III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

In the United States, chromium(VI) is manufactured from chromite ore obtained primarily from the Republic of South Africa, Southern Rhodesia, and the USSR, with minor amounts from other areas of the world. [1] No chromite ore has been mined in the United States since 1961. [2] Chromite ($FeOCr_2O_3$) is not found in nature in the pure forms, but generally has some FeO replaced by MgO or the Cr_2O_3 replaced with Al_2O_3. [2] Silica is also found in the ore in varying amounts. [2] According to Bourne and Yee [3] the approximate analysis of chromite ores from Rhodesia and Transvaal is 48% chromium(III) oxide, 18% iron(III) oxide, 15% aluminum oxide, 3% silicon dioxide, and 12% magnesium oxide.

In the United States, the 3 most common methods of producing chromium(VI) compounds are the high-lime, the low-lime, and the lime-free processes. [4,5] Each of these processes involves the roasting of chromite ore with soda ash and various amounts of lime with subsequent treatment to form sodium chromate. Other chromium(VI) compounds may be formed by a change of pH and the addition of other compounds. Solutions of chromium(VI) compounds thus formed may then be crystallized, purified, packaged, and sold.

The consumption of chromite ore in the United States is shown in Tables XI-1 and XI-2. Chromium(VI) compounds commonly manufactured include sodium dichromate, sodium chromate, potassium dichromate, potassium chromate, ammonium dichromate, and chromium(VI) oxide. [6] Other chromium(VI)-containing materials commonly manufactured are various paint

and primer pigments, graphic art supplies, fungicides, wood preservatives, and corrosion inhibitors. [2,6] Synonyms for chromium(VI) oxide are chromic acid anhydride and chromic trioxide. Some authors have also used the term "chromic acid" synonymously for chromium(VI) oxide, others have used it for aqueous solutions of chromium(VI), and still others for the doubly protonated chromate ion. Chromium(VI) has been used in the manufacture of paper matches, lithography solutions, and tanning solutions. [7] Chromium(VI) has been found in glue, [8] cement, [9-11] detergents, [12] and other materials, including chromite ore. [13] NIOSH estimates that 175,000 workers are potentially exposed directly to chromium(VI) and a list of their occupations compiled by the US Public Health Service [14] is shown in Table XI-3.

The significant chemical and physical properties of selected chromium(VI) compounds are shown in Table XI-4. This list consists of all the chromium(VI) compounds found in the Handbook of Chemistry and Physics. [15]

Before describing the effects of chromium on humans and animals, a brief analysis of the chemical properties should enable the reader to better understand the problems encountered in describing accurately the chromium(VI) agents which have been responsible for these effects. Under environmental conditions where oxygen is present, chromium exists in 3 principal forms: elemental chromium or chromium(0), trivalent chromium or chromium(III), and hexavalent chromium or chromium(VI). Chromite, a compound of chromium(III), and crocoite, a lead chromate mineral, are the 2 principal forms of naturally occurring chromium. The former mineral is used commercially for the production of chromium-containing materials. In

recovering chromium from chromite, chromium(III) is oxidized to chromium(VI) by atmospheric oxygen at a high temperature. Chromium(VI) is produced in a water-soluble form by adding soda ash to the melt. When leached by water a highly alkaline solution of sodium chromate is formed. Sodium bichromate is produced by acidifying this leachate with sulfuric acid.

The form that chromium(VI) assumes in aqueous solution depends on the pH and chromium(VI) concentration, but chromium(VI) is always hydrated and appears as a monochromate, bichromate, or polychromate ion, protonated to various extents. As the pH is decreased, chromium(VI)-containing ions are increasingly polymerized and monochromate and polychromate ions are increasingly protonated. As chromium(VI) concentration increases, these ions are increasingly polymerized.

The oxidizing ability of chromium(VI) in aqueous solution has a great dependence on pH and a much smaller dependence upon chromium(VI) concentration. Aqueous chromium(VI) solutions are stable towards redox (reduction-oxidation) at moderate and high pH but at low pH can oxidize water to oxygen, resulting in chromium(III). At pH above 4, chromium(VI) is thermodynamically a weaker oxidant than atmospheric oxygen. As the pH increases above 4, one would expect chromium(III) to be oxidized by oxygen to chromium(VI). Until the pH is increased to 11-12, however, too little chromium(III) can be maintained in solution to allow effective oxidation of chromium(III) by oxygen. Clearly, the compounds of chromium(VI)--chromates, dichromates, or chromic acid anhydride--lose their identity upon hydration and tend to be converted by water to whatever forms of chromium(VI) that are thermodynamically stable at the prevailing pH and

chromium(VI) concentration. During the process of dissolving a chromium(VI) compound by water, changes in pH may occur because of hydration. The presence of buffers and reducing materials may influence the pH of the resulting solution.

Detailed chemical analyses of airborne chromium aerosols are frequently not feasible, and as an approximation it is often assumed that aerosols in the workplace have characteristics identical or similar to those of the emission source. Perhaps any assumption made on this basis is no more than a first approximation of the characteristics of an aerosol. Factors which may influence aerosol characteristics are ambient temperature and humidity, the pressure of other airborne agents, and particulate size and lifetime of the aerosol. Dusts from chromic acid anhydride, sodium chromate, sodium dichromate, both anhydrous and dihydrate, are hygroscopic and deliquescent in humid air but potassium dichromate and chromate are not. The ultimate degree of droplet size is determined by time, temperature, and humidity. Any change of droplet size due to absorption of water would change both the pH and chromium(VI) concentration. The chemical properties of the aerosols may be changed by the presence of other airborne agents. Although these examples are oversimplified, it is obvious that the composition of these dry chromium(VI) sources may be readily modified through aerosol formation and transmission.

The fate of aerosols encountering skin surfaces or the respiratory tract is uncertain and has not been well studied. However, contact of chromium(VI) aerosols with moist, buffered, physiologic surfaces would be expected to modify the pH and any oxidizing capabilities of chromium(VI) aerosols. Generally the physiologic response, and not the fate of the

aerosol, has been of interest to most occupational health researchers.

Historical Reports

What were probably the first cases of occupational injury due to exposure to chromium(VI) were reported in 1827 by Cumin. [16] He observed 2 cases of ulceration of wrists and arms of dyers who immersed their hands in a solution of "bichromate of potass." He also observed another dyer who developed psoriasis diffusa of the hands which, after some time, degenerated to impetigo despite the fact that during this interval exposure to dichromate had been markedly diminished. A fourth person, who was employed in the manufacture of potassium bichromate, had tissue sloughs on the fingers and on the glans penis. The finger lesion was in an area where there had been either a wound or an abrasion of the cuticle. Cumin described the effects of habitual application of bichromate solution to the skin as an eruption of papulae which become pustular and, upon prolonged exposure, develop deep sloughs under the pustules. The sloughs were described as peculiarly penetrating to the extent of producing in one instance a complete perforation of the muscular substance of the hand.

Ducatel [17] in 1753 noted that ulceration of the skin could occur from the action of potassium bichromate. He also described a worker who accidentally drank some of it and vomited violently until his death 5 hours later.

Delpech and Hillairet in 1869 [18] described the manufacture of potassium chromate and bichromate in Argenteuil, France, and the effects on workers which resulted from exposure to those chromium(VI) materials. In the process described, chromite ore was either roasted with potassium

nitrate, thus producing potassium chromate, or with potassium sulfate and calcium carbonate, followed by treatment with sulfuric acid, to produce potassium bichromate. Seven cases were described in which all workers had perforated nasal septa and 3 also had skin ulcers. Their exposures were to both acidic and alkaline chromium(VI) salts but not to chromic acid anhydride.

In 1884 Mackenzie described [19] the toxic effects of potassium bichromate. He was told by a workman, who had been engaged in the factory for 15 years, that destruction of the nasal septum sometimes took place after 24-48 hours of exposure to bichromate. It is likely that exposures were massive in the plant for at that time hand-rabbled reverberatory furnaces were used [6] with little or no forced ventilation or good work practices.

DaCosta et al [20] in 1916 described in detail 19 of 44 cases of chrome ulcers in tanners and dyers. The most common sites of ulcers were the folds of the dorsal surface of the fingers over the knuckles, with other cases on palms, forearms, backs of hands, interdigital folds, sides of fingers, edges of finger nails, wrists, knees, and on other parts of the body, notably 1 near the groin and another on the foreskin of the penis. It was noted that the ulcerated area had been kept wet with chromate solution in practically all cases. Aside from describing the etiology of the ulcerations, the authors suggested preventive measures including various impervious coverings for the hands and wrists and a preventive ointment of lanolin and petrolatum; therapy consisted of soaking in hot lead water (diluted lead subacetate) and carbonate of soda.

In 1925, Parkhurst [21] reported 3 cases of chrome dermatitis in workers in contact with blueprints that were fixed in a solution of potassium dichromate. One case was a 19-year-old woman who had been engaged in the production of blueprints for 6 weeks. The appearance of the lesion was that of crowded vesicles of pinpoint size on a diffusely erythematous and edematous background on the hands, wrists, and forearms. She showed a positive patch test with a 0.5% solution of potassium dichromate. The eruption subsided a few days after discontinuation of exposure. Frequent rinsing of hands with a solution of sodium bisulfite and then with water was suggested as a preventive measure to reduce hexavalent chromium to trivalent chromium. The other 2 cases treated by another physician were apparently similar. He prescribed treatment with a 1% solution of aluminum acetate, Lassar's paste, and calamine lotion.

Bloomfield and Blum [22] in 1928 published a study of workers engaged in a chromium plating operation. Workers were exposed primarily to an acidic mist of chromium(VI), which the authors called chromic acid, emanating from plating tanks. Of the 23 workers examined in the operation, 20 had perforated or ulcerated nasal septa, inflamed mucosa, nosebleed, and cutaneous ulcers ("chrome holes").

In the same year, 12 cases of ulceration and signs of irritation of the respiratory tract from solutions of "chromic acid" were reported by Blair. [23] The workers suffered from coryza, sneezing, watery discharge from the eyes and nose, itching and burning of the nose, ulceration of the nasal mucosa, perforation of the nasal septum (chrome holes), and ulcerative lesions of the hands and fingers (chrome ulcers).

In 1930 the Inspectorate of Factories in London issued a report [24] which dealt with the examination of 223 persons engaged in chromium-plating and an unspecified number of people engaged in anodic oxidation. Of the 223 chromium-plating workers, 95 (42.6%) had dermatitis, skin ulcers, or scars from old skin ulcers; 116 (52%) had perforated or ulcerated nasal septa or "devitalization of the mucous membrane." Times from onset of exposure to appearance of symptoms were as short as 2 weeks for ulceration of the nasal mucous membrane and 6-48 months for perforation of the nasal septum.

Smith [25] in 1931 described a man who, upon admission to hospital, had ulceration of the skin of both hands, difficulty in breathing, and tenderness of muscles of extremities. Prior to hospitalization he was engaged in washing zinc plates with a solution of ammonium bichromate. Smith observed erythema of the forearms and hands, desquamation on areas of fingers and palms, vesicular lesions, and shallow ulcers on both hands and forearms. In addition, she noted 2 similar lesions on the abdomen. The diagnosis was chronic chrome poisoning with dermatitis venenata, acute nephritis, asthma, and acute myositis of the upper and lower extremities. The patient was patch- and intradermally-tested with solutions of ammonium bichromate followed by evidence of sensitization. Pfeil [26] in 1935 reported 2 cases of pulmonary carcinoma in men who worked in the chrome industry in Germany. In 1911, a foreman in a large chromium manufacturing plant in Germany complaining about coughing and expectoration was examined by Pfeil. [26] The man's sputum had a reddish tinge. Costal pleurisy set in accompanied by a bloody exudate. The patient also suffered fractured ribs and was diagnosed as having a lung tumor. Post mortem examination

confirmed his diagnosis of primary pulmonary carcinoma with metastases. In the next year, Pfeil treated a second patient for exudative costal pleurisy. This patient, who worked in the same chrome plant as the first, was found to have pulmonary carcinoma upon his death. The foreman was involved in a secondary process where he was apparently exposed to residues from quinone production which probably contained a complex mixture of chromium(III) and chromium(VI). The second man was said to work in the chrome industry but no further description was given. Five more men died from lung cancer in this same chrome plant before 1935. Of the cases of lung cancer and gastrointestinal cancer studied by Teleky, [27] some occurred among chrome workers. Teleky concluded from this that chromium is a lung carcinogen and might be a gastrointestinal carcinogen, but the data he presented do not support more than a suggestion of the relationships.

In later years, many additional deaths from lung cancer occurred in the German chromate industry, [27-32] but it was not until 1948 [33] that an excessive incidence of lung cancer was reported among workers in the United States chromate industry.

Effects on Humans

In a review, Mertz [34] summarized the occurrence of chromium in nature and its function in biologic systems. Later, Glinsmann and Mertz [35] studied the relationship between chromium(III) and glucose tolerance in humans by the oral administration of aqueous solutions of chromium(III) chloride. Six subjects with maturity onset diabetes (where the impairment in glucose tolerance did not appear to be related to a simple insulin deficiency but rather insulin effectiveness appeared to be reduced) were

given 0.06-1 mg chromium(III) 3 times/day with meals for periods of 15-120 days. During this time, oral glucose tolerances were determined. Three of the 6 had improved tolerances while on chromium(III), compared to control periods. In 10 nondiabetic subjects with normal oral glucose tolerance, administration of 0.15-1 mg chromium(III)/day for 21 days resulted in no detectable alterations. The authors interpreted these results to suggest that chromium is required for optimum glucose use in man.

Several studies have reported and reviewed concentrations of chromium in various biologic tissues and fluids. [5,36-42] However, any interpretation of the amounts of chromium found in biologic samples should be accompanied by a close scrutiny of the analytical chemical methods employed. As new, more sensitive, and precise methods have been developed and used, authors have reported lower estimates of the quantities of chromium in certain biologic materials. [38,43] The National Academy of Sciences-National Research Council Committee on Biologic Effects of Atmospheric Pollutants [44] reported a wide range of concentrations of chromium occurring in biologic samples from both unexposed and occupationally exposed populations. For this reason, it would be very difficult to interpret biologic concentrations of chromium as a measure of the absorption of chromium.

Mancuso [41] reported that men exposed to airborne water-soluble chromium compounds excreted more chromium in the urine than those exposed to water-insoluble ones. He also noted elevated concentrations of chromium in the blood and urine for several years after exposure to chromium-containing materials. However, because of the wide disparity of "normal" and "exposed" blood and urine concentrations reported in the literature,

any such correlations between exposure and biologic concentrations of chromium must be interpreted with caution.

Chromium(VI) as chromium(VI) oxide, chromic acid, chromate, or polychromate, is potentially an oxidizing agent that may react with reducing (organic) matter to form chromium(III). [45] It appears that some biologic interactions with chromium(VI) may result in reduction to chromium(III) with some subsequent combination with organic molecules. [44] Koutras et al [46] have shown that concentrations of 5.25 μg sodium chromate/ml of human blood inhibited the activity of glutathione reductase in vitro. Grogan and Oppenheimer [47] have demonstrated a strong bond between chromium(III) and human plasma proteins, but binding with chromium(VI) is quite weak at physiologic pH. Chromium(III) has been shown to affect glucose and lipid metabolism in animals [48-51] and man. [34,35,37]

Under various conditions, reactions of chromium(VI) and chromium(III) with human skin have varied. Samitz and Katz [52,53] found that 0.72 g potassium dichromate/liter (pH 4.5) was reduced by abdominal skin from autopsy in 2 days at 37 C, and proposed that cystine, methionine, hemoglobin, and lactic acid may have been the reductants. Mali et al [54] reported that cadaverous dermis did not chemically reduce sufficient chromium(VI) to be detectable after 2 days of exposure to 9.5 g potassium dichromate/liter (pH 4.05) but that lactic acid, a skin component, was rapidly oxidized at pH 4.3 by 9.8 g potassium dichromate/liter. In contrast, Spier et al [55] found that chromium(III) was oxidized in the presence of air and skin scrapings at pH's 4 and 10. In the absence of the scrapings, no oxidation occurred. In additional experiments, they found

that ultraviolet radiation and increased pH's enhanced the rate of oxidation of chromium(III). These authors proposed that squalene, an easily oxidized agent present in the sebaceous secretions of the skin, was one of the intermediates responsible for the oxidation.

