied a group of chromium plating workers exposed to airborne chromic acid levels ranging from 0.18 to 1.4 mg/cu m. The exposure period varied from 2 weeks to 12 months. Each of the workers studied had either perforated or ulcerated septum

or injection of the septum. These data again indicate that lengthy exposures are not necessary for adverse effects to be manifest, since septal perforation was reported after as little as two months exposure. The data do not suggest a safe exposure level.

The report by Vigliani and Zurlo [29] did not detail the frequency with which effects were observed, but reported on a three year observation of approximately 150 workers during which average concentrations were 0.11-0.15 mg/cu m. Exposures were to chromic acid mist and anhydride, and to alkali chromates. Health disturbances reported included ulceration of the nasal septum, inflammation of the laryngeal mucosa and conjunctiva, and chronic asthmatic bronchitis. Two cases of cancer were also observed, one a cancer of the nasal septum and one lung cancer. Vigliani and Zurlo recommended that the standard for chromic acid be reduced from 0.1 mg/cu m to 0.05 mg/cu m.

Gomes [27] reported the experience of electroplaters in the State of Sao Paulo, Brazil. The exposures of 81 platers were determined as representative of the exposures of 303 platers examined clinically. Air concentrations were determined using a universal testing kit with syringe-type pump and filter paper. Unfortunately, a direct correlation between those exposed to a given concentration and those free of symptoms cannot be made, but the results are nevertheless indicative of the level at which effects are observed. A total of 43.2% of the workers were exposed to atmospheric concentrations of 0.1 mg/cu m or less, yet only 37.6% of the workers examined were free of nasal ulceration and perforation. The incidence

of cutaneous lesions due to direct skin contact was greater due to improper use of or failure to use protective equipment. The author made no inferences from his data as to a safe exposure level. The percentage of the workers exposed to levels at or below 0.1 mg/cu m and the percentage free of respiratory symptoms are nearly the same, suggesting that threshold effects occur at or below this level.

In the reports by Zvaifler [26] and Gresh [41] of chromic acid exposures in an anodizing plant, a direct correlation again is not possible. However, in this case, a better estimate of changing conditions is possible. Nasal irritation and ulceration were observed in workers, and atmospheric concentrations were reported to range from 0.42-1.2 mg/cu m. After the ventilation system was improved, atmospheric levels in two samples were 0.09 and 0.10 mg/cu m. Four weeks later nasal irritation persisted, although none had worsened. After further revision of the ventilation system, atmospheric concentrations were reduced to negligible levels and the employees' nasal irritation cleared up within four weeks. Had exposure at 0.09-0.10 mg/cu m continued longer than four weeks the irritation may have cleared up eventually, but these data suggest again that effects are seen at 0.1 mg/cu m.

Because these reports all fail to give long-term environmental data, the effects observed cannot be directly related to the environmental data reported. Nevertheless, the five papers consistently illustrate that adverse effects can result after relatively short periods of employment and therefore short periods of exposure to

chromic acid. The papers also consistently indicate that nasal irritation does occur at atmospheric concentrations of 0.1 mg/cu m and may occur at lower levels.