From numerous reports in the literature, it may be stated unequivocally that chromium(VI) may cause skin ulcers, [5,16-20,22-25,41,56-62] ulcers of the nasal mucosae, [5,19,22-24,41,56-61,63] and perforations of the nasal septum. [5,18,19,22-24,33,41,56-58,60,61]

Chrome ulcers may appear anywhere on skin given sufficient contact with acidic [5,16-20,22-25,41,56-62] and alkaline [5,18,61,62] solutions of chromium(VI). The most frequently reported sites have been nail root areas, skin folds over the knuckles, finger webs, the backs of hands, and forearms. [16-18,20,61]

Edmundson [61] examined 285 workers in a US chromate-manufacturing plant. The chemicals produced from chromite ore in this plant were chromium(VI) oxide, potassium dichromate, potassium chromate, sodium dichromate, sodium chromate, and ammonium dichromate. He reported in 1951 that 198 (69.5%) had chrome ulcers or scars and 175 (61.4%) had perforations of the nasal septum. The full report of the study by the US Public Health Service [5] gave a detailed description of the lesions. DaCosta [20] in 1916 described the lesions as being associated with joint penetration to an extent where amputation was sometimes required. The author patch-tested 56 of those with chrome ulcers with a solution of potassium bichromate (0.5%) and recorded 2 positive responses in men who had a history of dermatitis. The author concluded that there was no evidence to indicate a relationship between the development of chrome

ulcers and sensitization of workers exposed to chromic acid or its alkali-metal salts.

Of several papers dealing with the inhalation of chromium(VI) in which atmospheric levels are given, a number have dealt predominately with exposure to mists of chromium(VI) from plating tanks. [22,56-60,63-65] Each of these papers reported airborne chromium(VI) concentrations measured at the time of the study, but none reported the pH's of the aerosols collected.

In the study by Bloomfield and Blum, [22] 6 plating plants were surveyed and the airborne concentration of chromium(VI) was determined in each. Nearly all of the 39 samples were collected above the plating tanks near the points where the operators stood, and at breathing level. Chromium(VI) was collected in 16-oz bottles fitted with Greenberg-Smith impingers. The samples were analyzed by iodometric titration in those instances where the concentration was high. Review of the authors' iodometric titration procedure suggests the sensitivity was about 270 μg chromium(VI) oxide/cu m. In the cases where the concentration was reported as 1.2 mg chromium(VI) oxide/10 cu m, the more sensitive hematoxylin method was probably used. The smallest concentration of chromium(VI) oxide this method was capable of detecting and estimating was 800 μg chromium(VI) oxide/10 cu m (41.6 μg chromium(VI)/cu m). Of 19 workers in the chromium plating area, 17 had inflamed mucosa, 11 nosebleed, 6 chrome holes, 4 ulcerated septa, and 3 perforated septa. Using these data and the occupational histories of the workers, the investigators estimated the airborne concentrations of chromium(VI) to which some workers were exposed daily during their employment in the plating room. The authors felt that

their determinations of the airborne chromium(VI) concentrations were closely related to the probable exposures of those persons who were employed only a short time, since the ventilation system in use at the time of the survey had been the same throughout these individuals' employment.

Exposures were estimated for 23 workers who were given physical examinations. Four of these were controls with no known exposure to chromium(VI) oxide or mists containing chromium(VI). Estimated exposures for the remaining 19 ranged from 60 to 2800 μg chromium(VI)/cu m. Six platers were exposed to chromium(VI) at an estimated concentration of 60 μg/cu m for 6-7 hours/day. Duration of employment for these 6 was 1 week-7 months. All 6 had inflamed mucosa and 4 had nosebleed. Their exposures in the past may have been different from those observed at the time of the study, but the data indicate that distinct injury to the nasal tissues can result after relatively short exposures. The exposures of 6 platers were short enough to suggest that 60 μg chromium(VI)/cu m may inflame nasal mucosae and produce nosebleed in a matter of weeks. The role that direct transfer of corrosive chromium(VI) from environmental surfaces to nasal mucosa may have played in the production of nasal pathology was not evaluated.

In 1953 Lumio [60] reported a study involving 33 chromium platers (20 men and 13 women) exposed to "kromgaserna" (chromium gases) and "kromangorna" (chromium fumes) in 16 plants in Finland. Twenty-four had signs of cutaneous injury; 14 had lesions and 10 had scars due to lesions. Thirteen reported burning eyes and excessive tearing, 10 had greater than normal exhaustion, and 6 had prolonged headaches in the evening. Ear, nose, and throat signs and symptoms which were reported were nasal catarrh

in 19, repeated nosebleeds in 17, persistent sore throat in 9, persistent hoarseness in 8, impaired olfactory sense in 6, coughing in 5, and ear irritation in 3. The author concluded from his investigation that the symptoms of ear irritation were not necessarily due to chromium. The pathological changes observed in the noses were ulceration and dried secretions in 9, scars and dried secretions in 14, septal perforation in 4, but 6 were free of nasal irritation and ulceration. Time spent in chromium plating was less than 1 year for 3 persons, 1-5 years for 17, 6-10 years for 5, and over 10 years for 8. Of the 33 workers, 3 did not use rubber gloves, 11 did not use rubber aprons, and 29 did not use protective goggles. None of the 33 used respirators. In 1 particular shop where there were 3 workers, no protective measures were employed except 1 suction pump. Two had perforated septa and 1 had an ulcerated nose. Nine shops lacked ventilation. Each of the shops was surveyed by taking samples 50-60 cm above the baths. The results from the different shops did not differ significantly in spite of the fact that 9 did not have ventilation. The highest airborne chromium concentration found was 3 μg/cu m, reported as chromium(VI) oxide. The authors felt that occasional accidents, such as failure of protective equipment, were responsible for the signs and symptoms reported. However, this particular failure should have only affected 9 of the shops, the ones with ventilation. It is likely that recently introduced ventilation had reduced the airborne chromium(VI) concentrations from what they had previously been.

Kleinfeld and Rosso [59] studied 9 chromium plating workers exposed to the solution and airborne mist emanated from tanks of acidic chromium(VI). The airborne chromium(VI) concentrations were 90-700

μg/cu m. The exposure periods were 2 weeks-12 months. Each of the workers studied, ages 18-48, sustained exposure to the mists intermittently throughout the normal workday. Six workers complained of lacrimation, nasal itching and soreness, and nosebleed. One worker suffered epigastric pain that subsided when he was transferred to a different job. Four of the men had perforated nasal septa, 3 had ulcerated septa, 2 had moderately injected septa, and 1 had moderate congestion of the turbinates. No abnormal pulmonary findings on auscultation were found. Chest X-ray findings were negative. These data again indicate that lengthy exposures are not necessary to produce adverse effects since septal perforation was reported after an exposure of as little as 2 months. Considerable splashing of the plating solution was encountered. Apparently work practices were poor.

Gomes [56] reported the experience of electroplaters in the State of Sao Paulo, Brazil. The concentrations of airborne chromium(VI) were determined in 81 electroplating operations using solutions of chromium(VI), probably prepared from chromium(VI) oxide. Concentrations of airborne chromium(VI) were determined by using a universal testing kit with syringe-type pump and filter paper. Unfortunately, a direct correlation between those exposed to a given airborne concentration of chromium(VI) and the 303 platers who were examined clinically cannot be made.

Of the 8 hard-chrome plating plants surveyed, 2 had airborne concentrations of chromium(VI) of less than 50 μg/cu m. In these 8 plants, 35 persons were examined, and all had cutaneous or mucous membrane lesions; ulcerated nasal septa were found in 14 workers, perforated nasal septa in 17, and other cutaneous or mucous membrane lesions in 4.

Sixty-three of the 73 brilliant-chrome electroplating industries were surveyed for airborne chromium(VI) concentrations. Of these, 33 had environmental levels of chromium(VI) of less than 50 μg/cu m. In the 73 industries, 223 workers were examined, 85 of whom had ulcerated nasal septa and 45 had perforated nasal septa. Of the remaining 93, 56 had other, unspecified mucous membrane or cutaneous lesions. Approximately 50% of the workers had yellowing and erosion of teeth. Coughing and expectorating were observed in half the workers in the brilliant-chrome industries. Duration of exposure was unstated, but it was mentioned that the harmful effects were noted in less than a year, and that few workers remained many years in the industry. Individual safety equipment was lacking in 26.6% of the plants; this may have been responsible for the high incidence of cutaneous ulcers.

Zvaifler [63] and Gresh [64] published separate reports of an anodizing plant study. Zvaifler [63] noted that there was a distinct difference in the physiologic effects of chromium(VI) mists from plating tanks and the mists from anodizing tanks but he presented no data to support his conclusion. He mentioned that the chromium(VI) poisonings which resulted from exposure to mists emanated from anodizing tanks containing "5% chromic acid" generally involved ulceration of the nasal mucosa and skin rashes but rarely perforation of the septum. Gresh [64] reported that the original ventilation system allowed chromium(VI) concentrations in the vicinity of the tanks to be 210-600 μg/cu m. Under these conditions, persons working up to 200 feet from the tanks were apparently affected by chromium(VI) aerosols and developed nasal ulcerations. When more powerful exhaust fans were installed, the airborne

chromium(VI) concentrations in the vicinity of the tanks decreased to 45-50 μg/cu m. Little or no improvement was observed in the physical condition of the employees. Operators were furnished with and required to wear cartridge respirators designed for "chromic acid mist." In 4 weeks the use of respirators did not improve the condition of the operators. At the same time, another group of workers was excluded entirely from chromium(VI) aerosols and at the end of 4 weeks they showed definite improvement to an "almost well" condition. Thus, even with respirators, the operators working in the vicinity of airborne chromium(VI) concentrations of 45-50 μg/cu m continued to have nasal irritation. Subsequently, the exhaust system was revised and when airborne chromium(VI) concentrations became "negative," the nasal irritation subsided. Unfortunately, the authors did not indicate what they considered to be a "negative" finding.

In 1973, an investigation of a chromium-plating establishment [57,58] was carried out by NIOSH. The 37 workers in the chromium- and nickel-plating area of the plant were examined. Twelve experienced nasal ulceration or perforation after having been employed less than 1 year. Fifteen others had been on the job more than 1 year and had ulceration or perforation of the nasal septum. The chromium- and nickel-plating line used a solution of technical grade chromium(VI) oxide at a concentration of approximately 300 g/liter at 118-120 F. In the chromium- and nickel-plating area, airborne chromium(VI) concentrations ranged from less than 0.71 up to 9.12 μg/cu m (mean 3.24 μg/cu m; SD 2.48 μg/cu m; 25 samples; for the purposes of calculating the mean and SD, those filters containing less than 0.34 μg chromium(VI) were taken as 0.34 μg). The method used for determining airborne chromium(VI) concentrations was that of Abell and

Carlberg. [66] The limit of detection was approximately 0.34 μg/filter. Fifteen workers in other areas of the plant were examined and 14 of these had normal nasal findings upon examination. One person had a perforated nasal septum but admitted to a previous occupation which may have involved chromates. The exposures to chromium(VI) of 3 of the 15 were found to be less than 1.34 μg/cu m. Spot tests revealed that chromium(VI) was present on most work surfaces in the plant and on the fingertips of most workers in the chrome- and nickel-plating area. The investigation revealed that personal protective equipment was not worn and employees frequently wiped their faces and picked their noses with unwashed fingers or while wearing gloves. The authors thus concluded, probably correctly, that poor work practices were responsible to some degree for the nasal involvement. Determinations of pulmonary involvement were not reported in the study.

In another study by NIOSH [65] of a different chromium plating plant, a maximum airborne chromium(VI) concentration of 3 μg/cu m was found. In this operation, the plating solution contained approximately 210 g chromium(VI) oxide/liter. No ulcerated nasal mucosae or perforated nasal septa were found, although half of the 32 employees had varying degrees of mucosal irritation. This incidence of mucosal irritation was not thought to be significant by the investigators because the survey was carried out at the peak of the 1972-73 influenza epidemic. Fifteen workers had been employed 8 years or more, 7 between 4 and 8 years, 4 between 1 and 4 years, and 6 less than 1 year.

Although he did not report airborne concentrations of chromium(VI), Meyers [67] in 1950 observed 2 patients who had inhaled chromic acid mists, for only a few hours one day. One man developed a cough, severe frontal

headaches, pulmonary congestion and edema, dyspnea, and persisting substernal pain. The other developed hoarseness and a cough productive of green mucoid sputum. Five months after exposure, the X-ray examination showed some emphysematous changes and a small pleural effusion.

Pascale et al [68] in 1952 reported 5 persons with hepatic injury apparently due to exposure to chromic acid mist from plating baths. One who had been employed 5 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 microscopic changes resembling those found in toxic hepatitis. To investigate the possibility that the liver damage was of occupational origin, 8 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 3 workers who had been exposed to chromic acid mists for 1 to 4 years, liver biopsies and a series of 12 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 1 of his liver function tests indicated a borderline abnormality. The urinary excretion of chromium (2.8 and 2.9 mg/24 hours) by the 2 workers employed 4 years was greater than the excretion (1.48 mg/24 hours) by the worker employed 5 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 5 exhibited some signs of damage to the nasal mucosa. This plus the concentrations of urinary chromium suggests that exposures to chromium(VI) were significant, but no

environmental data were reported.

Several authors [5,18,19,33,41,62] have dealt with exposures to chromium(VI) materials, exclusive of chromic acid anhydride and aqueous solutions thereof (known as "chromic acid").

In the chromate-producing industry in the United States, only a small part of which produced chromic acid anhydride, the principal exposures to chromium(VI) were probably to sodium chromate and bichromate. To a lesser degree, exposure to potassium chromate and bichromate was also present. In 1884 Mackenzie [19] described the toxic effects of potassium bichromate. He related having been told by a workman, who had been engaged in the factory for 15 years, that destruction of the nasal septum sometimes took place after 24-48 hours of exposure. From his own experience, Mackenzie observed that this destruction was preceded by general congestion of the mucous membrane, nosebleed, and coryza. The turbinates, nasal pharynx, and lower pharynx were also ulcerated. What he described as the lower respiratory tract (probably the lower part of the upper respiratory tract) was generally found to be highly inflamed and swollen. Accompanying the catarrhal symptoms, there were sometimes intense headache, inflammation and perforation of the tympanic membranes and subsequent otorrhea. At that time hand-rabbled reverberatory furnaces were used [6] and since there was little or no forced ventilation or good work practices, it is probable that exposure levels were high.

Much later, in 1948, Machle and Gregorius [33] described the incidence of nasal irritation and septal perforation in a chromate-producing plant that manufactured sodium chromate and bichromate. The incidence of nasal septal perforation was 43.5% in 354 employees. Airborne

chromate concentrations were determined to range from 10 to 2,800 μg/cu m at the time of the study, but the plant has been in operation for at least 17 years. Some employees had probably worked in the plant when reverberatory furnaces were used, a notorious source of high exposure.

In the early fifties, an epidemiologic study as reported by Bourne and Yee [3] and by Mancuso [41] was carried out in a single chrome plant in Ohio which produced sodium chromate and bichromate but no chromium(VI) oxide. In this study, the overall incidences of nasal septum perforations, chronic chemical rhinitis, and chronic chemical pharyngitis were significantly greater than those of the control group. The airborne chromium(VI) concentrations were 0-500 μg/cu m. However, the incidences of these disorders were not significantly greater than those of controls in the groups of workers exposed to less than 85 μg chromium(VI)/cu m.

In 1953 the US Public Health Service investigated the hazards associated with the chromium-producing industry in the United States, [5] excepting the plant in Painesville, Ohio, which had been studied earlier by Mancuso and others. [3,41] It is probable that throughout the industry most chromium(VI) exposures were to sodium chromate and bichromate since these are the principal intermediate and end products, respectively, of the usual alkaline roasting operations. The range of time-weighted exposures for the occupational groups was 5-170 μg, with a mean of 68 μg water-soluble chromium(VI)/cu m. This water-soluble chromium(VI), not specifically defined, was probably mostly sodium chromate and bichromate, from information on the manufacturing processes involved in the plants. In these plants there was also cross-contamination of the chromium materials generated in the various work areas. To illustrate, results of analysis of

airborne chromium showed airborne chromite ore and acid-soluble, water-insoluble chromium in nearly all areas of the plants. Airborne water-soluble chromium(VI) was found in all areas of the plants. Of the 897 workers examined, 509 had perforation of the nasal septum. A severely red throat was found in 95 of the 897 workers and edema of the uvula in 67. The incidence of these signs, as was the incidence of ear disorders such as discharge, impaired hearing, and tinnitus, was more than twice that found in nonchromate-worker control groups. Liver enlargement was noted in 14 chromate workers. Those with enlarged livers were at least 15 years older and had worked an average of 4 years longer in the chromate industry than those without enlarged livers, but the number in the group was too small to allow a statistical comparison with a group not exposed to chromate. Those with cutaneous ulcers or scars of ulcers numbered 451. Most of the active ulcers had occurred within the 6 months prior to the study. Lung cancers were also found in this group and will be discussed later.

Urinalysis revealed white and red blood cells and casts with greater frequency than is usually observed in the average industrial population. Casts in urine were found in a greater percentage of workers who had worked 10 years or more than in those who had worked less than 10 years. Frequency of white blood cells in urine of chromate workers showed an increase with years of exposure. The number of red blood cells in urine did not change appreciably with years of chromate exposure.

As a result of dental examinations of 561 workers, incidences of keratosis of the lips, gingiva, and palate; yellow-stained teeth and tongue; and periodontitis were greater than twice the incidences in a control population of 124.

The observed signs of excessive exposure to chromium(VI)--nasal mucosal irritation and ulceration and to a lesser extent nasal septal perforation--were likely, in the acute or subacute nature of the lesions, to be closely related to airborne chromium(VI) at the average concentration measured at the time of the study--68 μg/cu m. There is reason to suspect that liver and kidney damage occurred, based on observations of enlarged livers and casts in urine, as a result of long-term exposure to chromium(VI), but the results were not conclusive.

Numerous cases of allergic dermatitis with varying degrees of eczema have been reported. [7-11,21,25,61,62,69-81] Parkhurst [21] in 1925 reported the case of a woman employed in blueprint production using a process where a 1% potassium dichromate solution was used as a fixative. He rubbed a 0.5% potassium dichromate solution on the right thigh of the woman and soon there was a local sensation of itching and burning. Twelve hours later, the patient developed a follicular erythematopapular dermatitis where the solution had been applied. A similar application was made to the left thigh with resulting itching and burning. However, the application of an aqueous saturated solution of bisulfite prevented the development of a dermatitis in this area.

In 1931, Smith [25] observed a case of chrome poisoning with manifestations of sensitization in a man employed in a photographic printing firm, where his duties involved handling and washing sheets of zinc treated with a solution of ammonium dichromate, and occasionally preparing the solution. The man developed a mild erythema 24 hours following a patch test with 1% ammonium dichromate solution on a 1-sq cm area of normal skin on his forearm. After 3 days the erythematous area had doubled in size and had

developed vesicles. Eight days later, an intradermal injection of 0.1 cc of a 0.5% aqueous solution of ammonium bichromate was given in the right forearm. Within an hour the patient developed a generalized pruritus with soreness at the site of the injection. Within 6 hours he had (1) a slight erythema at the site of a previously negative patch test, (2) an erythematous area 5 cm x 3 cm with tenderness at the injection site, (3) a localized patch of maculopapules on the area in which the patch test had been 9 days earlier, (4) a vesicular erythematous dermatitis covering the entire hands and lower parts of the forearms, (5) generalized mild erythema with a few urticarial wheals on the buttocks, and (6) a recurrence of the diaphoresis and sibilant rales he had had some 15 days earlier, upon admission to the hospital. The man recovered after his exposure to chromium(VI) ceased. Three control subjects were similarly injected and showed no reaction.

Hall [70] in 1944 reported 132 dermatitis cases in aircraft workers who had contact with a primer consisting of a suspension of zinc chromate powder and magnesium silicate in a xylene solution of certain resins, including a phenol-formaldehyde resin. Apparently, the mean duration of employment was 7 months (range: 1 week-9 years) for those who had dermatitis from the primer and who were allergic to zinc chromate pigment. A series of patch tests showed 90 of the workers (68%) were sensitive to the zinc chromate pigment only. (The zinc chromate pigment was apparently a mixture of zinc chromate and calcium carbonate.)

In 1949, Pirila and Kilpio [71] reported 45 cases of allergic contact dermatitis observed in the Helsinki area from 1945-48. Forty-one reacted positively to patch-testing with a 0.5% aqueous solution of potassium

dichromate (pH 4.15). The breakdown of cases by occupation was as follows: bookworkers, 11; cement and lime workers, 10; radio factory workers using a photostatic procedure, 7; metal factory workers, 4; painters and polishers, 4; fur workers, 3; others, 6.

In 1952, Engebrigtsen [10] reported 8 cases of cement eczema among 300-400 Norwegian workers exposed "more or less directly" to cement dust that contained 0.002-0.020% water-soluble chromium(VI) described only as "water-soluble chromates." Seven of the 8 patients reacted positively to patch tests with 0.5% aqueous solutions of potassium bichromate. Four of the 8 also gave positive reactions to cement patch tests. None of the 10 persons who served as controls gave any positive reactions. Subsequently, the author tested the same 8 patients with a cement slurry that had been washed free of chromium(VI), and none of the people reacted positively. The authors found that chromium in the cement originated in the limestone and shale raw materials and in the chromium steel of ball mills. In 1954, Denton et al [72] analyzed portland cement for chromium, and reported a concentration of water-leachable chromium(VI) of 0.03-6.9 ppm and a concentration of total chromium of 28-60 ppm. These American cements tested contained much less water-soluble chromium(VI) on the average than the Norwegian cements. [10]

Denton et al [72] patch-tested a patient with a "strong specific hypersensitivity to potassium dichromate" with (1) a 50-ppm aqueous solution of potassium dichromate, (2) a filtrate containing 1 ppm water-soluble hexavalent chromium from American portland cement, and (3) a filtrate containing 4 ppm water-soluble hexavalent chromium from American portland cement. The patient repeatedly had erythematous, edematous, and

papulovesicular reactions. He did not react to distilled water. The control subjects did not react to any of these 3 chromium(VI) solutions. In 1960, Calnan [9] showed that British cement contained from nondetectable amounts to 12 ppm chromium(VI), expressed as potassium bichromate. He concluded that cement dermatitis was primary irritant dermatitis complicated by a secondary contact sensitivity to "hexavalent chromate" [chromium(VI)].

Winston and Walsh [73] reported that 6 out of 200 employees were incapacitated by chromate dermatitis in a diesel locomotive repair shop. One of the 6 cases was described; the dermatitis consisted of patchy, pruritic, erythematous, slightly scaly lesions extending from the dorsum of the hands over both forearms to the elbows. All were exposed to an alkaline diesel locomotive radiator fluid which was prepared from sodium dichromate, soda ash, disodium phosphate, and sodium silicate. One and one-half pounds of this powdered mixture, which contained 66% sodium dichromate, was dissolved in 2 gallons of water in an open pail. This solution (approximately 6% sodium dichromate) was poured into the radiator and diluted with about 210 gallons of water, giving a solution of about 0.08% sodium dichromate. All of the men gave positive reactions to 0.25% sodium dichromate (pH 4.25) patch tests and to samples of the radiator fluid (pH 10).

Walsh [62] in a summary report on chromate hazards in industry described results of some patch tests: 2% "chromic acid" applied for 24 hours on superficial skin abrasions produced a crusted lesion in 3 weeks; 0.5% sodium dichromate, reapplied daily for 3 days, produced a crusted lesion in 3 weeks; 0.5% potassium chromate, applied for 8 hours/day for 3

days, produced lesions in 3 days; 0.05% sodium dichromate, 0.005% sodium dichromate, and pure zinc chromate also produced lesions in 3 days after being in contact with the skin for 8 hours/day for 3 days. Lead chromate did not produce a reaction after the same exposure period. A 10% solution of chromium(III) nitrate produced redness after the solution was reapplied daily for 3 days.

Edmundson [61] patch-tested 56 men who had chrome ulcers with 0.5% potassium bichromate for 24 hours. Only 2 yielded positive reactions and they were said to have a history of chrome dermatitis. He interpreted his results to indicate that when chrome produces ulcers it does not sensitize workers.

Morris [8] in 1955 reported 2 cases of sensitization to chrome glue prepared at least in part from scraps of chrome tanned leather. Both patients gave positive reactions to the otherwise undescribed chrome-bearing parent material to which they were exposed, and both were allergic to chrome-dyed leather shoes. From the nature of the tanning process it seems probable that the substance causing the sensitivity was chromium(III). One of these patients reacted positively to a 0.1% solution of sodium bichromate.

McCord et al [7] described in detail the lithography process, as it existed in 1930, which used an extremely acidic solution of chromium(VI). Twenty-five lithographers and 12 tanning workers who had been exposed to chromium, but showed no signs of dermatitis, were selected for study. Each lithographer was patch-tested on normal skin with each of 3 different kinds of gauze dressings. The dressings were wetted with 1% potassium dichromate solution or 4.5% potassium dichromate solution (pH 4.05 and pH 3.75,

respectively) or water. Rubber tissue covers were placed over these dressings and observations were made after 24 hours when the dressings were removed. A second observation was made at the end of 48 hours. In a similar manner a 4.5% solution of ammonium bichromate, a 0.5% solution of chromium(VI) oxide (pH 1.4), and a control solution (pH 3.8) of monosodium phosphate, phosphoric acid, and water were applied on gauze pads to the forearms of the 12 tanners. Twenty of the 25 lithographers and 10 of the 12 tanners gave positive reactions to dichromate. Four of the 12 tanners developed a "trivial" papular dermatitis after testing with "chromic acid" (an aqueous solution of chromium(VI) oxide). Four of the 25 lithographers developed vesicles following applications of potassium bichromate but no vesicles following application of ammonium bichromate at equal concentration under similar conditions. No control solutions gave positive reactions. This report was apparently the first to note that injury from chromium(VI) could occur without previous skin trauma or disease.

Levin et al, [74] from similar studies conducted in the late 1950's, confirmed that chromium(VI) was the primary causative agent in lithographer's dermatitis. However, they found that trauma and the use of various other chemicals associated with lithography such as fat solvents and primary irritants made workers' skin more prone to irritation by the chromium(VI)-bearing materials.

In 1961, Fregert [69] described the manufacture of matches and demonstrated that match heads which contained chromium(VI) could partially dissolve when held in moist fingers and could cause an allergic eczematous contact dermatitis. The source of chromium(VI) was probably an ingredient of the manufacture since potassium dichromate is usually added both to the

igniting composition and to the striking composition. The author was, however, unable to find chromium(VI) in the striking composition, probably because it had been reduced to chromium(III). Although this study was done in Sweden, he analyzed matches from 21 countries and found concentrations as high as 1.7% water-leachable chromium(VI) expressed as potassium dichromate in unburnt matches and 1-10% of the original chromium(VI) concentration in the burnt matches. He stated that every patient in a group of 33 who had chromate eczema reacted positively to either unburnt or burnt match heads.

In 1963 2 separate studies [75,76] of dermatitis resulting from chromium(VI) used in the automobile industry were published. Engel and Calnan [75] investigated an outbreak of dermatitis in the British automobile industry among workers who were engaged in the wet sanding of primer paint containing zinc chromate. Almost all (91%) of them had positive reactions to a 0.5% solution of potassium dichromate (pH 4.15); however, a few did not react until the solution was made alkaline (pH 10.3)

Newhouse [76] found dermatitis in automobile assemblers from handling a chromate dip used as an antirust agent on bolts, nuts, screws, and washers. About one-quarter of these responded positively to potassium dichromate patch-testing.

Fregert and Ovrum [77] in 1963 reported a case of a welder who contracted a facial dermatitis after inhalation of and contact with welding fumes from either arc welding or oxygas welding. Subsequent investigation demonstrated that the chromium in certain welding rods could be oxidized to chromium(VI) and that chromium(VI) was dispersed into the air in the vicinity of the weld. The authors patch-tested 5 people who were

hypersensitive to chromate with an aqueous solution of collected welding fumes calculated to be 0.1% chromium(VI) (as potassium dichromate). All gave positive reactions. The authors elicited no response from 10 subjects not hypersensitive to chromate. Their analyses of various commercial welding rods showed chromium contents up to 18%.

A year later, Shelley [78] reported a similar case. A crane operator provided a history of chronic eczematous eruptions of both hands. Twenty-eight compounds were patch-tested and the only positive reaction was to an aqueous 0.25% solution of potassium dichromate (pH 4.28). Two and one-half months later, the man walked by an acetylene-welding operation where the fumes were strong and experienced appreciable inhalation of the fumes. On the next day he reported a rapidly developing vesicular flare on his hands. The dermatitis subsided after he avoided further contact with chromium-containing objects and welding fumes.

Jaeger and Pelloni [11] in France demonstrated that workers with cement eczema were sensitive to potassium bichromate. They patch-tested 32 patients with cement eczema and 168 patients with eczema from other causes. Thirty (94%) of those with cement eczema gave positive patch tests with aqueous 0.5% solutions of potassium bichromate while only 5% of the other eczema patients exhibited positive reactions from the bichromate. These authors further tested 8 of the patients with cement eczema who reacted to 0.5% aqueous solutions of potassium bichromate in patch tests. In addition, all reacted to aqueous 0.5% solutions of potassium chromate, chromic acid, ammonium bichromate, sodium bichromate, and ammonium chromate. These subjects failed to react to aqueous 0.5% solutions of chromium(III) fluoride or sulfate or to an aqueous suspension of lead

chromate (the concentration of chromate in an aqueous suspension of lead chromate should be approximately 0.2 ppm). All 3 masons with eczema reacted positively when tested with aqueous solutions of chromium(VI) oxide and of potassium bichromate at concentrations as low as 0.1%. One mason reacted to an aqueous 0.01% solution of chromium(VI) oxide and also to an aqueous 0.001% solution of potassium bichromate. In this part of the study, among 18 controls with eczema, there were no reactions to aqueous solutions of chromium(VI) oxide or potassium bichromate as concentrated as 3%, the most concentrated solution tested.

Perone et al [81] reported in 1974 the patch-testing of 95 construction workers who regularly worked with cement. An aqueous 0.25% potassium dichromate solution produced a reaction in 1 man and an aqueous solution containing 450 ppb (450 ng/g) chromium(VI) extracted from cement produced a reaction in another man. It is interesting to note that this second man did not react to the aqueous 0.25% potassium dichromate solution. At the time of patch-testing, 15 of the group had a mild dermatitis of the hands, and 25 had a more active disease manifested by eczematous lesions with vesicles, erythema, and fissures in various stages. Because of the paucity of reactions to chromium(VI) solutions, the authors considered cement dermatitis to be associated with the irritative nature of cement. The workers were clearly not generally hypersensitive to chromium(VI) solutions.

In 1962 Cairns and Calnan [80] treated a man who had been working with cement for approximately 6 months and who had developed cement eczema on the backs of the hands, fingers, and exposed parts of the arms and forehead. The man also noted that part of a green tattoo had become

nodular and itchy. The green pigment was found to contain chromium, but no determination of the oxidation state was made. The man reacted positively to patch tests of aqueous 0.1% and 0.5% solutions of potassium dichromate and a 2% solution of cobalt chloride, and scratch and intracutaneous tests with a 0.1% solution of potassium dichromate, but did not react when tested with a 1% solution of basic chromium(III) sulfate. Loewenthal [79] also observed a positive reaction to patch tests with 0.1-2% solutions of potassium dichromate in a man with a green tattoo shown to contain chromium(VI). The man was a bricklayer and had a persistent eczema of the hands and legs. An aqueous 0.1% solution of chromium(VI) oxide produced a positive reaction. Moistened portland cement, a solution of chromium(III) sulfate, and a solution of chromium(III) chloride did not yield positive reactions following patch testing.

The only report regarding the threshold of irritation came from the Soviet Union. [82] This study by Cooperman was intended to establish a maximum permissible concentration of chromium(VI) in atmospheric air. He exposed 10 "practically normal volunteers" to chromium(VI) condensation aerosols produced by heating chromium(VI) oxide. In attempting to establish the threshold of irritation for chromium(VI), he stated that 250 determinations were made with 12 different chromium(VI) aerosol concentrations ranging from 1.5 to 40 μg/cu m. None of the volunteers could perceive chromium(VI) at 1.5 μg/cu m. The threshold of perception for the most sensitive volunteer was 2.5 μg chromium(VI)/cu m. The authors felt that inhalation of air containing 10-24 μg chromium(VI)/cu m even for a brief period of time elicited the sensation of sharp irritation in the nostrils. Inhalation of chromium(VI) at lesser concentrations produced

slight irritation of the upper respiratory tract.

Goldman and Karotkin [83] in 1935 reported a case of acute exposure involving a 25-year-old woman who had swallowed an aqueous solution containing a heaping teaspoonful of potassium dichromate crystals. Shortly thereafter she had a paroxysm of vomiting. Two days later she was hospitalized. At this time she had severe nephritis and severe hepatitis, an erythematous skin eruption, and a "positive" chromium test in urine. The skin rash began to fade 13 days after the initial reaction and disappeared after 5 more days; she recovered from hepatitis and nephritis in 3 months.

Major [84] reported the development of severe nephritis in a patient the day after chromium(VI) oxide was applied to a wound as a cauterant; the man died 19 days later.

Vigliani and Zurlo [85] studied over a 3-year period approximately 150 workers in a plant producing alkali chromates; during this time the airborne chromium(VI) concentration range was 57-78 μg/cu m. Ulceration of the nasal septum, inflammation of the conjunctiva and laryngeal mucosa, and chronic asthmatic bronchitis were the most commonly seen disturbances, but their frequency was not mentioned. One case of nasal septal cancer and 1 of lung cancer were also observed. No data regarding sampling locations, sampling techniques, or analytical methods were presented.

Unequivocal evidence relating a specific chromium(VI) compound to the development of lung cancer in humans has not been developed. There is, however, epidemiologic evidence in workers and experimental evidence in animals that suggests carcinogenic properties of some chromium(VI)-

containing materials. This evidence is discussed in the following 2 sections.

Epidemiologic Studies

The first extensive epidemiologic studies involving exposure to chromium(VI)-containing materials and the risk of lung cancer were performed in Germany by Lehmann. [86] He found only 2 cancer cases and dismissed them as nonoccupational in nature but the reasons for this conclusion seem to be faulty in view of current knowledge. Lehmann gave no information on the extent of exposure to chromium(VI).

Later German reports, reviewed by Baetjer [87] in 1950, described at least 52 cases of pulmonary cancer in the chromate-producing industry and 11 cases in the chrome-pigment industry. She also reported 57 cases in the United States, and 1 case each in Switzerland and in England. All of the cases outside Germany involved the chromate-producing industry. She reported 22 years as the average length of employment of workers who developed pulmonary carcinoma in the German chromate-producing plants, in the German pigment plants as 12 years, and in the United States plants as 16 years.

One of the studies referred to by Baetjer is of particular interest. Gross and Kolsch [88] reported lung cancer in workers involved with the production of chrome pigments in Germany in 1943. In the industry investigated, lead chromate (chrome yellow) and zinc chromate (zinc yellow) were manufactured and shaded with other pigments. Lead chromate was prepared by precipitation from lead acetate and potassium dichromate. The precipitate was washed, filtered, pressed, and dried at 30-35 C with a

strong air draft. Longer washing produced higher percentages of basic lead chromate. Zinc chromate was prepared by adding zinc white (zinc oxide) to a small amount of water, keeping the temperature at 50 C, and then adding bichromate. The zinc yellow was then washed, filtered, cut, and dried at 50-90 C. It was noted that in these processes there was not much dust, but in the subsequent mixing with shading components, milling, grinding, and casking, a great deal of dust was evolved. Barium sulfate and iron(III) hexacyanoferrate(II) were often added at this point for shading chrome yellow to produce chrome green. From the 3 firms engaged in this manufacturing, 8 deaths from lung cancer were reported. The number of workmen involved was given for 2 of the 3 firms that reported 7 of the 8 deaths from lung cancer. The number of men involved in the 2 plants was probably less than 50, of which 7 died from lung cancer. The 7 had worked in the industry 5-17 years. The man with 5 years of exposure in the chrome-pigment industry also had worked 8 months in the chromate-producing industry. No estimates of the extents of exposure were given. It was noted that the 7 were exposed to dust of lead chromate and zinc chromate, and the eighth was exposed only to zinc chromate.

Very little was published [88] about the carcinogenicity of chromium(VI) pigments until 1975 when Langard and Norseth [89] reported their study of cancer in a Norwegian company comprising 3 separate plants. The company began operation in 1948 and produced only lead chromate pigment until 1951. From 1951 to 1956 both lead chromate and zinc chromate were produced. From 1956 to 1974, only zinc chromate was manufactured. Plant B began production in 1965 and plant C was built in 1972.

Airborne chromium concentrations were determined in plants A, B, and C; none of the workers examined, however, worked in plant C. No bronchial carcinomas were found in workers in plant B. Airborne chromium concentration was 0.19-0.43 mg chromium/cu m in Plant A, and 0.04-1.35 mg chromium/cu m in Plant B. Although chromium(VI) was not determined, most airborne chromium was probably chromium(VI) in light of the production processes involved. The authors noted that although ventilation had been altered in the plants during the period of production, the amount of pigment produced had increased; they conducted interviews which led them to conclude that the airborne concentrations of chromium were of about the same magnitude at present as in the past.

The company employed 133 persons between 1948 and 1972. Of these a cohort of 24 was derived comprising those who were employed for more than 3 years. Six members of the cohort were exposed for 4 years, 4 for 5 years, and 14 for more than 5 years.

Four cases of cancer occurred in the cohort--3 were in the bronchus and 1 in the pancreas.

One worker developed an anaplastic small cell carcinoma of the left main bronchus and died 20 years after his first exposure to lead chromate, and 17 years after his first concomitant exposures to lead chromate and zinc chromate. He left plant A after 6 contiguous years of exposure.

The second worker developed an oat cell carcinoma of the lower right bronchus and died 10 years after he was first exposed to lead chromate and zinc chromate in plant A. In his 7.5 consecutive years of exposure he mixed sodium bichromate and zinc white (zinc oxide) and sacked the finished pigment. He was described as a heavy smoker.

The third worker was diagnosed as having a highly differentiated carcinoma of the right lower lobe in 1972, 16 years after he began work in plant A. He was exposed to zinc chromate for about 8 contiguous years.

The fourth worker in the cohort developed gastrointestinal cancer diagnosed by the development of a large, metastatic liver and by the cytologic examination of ascites which showed adenocarcinoma. The man died in 1972, 18 years after his first exposure to lead chromate and zinc chromate; he had 4 continuous years of exposure.

Because the authors apparently determined that the pancreas was the primary site adenocarcinoma, and as there have been no other reports of chromium(VI) causing cancer of the pancreas, it seems improbable that chromium(VI) was the causative agent.

In addition to the cancer cases in the cohort, 1 man developed an adenocarcinoma of the prostate after an unmentioned exposure period and another, a 33-year-old man, was diagnosed as having an adenoid cystic carcinoma of the inferior nasal turbinate after working in the plant for 3 months. The plants in which these men worked were not designated.

In light of the short, less than 3-year, period of employment of the worker who developed prostate cancer and the lack of any other report linking exposure to chromium(VI) and prostate cancer, it is unlikely that chromium(VI) was responsible. Because the worker who developed a carcinoma of the nasal turbinate was exposed for only 3 months, an extremely potent carcinogen must have been present. Other reports [87,88] do not suggest that chromium(VI) is capable of producing cancer in such a short time.

The authors calculated the risk of getting lung cancer for each worker separately for each calendar year of the observation period. This

was accomplished by using the age-specific incidence rates of cancer supplied to them by the Cancer Registry of Norway. The total risk for the population of workers was then obtained by adding the risks for each worker for each year of the observation period. The expected number of cases of cancer obtained by this method was then compared to the observed number in the group. The expected number of lung cancer cases in the cohort was calculated to be 0.079 for the total period of observation. Since 3 cases were found, the observed/expected ratio was 38. The total number of man-years at risk of the cohort was 244.

The first study of the incidence of lung cancer in the United States chromate industry was reported by Machle and Gregorius [33] in 1948. Exposure in the plant had been to mixtures of chromium(III) and chromium(VI). This study was based upon data available from 7 chromate-producing plants for periods of 3-17 years, from 1930 to 1947. Available data regarding airborne concentrations of chromium(VI), reported as "chromates" were obtained from 4 of the plants. Among the plants, the concentrations of airborne chromium(VI) ranged from 5 to 11,500 μg/cu m. Evaluating individual workers' exposures is impossible, but a few conclusions may be drawn.

In plant A1 there were 18 deaths from lung cancer from 1936-46, 9 of which were diagnosed in 1944-45. Of these 9 men, 6 had exposure for only 6-12 years. In this plant, available exposure data indicate that chromium(VI) concentrations probably ranged from 10 to 500 μg/cu m during the years 1941-47. However, there was an excess of deaths from lung cancer in plant A1, 4.86/1000,(3,500 man-years, 1936-46) compared to the control population, 0.09 deaths/1000 (60,000 man-years, 1933-38). (The authors

used the term "male years" instead of "man-years" to indicate that the plant population was exclusively male).

There were 40-50 people in Plant C in the years 1938-47. Available data indicate that the chromium(VI) concentrations were in the range 5-1,400 μg/cu m. Mortality data were not reported.

During the years 1930-47, the population of plant D1 was approximately 150. Available data indicate that the chromium(VI) concentrations were in the range 20-2,300 μg/cu m. In this period, 5 workers died from lung cancer, 1 of whom died in 1947 after exposure for 7 years.

Between 1944 and 1947, 2 men of plant E died from lung cancer after working 8 and 11 years, respectively. The plant population was approximately 230. Exposure data indicated the range of airborne chromium(VI) concentrations was 1.5-11,500 μg/cu m. These 2 cases are also reported in the extensive epidemiologic study performed later by Mancuso, [41] Mancuso and Hueper, [90] Bourne and Yee, [3] Bourne et al, [91] Urone et al, [92] and Bourne and Streett. [93]

There were several shortcomings in the Machle and Gregorius study. [33] The lack of inclusion of workers who had left the chromate industry and the basing of conclusions on clinical findings alone led to a further study by Baetjer. [94] She analyzed the distribution by occupation of the lung cancer cases in the hospitals of Baltimore, Maryland, where a chromate producing plant is located, and compared this distribution with the distribution by occupation of control groups chosen from the same hospitals. The records of 1 of the 2 hospitals showed that there were 198 cases of men with lung cancer confirmed by microscopic examination of biopsy or autopsy

material. The records of the 2nd hospital for the period 1930-48 showed 92 such cases. Two control groups were selected from the 1st hospital and 1 from the 2nd. One in the 1st hospital consisted of all 226 males who remained in the hospital 10 days or longer, excluding those admitted for traumatic injuries or psychiatric illness. Baetjer further stated that this type of random sample was chosen because it was comparable to the cancer group in that the patients chose to come or were referred to the hospital for illnesses of varying severity. The 2nd control group from the 1st hospital consisted of 177 males with cholelithiasis. This group was selected, according to the author, because cholelithiasis, like lung cancer, poses difficult diagnostic problems in necessitating the facilities of a large medical center. The control group from the 2nd hospital consisted of 499 men meeting the criteria imposed on the 1st control group of the 1st hospital. All 3 control groups were of the same age distribution as the cancer groups. Groups were mutually exclusive.

Results indicated that 7 (3.5%) of the 198 lung cancer cases in the 1st hospital and 3 (3.3%) of the 92 lung cancer cases at the 2nd hospital occurred in chromate plant workers. None of the control population reported exposure to any chromium compounds. Chi-square analysis of the data using the Yates small-sample correction indicated that in the patients with lung cancer, the percentage of those who had worked with chromate was significantly higher than those who had not. Comparisons of the combined percentage of chromate workers in the 2 hospital lung cancer series with the percentage of chromate workers in the employed population of Baltimore also show lung cancer rates in the chromate-exposed group to be significantly higher. No exposure levels were reported. This study

supported the conclusions of Machle and Gregorius [33] regarding the increased incidence of pulmonary cancer in the chromate-producing industry.

In the late 1940's, an epidemiologic study was undertaken at a chromate-bichromate manufacturing plant in Ohio, mentioned among others by Machle and Gregorius. [33] Aspects pertaining to health were reported by Mancuso and Hueper, [90] and by Mancuso. [41] Laboratory evaluation of the air-sampling methods was reported by Bourne and Streett. [93] Determinations of chromium(VI) in the air in the chromate plant were reported by Bourne and Yee [3] and outside the chromate plant by Bourne and Rushin. [95]

The authors differentiated exposure to 2 categories of chromium compounds, ie, soluble and insoluble, but did not differentiate between chromium(III) and chromium(VI).

Chromium(III) and chromium(VI) materials leachable by water were classified as the soluble group. [92] The insoluble group of compounds included all those not leached by the repeated treatment with water. This group probably included primarily chromite ore, based on the degrees of water-solubility of the compounds which were probably present. Thus, although the authors did not determine chromium(III) and chromium(VI) directly, it appears that "insoluble" compounds were predominately chromium(III) and "soluble" compounds were predominately chromium(VI). Chromium(VI) of only slight water solubility was not determined in this study, but based on the analytical procedure used [92] part of it was likely found in the soluble group and part in the insoluble group. The pH's of airborne samples were 6.7-9.4, indicating that most samples included both chromates and dichromates.

All samples germane to the chromate-plant study were apparently taken by air filtration using the apparatus mentioned by Bourne and Streett. [93] Collection efficiencies for chromium(VI) oxide as a mist using this apparatus were determined at 0.07 mg/cu m, 0.14 mg/cu m, and 0.22 mg/cu m to be 93.6%, 98.3%, and 92.5%, respectively, for 15-minute samples at a flow rate of 28.3 liters/min. Collection efficiencies for dust were determined at 4.62 mg/cu m and 25 mg/cu m to be 99.0% and 99.9%, respectively. Mists used in the collection efficiency test were generated using an apparatus, described by Silverman and Ege, [96] which nebulized into the air stream an aqueous solution of chromium(VI) oxide (25%) and sulfuric acid (0.125%). The dusts were generated in the same equipment except that the nebulizer was replaced with a vibrating vessel into which dust was introduced.

The size distribution of the particles in the mist in the chromate plant was: 15.87% less than 1.5 μm, 50% less than 3.8 μm, and 84.13% less than 9.8 μm. In the dust the distribution was 15.87% less than 0.8 μm, 50% less than 1.7 μm, and 84.13% less than 3.7 μm.

Mancuso and Hueper [90] investigated the incidence of cancer in this chromate plant. Using the results of analyses of air samples for soluble and insoluble chromium, they calculated the possible exposures of 7 men who died from lung cancer between 1938 and 1950. Although none of the 7 were working in the plant when the sampling and analysis were performed, the calculated TWA exposures could have had some relationship to their actual exposures. The years of first exposure in the chrome plant for the 7 were 1931-41. Changes in the concentrations of chromium in airborne dusts and mists could have occurred during the years of exposure of these men to

decrease the relevance of determinations of TWA exposures made at the time of this study. The scope of such changes is very difficult to evaluate.

The airborne concentrations of chromium leachable by water determined by Mancuso and Hueper [90] to which the 7 were exposed were 0.01-0.15 mg/cu m (Table XI-5). These concentrations were apparently calculated time-weighted average concentrations taking into account the various jobs the men accomplished during the average day. The men were also exposed to chromium not leachable by water, in addition, at airborne concentrations of 0.1-0.58 mg/cu m. Because of the lack of specificity in the analytical method used [92], the airborne concentration of the only slightly water-soluble chromium(VI) is inestimable.

In another paper, Mancuso [41] reported the incidences of other effects found in the epidemiologic study. Although the various groups were defined by total chrome exposure and ratio of insoluble to soluble chrome, the actual maximum ranges of concentrations of chromium, either leachable or not leachable by water, have been calculated from their data and appear in Table XI-6. Even though some chromium(VI) may have been reported as insoluble and some chromium(III) may have been reported as soluble, the insoluble group is denoted Cr(III) and the soluble group Cr(VI). Again, it must be emphasized that it is impossible to assign only slightly water-soluble chromium(VI) exclusively to either group. Significant incidences of nasal septum perforation, chronic chemical rhinitis, and chronic chemical pharyngitis were indicated. In a 31-member control group, 2 exhibited nasal septal perforation and 2 were diagnosed as having chronic chemical rhinitis. (The authors studied a 33-member control group but found that 2 with perforated nasal septa had had 2 weeks of direct exposure

to chromates; these are excluded from their control group for consideration here.) The exposed groups had incidences of these conditions of 29-85% and 57-100%, respectively. None of a 33-member control group experienced chronic chemical pharyngitis, but 29-75% of the exposed groups had this condition. Symptoms are not included in Table XI-6 in instances where the incidence is not at least twice as high as that of the control group.

In 1959 Baetjer et al [97] reported the determination of chromium in the lungs of 16 decedents who had been employed in old chromate plants. Eleven of the men who had been employed for 2-42 years had lung cancer; 5 of the men employed 1.5-19 years did not. The results of analyses by the method presented in an appendix to their report [97] were both highly variable and inconclusive, that is, there was no significant correlation between the presence of lung cancer and chromium in lung tissue.

The US Public Health Service published in 1953 a report [5] of an extensive study of the health of 897 workers in the chromate-producing industry. Morbidity and mortality data were based upon paid death claims and cases of sickness and nonindustrial injuries disabling for 8 calendar days or longer among the members of the sick benefit plans of the plants. From 1940 to 1948, there were 28.9 times as many deaths from respiratory cancer among males in the study as would have been expected on the basis of the average death rate for the United States for the period 1940-48 inclusive, excluding violent, accidental deaths.

Medical examinations were performed on about 96% (897 males) of the total work force of the 6 study plants. Ten workers were considered to have bronchogenic carcinoma, a rate for chromate workers of more than 50 times the rate for the general population. Three of these men were known

to have had lung cancer prior to the survey. These 10 men, who averaged 54.5 years of age, had a mean duration of exposure of 22.8 years (Table XI-7). This represents a very high lung cancer incidence. Five hundred nine (56.7%) had perforation of the nasal septum. The incidence of perforation of the nasal septum was stated to have no relation to either years of exposure or to the incidence of lung cancer. Studies relating exposure to chromium compounds and incidence of dental caries indicated a low degree of correlation, but there was an increased incidence of gingivitis and periodontitis. X-ray examinations showed no significant fibrosis, but bilateral hilar enlargements were noted. There was no significant correlation between duration of exposure and heart disease. Other positive correlations mentioned were an increased frequency of white blood cells and casts in the urine and a decreased sedimentation rate of erythrocytes, all of which were related to years of exposure. Blacks appeared to be more severely affected, in general, than whites, perhaps due to a greater exposure among blacks.

This study also involved an extensive sampling program in which over 1,800 samples of air contaminants, settled dust, and process material were collected and analyzed. The report stated that the dry-end processes, ie, milling, roasting, and leaching, generated dusts containing principally lime, chromite ore, soda ash, roast residue, and sodium chromate. Sodium dichromate and sodium sulfate were usually associated with the wet-end operations of neutralizing, treating, and concentrating.

In 1952, Brinton et al [98] published a study of the morbidity and mortality in the chromate workers of another study. [5] They demonstrated a greater rate of sickness and nonindustrial injury in chromate workers as

compared to a large industrial group. This difference was due to the 10-fold increase in the incidence of cancer in chromate workers, largely because of respiratory cancer, which was increased 14-fold for whites and 80-fold for nonwhites.

In 1966 Taylor reported a study [99] in which a group of chromate workers was examined over a period of 24 years (1937-60, inclusive) using records of Old Age and Survivors Disability Insurance (OASDI). The study encompassed all male workers in 3 chromate plants, 70% of the total population of chromate workers in 1937, who were born during or after 1890 and worked long enough to have earnings reported to OASDI for 1 or more calendar quarters. In all, 1,212 chromate workers were included in the chromate-exposed cohort. Deaths were classified by cause stated in death certificates and compared to age-specific expected deaths for the total male population of the United States. Respiratory cancer was shown to be the chief cause of excess mortality. Of the 263 deaths, 71 (27%) were due to respiratory cancer when only 8 were expected. Other lesser increases of observed deaths over expected were found for all other cancers (32 observed, 24 expected) and respiratory diseases (19 observed, 8 expected). The concentrations of chromium(VI) to which the workers were exposed were not reported, but there was a definite positive trend between age-adjusted respiratory cancer rates and cumulative years of experience in the chromate industry.

There was sufficient overlap of the persons studied and plants investigated in the above [5,33,41,90,97-99] that an accurate grouping of data is not possible.

Bidstrup [100] in 1949 found only 1 case of lung cancer after interviewing and taking 14 x 17-inch chest X-rays of 724 British chromate workers in plants where airborne concentrations of chromium(VI) were found by Buckell and Harvey [101] to range from 0.4 to 17,000 ug/cu m. From such a wide range in airborne chromium(VI) concentrations it is very difficult to construct a dose-response relationship. Thirty-one other workers were X-rayed, but not interviewed. Bidstrup and Case [102] in 1956 reported a follow-up study which encompassed the nearly 6-year period from the completion of the previous study in 1949 to August 1955. During this period 217 workers left the chromate industry and were not followed up, 57 men retired because of age or ill health, and 59 men died. Of the 59 deaths, 12 were due to lung cancer. The mean latent period for the 12 who died from carcinoma of the lung was 21 years. The expected number of lung cancer deaths was 3.3, based on the age-adjusted mortality data from the population of England and Wales. Thus, 3.6 times as many workers died of lung cancer as would have been expected in the male population of England and Wales. This difference was shown to be statistically significant. The authors examined the possibility that the increase might have been due to nonoccupational factors such as diagnostic bias, place of residence, social class, or smoking habits, and concluded that these did not markedly alter their conclusions. Questions or responses regarding smoking habits were not reported and employee-specific exposures to chromium(VI) were not provided.

Vigliani and Zurlo [85] in 1955 reported a study of 150 workers exposed to alkali chromates. They reported only that atmospheric chromium(VI) concentrations were 55-75 μg/cu m during a 3-year period and

observed 1 worker with ulceration of the nasal septum, a few with inflammation of the conjunctiva and laryngeal mucosa, some with chronic bronchitis, 1 with cancer of the nasal septum, and 1 with lung cancer.

The US Public Health Service [5] studied a refractory plant in which chromite ore was used to make chromite bricks. Deaths occurring from 1937 to 1950 were investigated and, because there was 1 lung cancer death observed and 1 lung cancer death expected, the report concluded that chromite ore was not carcinogenic. However, no environmental data or lengths of exposure were reported.

The chromate workers in the preceding studies [3,5,33, 41,90,94,97,99,100,102] were exposed to various chromium(III) and chromium(VI) compounds as well as to other materials. None of the studies presented conclusive evidence regarding the causative agent of the pulmonary carcinomas observed, neither did they correct lung cancer rates for exposure to other pulmonary carcinogens or for cigarette smoking. There is very little good evidence implicating chromite ore, a water-insoluble chromium(III) material, as a carcinogen. It is apparent from these studies that the increased incidence of lung cancer resulted from increased duration of exposure to materials present in plants manufacturing chromium-bearing compounds. However, it is not known from these reports whether all chromium(VI) compounds or only certain ones were responsible for this increased incidence.

In another study in 1972 by Korallus et al [103] in Germany, 106 workers who had been exposed to 0-13.2 mg/cu m chromium(III) oxide and 0-2.7 mg/cu m chromium(III) sulfate (42 for less than 10 years, 64 for more than 10 years) were examined clinically. Medical histories and clinical

results, including FEV, exhaling capacity, and urine and blood status appeared normal. X-ray examinations revealed 6 instances of pneumoconiosis but no lung tumors.

In a presentation at the 5th Merseburger Symposium in 1972 on "Health and the Working Environment," Bittersohl [104] described the results of a study of 30,000 employees of a large chemical unit for the period 1921-1970. In particular, 588 malignancies in men and 170 in women were evaluated for the period 1957-70. In 1971, 108 new malignancies in men and 29 in women came to light. In a chromate factory the carcinoma rate was far above average. The factory manufactured catalysts through the reaction of chromic acid and iron(III) oxide and nitric acid. The airborne concentration of chromium was often in the same order of magnitude as the MAK (undefined), but short-term excursions above 400 μg/cu m occurred. The perforation of the nasal septum was apparently a commonplace occurrence. The incidence of malignant neoplasms in employees in the chromate factory was 852/10,000 employees. In "non-exposed" personnel, the incidence of malignant neoplasms was 84/10,000 employees. Approximately 86% of all with malignant neoplasms were smokers, and 78% of those without malignant neoplasms were smokers.

In 1974 and 1975, representatives of Allied Chemical Corporation presented the results of a mortality study to NIOSH (WJ Hill, written communications, July 1974 and February 1975). The retrospective study examined the personnel of the Baltimore Chrome Works in Maryland. The objectives were to determine (1) whether there was a downward trend in lung cancer incidence at the Baltimore plant and (2) if employees entering the plant after the last process change (1961) are at no greater risk than the

Baltimore City employment pool. One hundred five cases of lung cancer have appeared among the employees of this plant since 1932. The workers who began employment prior to 1932 had an average exposure time of 24 years before developing lung cancer. The author calculated standardized mortality ratios (SMR's) for 4 groups of employees. The SMR's were the observed number of deaths divided by the expected number of deaths. The groups were selected by the author to allow the effects of process changes to be examined. For the 1932-41 group the SMR was 680, for the 1942-51 group the SMR was 480, and for the 1952-61 group the SMR was 160. Little could be said about the 1962-73 group. The conclusions the author made were (1) that a significant downward trend in incidence and death had occurred, and possible causes included "reduction in dust exposure levels, changes in race ratio, smoking habits, employment levels, age patterns, and other prior exposure experience of employees" and (2) "the present employee population (1962-present) cannot be said to be at a greater risk than the employee pool from which it comes, but ten or more years of further observation will be needed to draw more statistically powerful conclusions." In view of the long latent period associated with the development of lung cancer from exposure to chromium compounds, at least 10 years of further observation are necessary in order to develop better data.

No epidemiologic studies of lung cancer in the chromate-using industries have been reported, as contrasted to chromate-producing, that included determinations of airborne chromium(VI) concentrations. This is unfortunate because the chromate-using group is much larger than the chromate-producing group.

Animal Toxicity

Lukanin [28] in 1930 reported placing 30 rabbits and 3 cats alongside workers in a chromate-producing plant in Germany for 1-8 months. Chromium(VI) concentrations were less than 1 up to 25 mg/cu m. The author observed either diffuse thickening or rupture of alveolar walls and proliferation of cellular elements along the blood vessels and bronchi. Desquamation of the bronchial epithelium was also found. No tumors were found, but the maximum exposure was only 8 months.

In 1930, Hunter and Roberts [105] injected subcutaneously Macacus rhesus monkeys with various amounts of an aqueous 2% solution of potassium bichromate. One monkey given 36.3 cc of the solution (0.02 g/kg) and another given 10 cc were dead 12 hours later. Evidence of acute lesions was present in the kidneys of both animals. Four other monkeys were given repeated, 1-5 cc doses of the solution at 3- to 7- week intervals. In 2 of these, acute lesions were also found in the kidneys. The other 2 animals lived longer, for about 160 days, and sustained chronic renal damage; in 1, practically all the original epithelium of both proximal and distal convoluted tubules was destroyed. The authors further remarked that the regeneration of tubular epithelium was of distinctly atypical morphology and that the tissue was apparently resistant to further injury by bichromate.

In 1940 Shimkin and Leiter [106] reported the intravenous injection of various materials into tumor-susceptible strain A mice. Single, 5-mg injections of chromite ore did not result in an increased incidence of pulmonary tumors over control animals despite the observation of chronic irritation. Chromite ore also did not affect the development of tumors by

intravenous injection of 20-methylcholanthrene.

Hueper [107] implanted finely divided chromite ore roast mixed with benzene-extracted sheep fat into the thigh muscle tissue and pleural cavity of rats. After 2 years, 2 of 25 male rats with pleural implants developed squamous cell carcinomas coexisting with sarcomas of the lung, and 2 developed tumors, 1 of which was benign, remote from the site of implantation. The authors stated that only 4 of the 25 rats survived into the cancer-bearing period. Three fibrosarcomas of the thigh and 10 tumors, 4 of which were benign, developed in the 31 female rats which received thigh implants. Twenty-nine of the 31 rats in this group were alive at the appearance of the first of these tumors. Two series of controls consisting of 15 female rats each were implanted only with extracted sheep fat in the pleural cavity in 1 series and in the thigh in the other. Of the pleural implant controls, 1 developed a benign tumor at the implantation site and 3 developed tumors remote from the site, 2 of which were benign. No tumors developed at the site of implantation in the thigh implant controls, but 3 developed tumors, 1 benign, remote from the implant. The author concluded that his results suggested that the chromite ore roast contained carcinogenic material. However, he may have given undue weight to injection-site sarcomas.

Hueper and Payne [108] implanted pellets of finely pulverized calcium chromate, sintered calcium chromate, sintered chromium(VI) oxide, and barium chromate in sheep fat into the pleural cavity and into the thigh muscle of rats. Each pellet contained 25 mg of the respective chromium compound and 75 mg of sheep fat. Sintered compounds were formed from their parent materials by heating the respective compounds to 2,000 F for 1 hour.

The authors assumed that during this process some of the chromium(VI) had been converted to a lower oxidation state, thereby forming some chromium(III) chromate. Of the 20 male and 15 female rats in each series, those 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(VI) oxide developed 15 thigh tumors and 14 pleural tumors. On the other hand, rats implanted with barium chromate did not develop any tumors either in the thigh muscle or in the pleural cavity. With 1 exception, a squamous cell carcinoma of the lung produced by pleurally implanted calcium chromate, all tumors were sarcomas, usually spindle cell sarcomas or fibrosarcomas. No tumors were observed in the control groups, which consisted of 2 series of 20 male and 15 female rats, each implanted with pellets containing only sheep fat. The duration of exposure was 12-14 months for each exposure group and was 12 months for the control groups. The authors determined the concentrations of chromium(VI) in water and Ringer's solution at 37 C that resulted from leaching of various chromium(VI)-bearing materials (Table III-1).

TABLE III-1

SOLUBILITIES OF CHROMATES

Compound	Solubility, mg/ml	
	Water	Ringer's Solution
Calcium chromate	2.47	3.04
Sintered calcium chromate	1.28	1.50
Sintered chromium(VI) oxide	1.71	1.78
Zinc chromate	0.61	0.83
Strontium chromate	0.23	0.32
Barium chromate	0.0085	0.0090
Lead chromate	<0.001	<0.001

These data suggested to the investigators that certain materials containing chromium(VI) of moderate leachability may produce cancer when introduced into rat tissue in the form of a depot assuring prolonged exposure to chromium(VI) in small amounts.

Payne [109] in 1960 implanted pellets of calcium chromate and sintered calcium chromate mixed with extracted sheep fat in the thighs of mice. After 14 months of observation of the 26 male and 26 female mice implanted with chromium(VI)-containing pellets, 9 mice receiving sintered calcium chromate and 2 mice receiving calcium chromate developed tumors at the site of implantation. Pellets consisted of 10 mg of chromium(VI) compound mixed with 20 mg of sheep fat. No tumors were observed in a control group of 26 male and 26 female mice implanted with pellets containing only sheep fat. The tumors found were usually spindle cell sarcomas or fibrosarcomas. Hueper and Payne [108] also injected calcium

chromate, and sintered chromium(VI) oxide in a tricaprylin vehicle subcutaneously into the nape of the necks of mice. The dose given to each mouse was 10 mg of dust in 0.2 ml of vehicle. One tumor was observed in 26 male and 26 female mice injected with calcium chromate. No tumors were seen in similar groups injected with sintered calcium chromate, sintered chromium(VI) oxide, or the control group which received only the tricaprylin vehicle. In another series, 12.5 mg of calcium chromate in gelatin capsules was implanted intramuscularly and intrapleurally in rats. After 7 months, of the 6 rats with intramuscular implants, 2 developed tumors; of the 6 rats with intrapleural implants, 3 developed tumors. The latter experiment, despite its lack of a control group, appears to verify that the chromium(VI) compounds and not the sheep fat were the causative agents for the tumors observed.

Payne [110] fractionated and analyzed the residue from the first leaching of roasted chromite ore, and tested the material in animals. This residue had been suggested by the US Public Health Service study [5] as being most apt to contain carcinogenic agents. The residue was fractionated into 4 particle-size ranges by diameter: (1) > 10 μm, (2) 5-10 μm, (3) 2-5 μm, and (4) < 2 μm. Analyses for chromium indicated that the weight percentage of chromium(VI) leached by water from the residue increased with decreasing particle size. Animal testing was performed in 2 parts. First, 10 groups of 26 male and 26 female mice were given single subcutaneous injections of various materials into the nape of the neck. The various materials contained a known carcinogen in a tricaprylin vehicle. The 10 groups were as follows: (1) tricaprylin vehicle only (controls), (2) 3,4-benzpyrene, (3) water-extracted residue < 10 μm, (4)

water-extracted residue and 3,4-benzpyrene, (5) chromium(III) phosphate < 10 μm, (6) chromium(III) phosphate and 3,4-benzpyrene, (7) residue, 5-10 μm, (8) residue 5-10 μm and 3,4-benzpyrene, (9) residue < 2 μm, and (10) residue < 2 μm and 3,4-benzpyrene. Of the 4 sets of animals given only a chromium-containing substance, 3 injection-site sarcomas were found in the group receiving extracted residue; no tumors were found in the other 3 groups or in the control group. By comparing the tumor incidences in the 5 groups tested with 3,4-benzpyrene alone and those tested with the mixture of 3,4-benzpyrene and chromium compound the authors observed that increased amounts of chromium(VI) were associated with a decreased tumor incidence. In the second phase of the experiment, groups of rats and mice received pellet implants of roast residue in sheep fat in the thigh and in the pleural cavity and tumors developed in 3 of 35 rats receiving pleural implants and in 1 of 35 with thigh implants. No tumors were found in a control group of 35 rats that received implants of sheep fat only. All of the tumors observed in both phases of the study were injection-site sarcomas. None of the 52 mice receiving thigh implants developed any tumors. No mice received pleural implants. None of the 52 mice in a control group, which received only sheep fat, developed tumors. The authors postulated that leaching of the more acutely toxic sodium chromate from the residue without removing other constituents might have been responsible for the higher tumor incidence in the water-extracted residue fraction. The chromium(VI) leached from the residue was presumed by the author to be sodium chromate.

In a further study, Hueper and Payne [111] gave rats monthly intrapleural and intramuscular injections of sodium dichromate in gelatin.

Each injection consisted of 2 mg of sodium dichromate dissolved in 0.05 ml of a 10% gelatin solution. A total of 16 injections were given. Survivors were sacrificed at the end of a 24-month observation period. Various tumors were seen. Of the 20 male and 19 female rats in each series receiving intrapleural injections, 3 developed malignant tumors, 1 of which was at the site of injection. Rats receiving intramuscular injections developed 4 benign and 2 malignant tumors, none at the site of injection. The 4 tumors which were not at the injection sites were of a type found in a similar incidence in control animals. Four benign and 12 malignant tumors, none at the site of injection, were observed in the control group. Because of the greater incidence of malignant tumors in control animals, it is impossible to conclude that sodium dichromate was responsible for any malignancies. In another experiment, [111] the authors gave 218 anesthetized rats intratracheal instillations of calcium chromate, strontium chromate, and zinc chromate in gelatin. Each dose consisted of 2 mg of the compound in 0.05 ml of a 10% gelatin solution. The dose was given every 2 months until a maximum of 5 instillations containing up to 10 mg of chromate had been given. Equal amounts of the gelatin solution were administered intratracheally to a control group. Despite large death rates from pulmonary complications during the first 4 weeks after each application, tumors were observed. Of the 85 rats receiving calcium chromate, 78 of which died early in the experiment, 3 developed malignant tumors, 2 of which were at the site of instillation; of the 60 rats receiving strontium chromate, 40 of which died early, 3 developed tumors (1 benign, 2 malignant), 1 of which (a malignancy) was at the site of instillation. The 3 malignancies at the site of instillation were all

fibrosarcomas. No tumors were observed at the site of instillation in either the zinc chromate or the gelatin control groups, although 1 malignancy in the former and 4 malignancies in the latter groups were observed at other sites. In a second control series, 12.5 mg of calcium chromate was implanted in a gelatin capsule into the right pleural cavity and into the thigh muscle of 2 sets of rats. Of the 14 rats with pleural implants, 8 developed malignant tumors at the site of implantation; of the 8 rats receiving muscle implants, 6 developed malignant tumors, 4 of which were at the site of implantation. Hueper and Payne concluded from this [111] and previous work [107-110,112] that chromium(VI) and chromium(III) possess carcinogenic properties, but they placed unwarranted significance on injection-site sarcomas.

Baetjer et al [113] reported an extensive series of experiments with different animal species, chromium materials, and routes of entry. Three strains of mice--A, Swiss, and C57 Black--with very high, moderately high, and very low incidences of spontaneous lung tumors, respectively, and 1 mixed strain of rats from Wister (sic) and McCollum stock were exposed by inhalation to a roast dust (pH 10-11) from a chromate-producing plant with 1% potassium dichromate added. This dust was said to be similar to that found in the air of the old chromate-producing plants. The median particle diameter of the exposure material was 0.8 μm. The mice were exposed to a dust prepared from a mixture of finely ground roast material (13.7% chromium(VI) oxide, 9.3% sodium oxide, 6.9% chromium(III) oxide, 17.7% iron(III) oxide, 9.4% aluminum oxide, 8.7% magnesium oxide, 31% calcium oxide, 0.2% vanadium(V) oxide, and 2.4% silicon oxide) to which was added 1% potassium bichromate. The analysis of the dust indicated that it was

97% water- or acid-soluble, and that 90% of this "soluble" chromium was water-soluble and 10% was acid-soluble. The concentration of airborne chromium(VI) in the dust chamber containing mice was 0.47-0.94 mg/cu m water-soluble chromium(VI) and 0.052-0.104 mg/cu m water-insoluble, acid-soluble chromium(VI). The concentration of airborne chromium(VI) in the dust chamber containing rats was 0.94-1.4 mg/cu m water-soluble chromium(VI) and 0.104-0.156 mg/cu m water-insoluble, acid-soluble chromium(VI). The animals were exposed for 4 hours/day, 5 days/week until they died or were killed. In another series of experiments a few mice were exposed to 7.5-12.5 mg chromium/cu m 30 minutes/day, 5 days/week (the fraction of this chromium which was chromium(VI) was not stated, but, based on interpretation of data in the report, was about 50%). Similar groups of animals were maintained as controls in all inhalation experiments. In further experiments, the mice and rats were subjected to repeated (5-6 doses at 4-week intervals for mice and 15 doses at 2-week intervals for rats) intratracheal or intrapleural injections of the mixed roast-dichromate material suspended in olive oil or to intratracheal or intravenous injections of either basic potassium zinc chromate ($K_2O.4ZnO.4CrO_3.3H_2O$) or barium chromate in saline solutions. Control animals were given injections of either olive oil, zinc carbonate, barium sulfate, or saline solution. No increase in the incidence of benign or malignant tumors over controls was observed in any of the experimental animals. The pulmonary adenomas present in experimental mice occurred at an earlier age than in respective control mice when exposures were to mixed roast-dichromate dust by inhalation or intraperitoneal injection, or to potassium zinc chromate by intratracheal or intravenous injection. The

intratracheal injection of basic potassium zinc chromate produced an epithelization of the alveoli in mice.

Later Steffee and Baetjer [114] repeated their inhalation and intratracheal experiments [113] using rabbits, guinea pigs, rats, and mice. Inhalation exposure of all animals was to a sequence of (1) a mixed dust similar to that previously used [113] with the difference that the dichromate was blown into chambers as a mist rather than being mixed with the dust, (2) a mist produced by atomizing a 17.5% solution of sodium chromate, and (3) pulverized residue dust consisting of roast material from which sodium chromate had been leached. Chromium(VI) concentration [both water-soluble chromium(VI) and acid-soluble, water-insoluble chromium(VI)] was 1.5-2 mg/cu m. Animals were exposed for 4-5 hours/day, 4 days/week. Unexposed animals were inhalation controls. Intratracheal exposures were to mixed dust, basic potassium zinc chromate, lead chromate, and residue. Control groups received dry portland cement, wet portland cement, lead titanate, saline, or no injection. No bronchogenic carcinomas were produced, but a number of so-called alveologenic adenomas and lymphosarcomas were produced in guinea pigs, rats, and mice. One rat exposed by inhalation to chromate dust developed a keratinizing tumor of the lung which the authors felt to be benign. An increased incidence of prominence of alveolar epithelium was found in rabbits, guinea pigs, and mice receiving intratracheal injections of basic potassium zinc chromate. Increased incidences of alveolar and interstitial inflammation were found in guinea pigs inhaling mixed dust and mist and in mice injected with basic potassium zinc chromate. Granulomas appeared in most chromate-exposed animals regardless of chemical or group, but were rare in control groups.

Roe and Carter [115] injected rats intramuscularly with calcium chromate in arachis oil. Injections were given weekly for 20 weeks. The first 2 injections contained 5.0 mg of calcium chromate, but signs of severe local inflammation developed, so the dosage of the last 18 injections was 0.5 mg. Of 24 test rats, 11 (45.8%) developed spindle cell sarcomas and 7 (29.2%) developed pleomorphic sarcomas at the site of injection. All sarcomas were invasive but did not metastasize. No tumors were seen in 16 controls.

Hueper summarized [116] the neoplastic responses of rats to various chromium-containing materials. For each substance, intramuscular and intrapleural implantations in a sheep fat vehicle were made in 35 rats. In the 35 rats with intramuscular implantations of calcium chromate, 10 developed implantation site cancers. In the 35 rats with intrapleural implantations of calcium chromate, 28 developed implantation-site cancers. For the other materials the following malignant tumors at the implantation sites were reported: strontium chromate, 16 intramuscular, 17 intrapleural; barium chromate, none intramuscular, 2 intrapleural; lead chromate, 3 intramuscular, 3 intrapleural; sodium dichromate, none intramuscular, 2 intrapleural; chromite roast residues, 1 intramuscular, 8 intrapleural; zinc yellow, 16 intramuscular, 22 intrapleural; chromium(III) acetate, 1 intramuscular, 1 intrapleural; chromium(III) chromate, 30 intramuscular, 34 intrapleural; sintered calcium chromate, 13 intramuscular, 21 intrapleural; sheep fat (the implantation vehicle in all the above) no cancers by either route.

In 1968 and 1969 Laskin et al [13] reported a study of selected chromium compounds in a cholesterol carrier using a new intrabronchial

implantation technique. The pellets used were in the form of a cylindrical matrix of stainless steel mesh and about 1 mm in diameter and 5 mm in length. They were implanted in the bronchus and held in place by a trochar fitted with spring-wire hooks and introduced through a tracheotomy. Pellets were prepared from molten mixtures of exposure materials dispersed in equal quantities of cholesterol carrier. Compounds under investigation included chromium(III) chromate, chromium(III) oxide, chromium(VI) oxide, calcium chromate, and process residue. Process residue contained mixtures of various water-leachable chromium(VI) materials, chromate-chromite complex material, and chromium(III) oxide. The studies included material of various solubilities and oxidation states and involved over 500 rats under observation for periods of up to 136 weeks.

Lung cancers that closely resembled lung cancer in man (ie, squamous cell carcinoma and adenocarcinoma) were found. [13,117] Of the 100 rats implanted with calcium chromate, 6 squamous cell carcinomas were found in animals dying from 386-671 days (mean: 540 days) and 2 adenocarcinomas from exposures of 366 and 609 days developed at the sites of implantation. One of 100 rats implanted with process residue developed a squamous cell carcinoma at the site after 594 days. No other compounds produced tumors at the site of implantation, although among the 100 rats in each group hepatocell carcinomas were observed in 1 rat given process residue, in 1 rat given chromium(III) chromate, and in 2 rats given chromium(VI) oxide. Five of 24 control rats developed squamous metaplasia and, in addition, 1 developed a sarcoma. Of the tumors seen, all were invasive and some had metastasized. In all experimental groups except the 1 exposed to chromium(VI) oxide, there was evidence of atypical squamous metaplasia of

the bronchus.

Since these studies implicated calcium chromate as a lung carcinogen, inhalation studies using this compound were begun. [118] Early range-finding studies [119] with calcium chromate resulted in rapid and significant mortality at both 10 and 20 mg/cu m (2.7 and 5.4 mg chromium(VI)/cu m, respectively) in both rats and hamsters. Results [118] reported in 1972 suggested a carcinogenic action in rats and possibly in hamsters after chronic exposure to calcium chromate aerosols at 2.0 mg/cu m (0.67 mg chromium(VI)/cu m). After 589 exposures over 891 days, 4 carcinomas were observed. Of the original 100 rats, 1 keratinizing squamous cell carcinoma of the lung, 1 laryngeal squamous cell carcinoma with invasion of perineural spaces and adjoining cartilaginous rings, and 1 malignant peritruncal tumor of undetermined type and origin were observed. One squamous cell carcinoma of the larynx was found among the original 100 hamsters. In addition, a number of mucosal changes were noted. [118] In rats, 2 animals showed laryngeal hyperplasia and 3 showed laryngeal squamous metaplasia. Effects in hamsters were more marked with 8 animals showing laryngeal hyperplasia. Eight additional animals showed squamous metaplasia of which 5 were atypical with downgrowth. Another hamster, dying at 611 days, showed a squamous papilloma in the larynx with hyperplasia and hyperkeratosis. [118]

Nettesheim et al [120] exposed 136 female mice and 136 male mice, all germ-free derived and specific-pathogen-free C57BL/6, to 1 μm diameter calcium chromate aerosol at a concentration of 13 mg/cu m. He also exposed 545 mice of the same type to PR8 influenza virus prior to the calcium chromate exposure. Two control groups of the same size and composition

breathing filtered air were used and only 1 was infected with the virus. In all, 21 pulmonary adenomas were observed in the 2 exposed groups and only 5 in the uninfected controls. No tumors were found in the infected controls. No bronchogenic tumors were found. The authors determined that there was a significantly larger ($P<0.0077$) incidence of lung tumors in mice exposed to calcium chromate, compared to controls. Prior exposure to 100 roentgens of whole-body X-radiation in another series of mice did not affect tumor incidence, but prior PR8 influenza infection appeared to reduce the incidence of tumors from calcium chromate. The authors [120] also gave 15 weekly intratracheal injections of calcium chromate to 2 groups of hamsters. Hamsters in 1 group received 0.5 mg/week, the hamsters in the other group received 0.1 mg/week. The lesions produced were similar to those observed in the mice, but scarring of the lung parenchyma was more widespread and adenomatosis was regularly observed. Hamsters also had frank bullous emphysema and extensive goblet cell hyperplasia in all parts of the tracheobronchial tree.

In a study by Zekeev et al [121] in 1973, the blastomogenic and toxic effects of chromium(III) oxide, ammonium bichromate, sodium bichromate, chromium ores, and dolomite were observed in rats. Some rats were preliminarily treated with "non-carcinogenic" doses of 3,4-benzpyrene. Chromium(III) oxide was intrapleurally administered in wool fat. Chromium ore (380-515 mg/cu m), dolomite (540-837 mg/cu m), sodium bichromate (0.05-0.10 mg/cu m), and ammonium bichromate (0.05-0.10 mg/cu m) were administered to rats in a dust chamber 3 times/week for 2 hours for 6 months. Microscopic examination of the lungs of those dying during the experiment revealed "precancerous changes." Exposure to chromite and

dolomite dust did not result in the development of any precancerous changes. Precancerous changes were observed in rats exposed to dusts of sodium bichromate and ammonium bichromate. The authors did not indicate whether control animals were used. The exposure of experimental rats to supposedly noncarcinogenic doses of 3,4-benzpyrene prior to exposure to chromium materials makes an interpretation of the results extremely difficult. Thus, it is not possible to assess the significance of this study.

A written communication from LS Levy in 1975 described an animal study done at Chester Beatty Research Institute, London. Random-bred Parton Wistar rats of both sexes received a pellet in the left inferior bronchiolus via trachectomy under anesthesia. The rats were kept for 2 years. One hundred rats were set up for each of the chromium-containing material test groups. The pellets which were implanted contained 2 mg of test material suspended 50/50 (w/w) in cholesterol. Negative control groups received either blank metal pellets or pellets and vehicle. Positive control groups received 3-methylcholanthrene. Lungs of all rats either dying during the study or killed at its termination were examined both macroscopically and microscopically. Apart from those in the lung, tumors were similar both in type and number in all groups. The bronchial tumors found and microscopically confirmed are given in Table III-2 along with the average induction periods. Additional lung tumors, not of bronchial origin and not considered by the authors to be causally related to implantations are also listed in Table III-2. The majority of bronchial tumors were large keratinizing squamous cell carcinomas. Intrathoracic invasions, particularly to the right lung in the hilar region, were common

and metastases to local lymph nodes and to kidneys were seen.

Squamous cell carcinomas were found in 8/100 rats receiving calcium chromate, 3/100 rats receiving zinc chromate (zinc potassium chromate), 3/100 rats receiving chromic chromate dispersed in silica, and 1/100 rats receiving ground chromic acid. It may be that the chromic acid implantation produced a carcinoma only because it was converted to a less-soluble chromium(VI) material by reaction with cholesterol. Because of its extremely great oxidizing ability, some of it may have been chemically reduced by cholesterol, forming chromic chromate. Calcium chromate produced carcinomas in 5/100 rats when mixed with primene, and carcinomas in 7/100 rats when mixed with diphenylguanidine. Primene 81-R benzoate and diphenylguanidine failed to produce tumors when administered by themselves. No bronchial carcinomas were found in negative control groups and in rats receiving sodium dichromate dihydrate or sodium chromate.

TABLE III-2

LUNG TUMORS FOUND AND MICROSCOPICALLY CONFIRMED

Experimental Group No.	Compound No.	Test Material	No. Rats in Group	Bronchial Carcinoma of Left Lung	Induction Period in Days (Range)	Lung Tumors not Associated with Treatment
1	1	Ground chromite ore	100	0		
2	2	Bolton high lime residue	"	"		
3	3	Residue after alumina precipitation	"	"		
4	4	Residue from slurry tank-free of soluble Cr	"	"		
5	5	Residue from vanadium filter	"	"		Pulmonary adenoma of left lung
6	6	Residue from slurry disposal tank	101	"		Anaplastic carcinoma of upper left lung Adenoma of right lung
7	7	Sodium dichromate dihydrate	100	"		Fibrosarcoma of upper left lung
8	8	Sodium chromate	"	"		
9	9	Chromic acid (ground)	"	1	560	
10	10	Chromic oxide (metal)	"	0		
11	11	Calcium chromate	"	8	604(473-734)	
12	12	Chromic chloride hexahydrate	"	0		Lymphoma of right lung
13	13	Zinc chromate-type II*	"	3	708(657-734)	
14	14	Chrome tan	"	0		
21	15A	Diphenylguanidine (DPG)	"	"		
22	15B	DPG + calcium chromate	"	7	656(502-732)	

* Zinc potassium chromate

TABLE III-2 (CONTINUED)

LUNG TUMORS FOUND AND MICROSCOPICALLY CONFIRMED

Experimental Group No.	Compound No.	Test Material	No. Rats in Group	Bronchial Carcinoma of Left Lung	Induction Period in Days (Range)	Lung Tumors not Associated with Treatment
23	16A	Primene 81-R benzoate	100	0		
24	16B	Primene + calcium chromate	"	5	620(440-732)	
25	17A	Chromic chromate	"	0		
26	17B	Chromic chromate dispersed in silica	"	3	698(666-730)	
15	15	Pellet + cholesterol	150	0		Adenoma of right lung
16	16	Blank pellet	"	"		Adenocarcinoma of right lung
28	28	Pellet + cholesterol + Kieselguhr	100	"		
20	20	100% 3-MCA	48	34	493(217-730)	
17	17	100% 3-MCA	"	36	498(270-701)	
18	18	50% 3-MCA	"	18	474(284-696)	
19	19	25% 3-MCA	"	13	517(297-698)	
27	27	50% 3-MCA	50	36	498(269-732)	

Correlation of Exposure and Effect

Chromium(VI) materials have been implicated as responsible for such effects as: skin ulceration, [5,16-20,22-25,41,56-60,62] ulcerated nasal mucosae, [5,19,22-24,41,56-60,63] perforated nasal septa, [5,18,19,22-24,33,41,56-58,60] rhinitis, [5,19,23,41,56-58,60] nosebleed, [5,19, 22,56] perforated eardrums, [19] kidney damage, [84,105] pulmonary congestion and edema, [67] epigastric pain, [59] erosion and discoloration of the teeth, [5] and dermatitis. [7-11,21,25,61,62,69,71-81] In addition they have been associated with an increased incidence of lung cancer. [5,33,41,85-

90,94,98-100,102,104,116] In the trades which have used chromic acid anhydride or alkali-metal salts of chromic acid, rather than compounds of lesser water solubility, chromium(VI) has been responsible for allergic contact dermatitis, [7-11,21,25,61,69,71-81] skin ulcers, [16,17,20,22-25,56-60,62] nasal membrane irritation and ulceration, [22-24,56-60,63] nasal septal perforation, [22-24,33,56-58,60] rhinitis, [23,56-58,60] nosebleed, [22,56] liver damage, [68] pulmonary congestion and edema, [67] epigastric pain, [59] erosion and discoloration of the teeth, [5,56,] and nephritis. [84] In the chromate-bichromate producing industry which uses the alkaline oxidation of chromite ore, and in the pigment-manufacturing industry, chromium(VI)-bearing materials have been associated with an excessive incidence of lung cancer, [5,33,88-90] skin ulcers, [5,19] nasal membrane irritation and ulceration, [5,19,33,41] nasal septal perforation, [5,19,33,41,88] perforated eardrums, [19] and discoloration of the teeth. [5] Although it is apparent that any chromium(VI) materials may cause the less severe effects if they are present in aqueous solution in sufficient concentrations, the specific materials which were responsible for lung cancer have not been identified. To some extent the toxicities of chromium(VI) materials vary with their solubilities, but denotation of compounds on the basis of solubility alone has not been sufficiently precise to suggest a dichotomy of toxic effects.

(a) Chromium(VI) Materials Not Implicated in Lung Cancer Production

In the 1948 study by Machle and Gregorius, [33] it was determined that in a part of the chromate industry which only dried and packaged sodium bichromate and manufactured and packaged chromium(VI) oxide (chromic

acid anhydride) and basic chromic sulfate, no deaths from lung cancer, among 33 deaths, occurred from 1930-47. In comparison, the plant which supplied this plant with sodium bichromate had 5 deaths from lung cancer from 1930-47. In this supplying plant alkaline roasting of chromite ore was done. The significance of this difference in mortality due to lung cancer is amplified by the lack of adequate evidence at this time that sodium and potassium chromate and bichromate and chromic acid anhydride by themselves cause lung cancer. Significant quantities of highly water-soluble chromium(VI) materials are used in chromium plating and anodizing. These operations were discussed in the previous chromic acid criteria document. [122] Reports [57,58,65] which have been prepared since the document was written tend to substantiate the position assumed in the document that the environmental limit and work practices recommended therein are appropriate to prevent adverse effects from exposure to chromic acid anhydride. The chromic acid criteria document [122] did not apply to the manufacture and use of any chromium(VI) materials other than chromium(VI) oxide and the hydrogen chromates and hydrogen polychromates. A series of references pertaining to chromic acid mist exposures [22-24,56,63,68] formed the basis for the recommended environmental standard in the chromic acid document. [122]

Since the document [122] was prepared, 2 studies of chromium-plating operations were made by NIOSH [57,58,65] and a third was found in the literature. [60] In 1 of these studies, from which 2 reports were made, [57,58] NIOSH reported high incidences of nasal mucosal irritation and septal perforation where the greatest concentration of airborne chromium was 9.1 μg/cu m. However, in this workplace there was strong evidence that

direct transfer of chromium(VI) from work to nasal surfaces occurred frequently.

In a study by Lumio [60] where the airborne chromium(VI) concentration was reported as 3 μg/cu m or less, the lack of proper work practices, ventilation, and protective equipment was probably primarily responsible for the signs and symptoms of chromium(VI) poisoning. The fact that 24 of the patients had cutaneous ulcers or scars of ulcers indicates that sloppy conditions existed in most workplaces studied. It was not stated in the article [60] what the total population at risk was in the plating shops, making an evaluation of the overall prevalence of signs and symptoms of chromium(VI) poisoning difficult.

In the other study by NIOSH, [65] a maximum airborne concentration of 3 μg chromium(VI)/cu m, a concentration similar to that in the other 2 plants, was found. [57,58,60] No ulcerated or perforated nasal septa were found although half the 32 workers had varying degrees of mucosal irritation. This incidence of mucosal irritation was not considered by the investigators to be necessarily significant because the survey was carried out at the peak of the 1972-73 influenza epidemic.

Of particular importance is the difference in duration of employment in the 3 plating establishments. [57,58,60,65] In the first one, [57,58] where high incidences of ulceration and perforation occurred, there were 37 employees. Twelve of the 21 workers employed 1 year or less and 15 of the 16 workers employed more than 1 year had ulceration and crusting of septal mucosa, avascular scarified areas of septal mucosa without erosion or ulceration, or perforation of the nasal septum. In the plant in Finland, [60] the incidence of signs and symptoms of chromium(VI) poisoning is

impossible to establish because insufficient information was provided. However, it is apparent that most persons with signs and symptoms had been employed for 1-5 years, during which time the working conditions were less hygienic than those in effect at the time of the study. The third plant [65] with 32 employees provided great contrast with the other 2. [57,58,60] In this plant [65] no ulceration or perforation occurred, despite the fact that the workers had been employed for a much longer period of time--15 were employed 8 years or more; 7, between 4 and 8 years; 4, between 1 and 4 years; and only 6, less than 1 year.

There were apparently significant differences in work practices in the 3 similar electroplating plants. [57,58,60,65] In 1 of the 2 plants [57,58] with high incidences of effects on nasal mucosae, employees were frequently observed putting contaminated fingers to their noses. [57] The plant in Finland [60] apparently also had poor work practices. Based on the well-documented [16,17,20,22-25,56,59,62] relationship between exposure to "chromic acid" and resulting skin ulceration, the lack of skin ulceration in the third contrasting study [65] suggests that good work practices were used in this plant.

The criteria document [122] on exposure to chromic acid concluded that, in the presence of good work practices, an environmental limit of 50 μg chromium(VI) oxide [26 μg chromium(VI)/cu m] as a time-weighted average and 100 μg chromium(VI) oxide [52 μg chromium(VI)/cu m] as a 15-minute ceiling would be sufficient to protect against irritation and ulceration of nasal mucosae, perforation of nasal septa, and other harmful effects. These 3 studies [57,58,60,65] provide additional basis for the recommendations in the criteria document that appropriate work practices

are important in preventing occupationally related health problems.

As stated above, the ability of mists from chromium-plating tanks and splashes from plating solutions to cause skin ulcers, nasal mucosal irritation and ulceration, nasal septal perforation, [22-24,56,59,63,68] and liver damage [68] has been documented. One case history [84] reported severe nephritis followed by death due to the application of chromic acid anhydride to the wound resulting from the surgical removal of a facial carcinoma. The same effects, however, have been reported in persons having mixed exposures to sodium bichromate and sodium chromate, [5,19,33,41] being exposed to mists of chromium(VI) from plating or anodizing operations. In 1 instance [83] an acute oral poisoning with potassium bichromate resulted in severe nephritis and severe hepatitis. An animal study [105] of the effects of subcutaneous injections of potassium bichromate on monkeys' kidneys served to demonstrate that large, single doses and smaller, repeated doses damaged epithelium of proximal and distal convoluted tubules.

In 1884, Mackenzie [19] reported that ulceration of the nasal mucosal membrane followed by nasal septal perforation usually occurred after an exposure to bichromate of only a few days. Corrosion of both the nose and throat was also common and was occasionally accompanied by inflammation and perforation of the ear drums. No estimates of the degree of exposure required to produce these disorders were presented, but at that time the manufacturing processes were undoubtedly accompanied by an extremely dusty environment.

In a survey of the chromate-producing industry in 1948, Machle and Gregorius [33] reported a wide range of airborne mixed chromate

concentrations of 3-21,000 μg/cu m. In only 1 plant the degree of nasal septal irritation and perforation and airborne chromate concentrations were recorded. This plant comprised only the alkaline roasting operations, leaching to produce sodium chromate, and acidification to produce sodium bichromate and did not produce chromic acid anhydride. Among 354 employees examined, 35 reported nasal irritation and 154 reported nasal septal perforation. In this plant the range of "chromate" concentrations was 40-4,600 μg/cu m. It is not unreasonable to assume that many of those with nasal perforation had been exposed to airborne "chromate" concentrations in excess of 4,600 μg/cu m, because the plant began operation at least as early as 1930 at which time the several plants used reverberatory furnaces, notorious sources of exposure.

In a later extensive retrospective study by Mancuso [41] of 1 of the plants studied by Machle and Gregorius, [33] excessive incidences of nasal septal perforation and chronic chemical rhinitis and chronic chemical pharyngitis were found in workers who had been exposed to chromium(VI) concentrations in areas which, at the time of the study, were near 0-0.5 mg/cu m. In this plant sodium chromate and sodium bichromate were manufactured, but chromic acid anhydride was not. Although there was insufficient sampling to allow a statistically significant correlation between urinary chromium and chromium(VI) exposure, it was noted that the workers exposed primarily during those operations that follow roasting had urinary chromium concentrations greater than those whose exposure was during operations preceding leaching. Workers in the cement plant control group had significantly less urinary chromium than the chromate workers.

In a survey by the US Public Health Service in the early fifties, [5] 509 of the 897 chromate workers had a nasal septal perforation. The duration of employment prior to developing a nasal septal perforation was determined for 473 of these 509 workers. About 23% of these workers developed nasal septal perforations in the first 6 months of employment, 50.2% during the first year, and 71.5% during the first 3 years. Four hundred fifty-one of the 897 chromate workers had skin ulcers and scars produced by skin ulcers. Seventeen had lesions which were suggestive of chromate dermatitis. Seven separate plants were surveyed; sodium bichromate was the principal manufactured product of 6. One produced pigments from all of the bichromate it produced. Two of the 7 plants manufactured chromic acid anhydride as well. Two of the plants packaged sodium chromate and 2 manufactured potassium bichromate. All the plants apparently used alkaline roasting and thus sodium chromate was present as an intermediate. It is possible that some of the workers with these disorders had exposure to chromium(VI) oxide, but the vast majority were probably exposed only in processes not associated with chromic acid anhydride production. In addition, of all the operations surveyed, the chromic acid cookers-packers had nearly the lowest exposure to airborne chromium(VI) exposure of all the groups studied, less than 50 μg total chromium/cu m and less than 30 μg water-soluble chromium(VI)/cu m. This further supports the contention that chromic acid anhydride contributed only very little to the airborne chromium(VI) concentration.

Thus, it is apparent that identical effects on health occur, regardless of whether the chromium(VI) exposure is to sodium chromate and sodium bichromate, or to mists from plating or anodizing tanks filled with

acid solutions of chromium(VI). Indeed, the chromium(VI) in either solutions of soluble bichromate or chromium(VI) oxide is mostly in the same form, viz, hydrogen chromate ion. Although the acidities of the 2 solutions and the chemical oxidation potentials of the solutions may differ, the corrosive abilities of solutions of bichromates prepared from chromates and chromic acid anhydride are all apparently sufficient to produce nearly identical effects on nasal mucosal membranes, nasal septa, and exposed skin.

Although there is no information on the inhalation toxicity of ammonium bichromate that allows comparison with other chromium(VI) compounds, on the basis of chemical and physical properties (Table XI-4), it might be expected to be similar in toxicity to sodium and potassium bichromates. Ammonium bichromate was among the materials produced in the plant in which 198 workers out of 285 examined had ulcers, scars, and nasal septal perforations. [61] The literature is extensive relating exposure to sodium chromate and bichromate, potassium chromate and bichromate, and ammonium bichromate to the production of contact dermatitis. [7-11,21,25,61,62,69,71-81]

Fregert [69] found positive reactions to water-soluble hexavalent chromium in patients with chromate eczema. Morris [8] reported positive reactions to chrome-containing glue and chrome-dyed leather shoes. Calnan [9] concluded that cement dermatitis was primary irritant dermatitis complicated by a secondary contact sensitivity to "hexavalent chromate" [presumably chromium(VI)]. Engebrigtsen [10] confirmed that workers with cement eczema reacted positively to patch tests with aqueous 0.5% solutions of potassium bichromate. Jaeger and Pelloni [11] found that 94% of those

with cement eczema gave positive patch test results with aqueous 0.5% solutions of potassium bichromate. McCord et al [7] reported that 4 out of 25 lithographers developed vesicles following applications with aqueous 1% and 4.5% solutions of potassium dichromate but none had blisters following application with aqueous 4.5% solutions of ammonium bichromate. Parkhurst [21] observed a woman who produced blueprints and developed a follicular erythematopapular dermatitis following application of an aqueous 0.5% solution of potassium dichromate on her thigh. Smith [25] reported the allergic reactions of a man sensitized to ammonium bichromate, which included a vesicular erythematous dermatitis, profuse perspiration, and sibilant rales. Edmundson [61] found that few workers who developed chrome ulcers were sensitized to an aqueous solution of 0.5% potassium bichromate. Pirila and Kilpio [71] reported that some workers who had been exposed to materials likely to contain chromium compounds--bookworkers, cement and lime workers, persons working with fish glue, metal factory workers, painters and polishers, and fur workers--were allergic to aqueous 0.5% solutions of potassium dichromate. Denton et al [72] reported on a man who reacted strongly to an aqueous 0.005% solution of potassium dichromate. Winston and Walsh [73] reported on a man who had a patchy, pruritic, erythematous dermatitis from working with a chromate-silicate-phosphate mixture (pH 10); the man had positive reactions to 0.25% sodium dichromate and to the above mixture. Levin et al [74] reported that lithographers developed an allergy to chromium(VI) which was elucidated by patch tests with various chromium(VI) materials including an aqueous 1% solution of potassium dichromate and other nondescript solutions. Engel and Calnan [75] found a group of workers who wet-sanded zinc chromate primer paint and

who reacted positively to aqueous 0.5% solutions of potassium dichromate, and a group who did not react to an aqueous 0.5% solution of potassium dichromate until it was made alkaline (pH 10.3). Newhouse [76] found that 24% of the automobile assemblers studied yielded positive reactions to aqueous 0.5% solutions of potassium dichromate. The chromate dip used on bolts, nuts, and washers as an antirust agent was ascertained to have been responsible for the dermatitis. Fregert and Ovrum [77] found that welders exposed to aerosols of chromium(VI) developed hypersensitivity which was confirmed by patch testing with aqueous 0.1% solutions of chromium(VI) as potassium dichromate derived from welding fumes. Shelley [78] reported a similar sensitivity to welding fumes; a man with chronic, eczematous eruptions had positive reactions to aqueous 0.25% solutions of potassium dichromate. Loewenthal [79] observed a green-tattooed bricklayer with eczema who yielded positive reactions to aqueous 0.1% and 2% solutions of potassium dichromate. Cairns and Calnan [80] described a green-tattooed cement worker with eczema who reacted to aqueous 0.1% and 0.5% solutions of potassium dichromate and to an aqueous 2% solution of cobalt chloride.

Walsh [62] ascertained that aqueous 0.5% sodium dichromate, 0.5% potassium chromate, 0.05% sodium dichromate, and 0.005% sodium dichromate solutions produced lesions on abraded skin. Perone et al [81] found that among 95 construction workers who worked regularly with cement, 1 reacted to an aqueous 0.25% solution of potassium dichromate and 1 other man reacted to an aqueous extract of cement containing 450 ppb (450 ng/g) hexavalent chromium but not to the 0.25% solution of potassium dichromate.

(b) Chromium(VI) Materials Implicated in Lung Cancer Production

Chromium(VI) materials of some slight degree of water solubility appear to have had primary responsibility for the high incidence of lung cancer in 2 industries. [5,33,88-90] The industry [5,33,90] which has been examined the most extensively is that which uses alkaline oxidation of chromite ore to produce chromate. Another industry [88,89] which has been found to have a seemingly high incidence of lung cancer is the chromium(VI) pigment industry. Other industries which use or produce slightly soluble chromium(VI) materials have not been studied to any extent, [5,11,33,62,70,75] but through evidence supplied by animal studies, [13,107-111,115-118,120, written communication from LS Levy, 1975] it appears that workers exposed to any slightly soluble salts of chromic acid are probably at greater than normal risk from lung cancer.

In the chromate-producing industry, an excessive incidence of lung cancer was reported in the late 1940's by Machle and Gregorius [33] who found a total of 42 fatal cases of lung cancer in the industries in the United States producing sodium chromate and bichromate from chromite ore by alkaline oxidation between 1930 and 1947. These workers had begun their employment in the chromate industry between 1898 and 1939. One plant which used alkaline oxidation of chromite ore and produced sodium bichromate, chromium(III) oxide, and lead chromate employed 30-50 people and recorded no deaths from any cause. It had been in operation from 1938 to 1947. Whether or not this lack of deaths is significant cannot be determined from the data provided.

One particular plant, plant E of the Machle and Gregorius study, [33] was extensively studied later by Mancuso and others. [3,41,90] Exposures

of job classifications in the various production departments were determined by extensive air sampling and several individual workers' exposures were estimated. Chromium(VI) concentrations were the greatest in the roasting and finish crystals departments. The smallest concentrations were found in the ore preparation and neutralizing operations.

The smallest average departmental concentration of chromium(VI) was 30 μg/cu m; the largest was 280 μg/cu m. The mean chromium(VI) concentration of all 9 departments was 140 μg/cu m. In this plant, many of the departments and processes were not isolated from one another, thus allowing cross-contamination of airborne contaminants. Although the authors [90] estimated time-weighted average exposures for the 7 persons who died from lung cancer, it was acknowledged that the number of deceased lung cancer victims was too small to provide a good basis for a statistical correlation with the calculated "exposure years". In addition, it should be noted that the calculated exposure years were based upon measured environmental chromium(VI) concentrations which were thought to be the lowest ever attained in this plant which had begun operation around 1932. In order to meet price and quality competition, improvements in equipment and processes had been made periodically. Therefore, it is reasonable to assume that the environment was less dangerous in the late 1940's than in 1932. A cleanup plan was instituted in 1949, which was largely completed in 1951, and produced substantial reductions in airborne chromium concentrations in all departments. [91] At about the same time improvements were also made in other plants. [123]

At the time of the study in 1949 [3,41,90] the range of exposures for the 7 who died from lung cancer was estimated from employment histories,

job classifications, and 1949-50 environmental chromium concentrations. The range of exposures was calculated to be 10-150 μg/cu m and the mean was 50 μg/cu m. (Table XI-5). It is important to note that with 1 possible exception, all men died before the environmental data were gathered with 1 death occurring approximately 10 years before the study. The 2 persons with the lowest calculated exposures to chromium(VI), 10 μg/cu m, were apparently in the same job category; 1 was a crane operator who had some coke plant exposure following his chromate employment.

Animal studies have been performed [13,28,106-121, LS Levy, written communication, March 1975] in attempts to identify the materials responsible for lung cancer in the chromate-producing industry. The dust in the plants where alkaline oxidation was done in the absence of lime was found to contain greater than 10% each of chromium, iron, magnesium, sodium, and aluminum; 1-10% each of silicon and manganese; 0.05-1% each of vanadium and potassium. Less than 0.05% each of copper, zinc, calcium, and lead was also found. [5] In a lime-using process one would expect to find much larger amounts of calcium. The refuse created by a high-lime roasting process has been found to contain 38% calcium oxide, 23% iron(III) oxide, 15% aluminum oxide, 10% magnesium oxide, 3% silicon dioxide, 2% sodium oxide, 2% chromium(VI) [expressed as chromium(VI) oxide], 3% chromium(III) [expressed as chromium(III) oxide], 0.15% vanadium, 0.23% titanium, and 0.15% manganese according to WS Ferguson, written communication, September 1974. The chromium(VI) in the refuse comprised sodium chromate, calcium alumino-chromate, and calcium chromate(V), a "pentavalent chromium compound." The chrome residue following leaching contains similar percentages of the nonchrome materials and slightly larger percentages of

chromium(VI) and chromium(III).

Because residue from the leaching operation contained chromium(III), calcium, and chromium(VI), it was suggested [107,108, 112-114] that calcium chromate, chromium(III) chromate, or a complex containing the 3 species were carcinogenic. For this reason, animal toxicities of calcium chromate, residue, mixed chromate dusts, and sintered chromium(VI) oxide were evaluated. Calcium chromate of indefinite composition was found to produce tumors. [107-109,111,113-117,120, written communication from LS Levy, March 1975] Intramuscular injection in rats using arachis oil as a medium produced spindle cell sarcomas and pleomorphic sarcomas but no metastases. [115] Intramuscular implantation of calcium chromate in sheep fat produced a spindle cell injection-site sarcoma in 1 of 52 mice. [109] By intramuscular implantation of calcium chromate in gelatin capsules, 2 of 6 rats developed injection-site sarcomas. [109] By intrapleural implantation of calcium chromate in gelatin 3 of 6 rats developed injection-site sarcomas. By subcutaneous injection in tricaprylin, 1 of 52 mice developed an injection-site sarcoma. [109] Calcium chromate was found to produce tumors in 21 of 35 rats, both sarcomas and carcinomas following intraplural implantation. [108] Intratracheal injection of calcium chromate produced 3 malignant tumors in 85 rats in less than 12 months. [111] Calcium chromate implants in gelatin capsules produced 14 malignant tumors among 22 rats. [111] Eight cancers were found in a group of 100 rats when pellets of calcium chromate in a cholesterol carrier were implanted intrabronchially. Six of these were squamous cell carcinomas and were found in animals dying after 386-671 days. One animal dying after 474 days had metastases to the kidney. Two adenocarcinomas produced by calcium chromate were observed at

366 and 609 days. Both of these demonstrated mucus production. These rats showed atypical squamous metaplasia of the bronchus. [117] Calcium chromate produced cancers in 10 of 35 rats at the sites of intramuscular injections. [116] In addition, it produced cancers in 28 of 35 rats at the sites of intrapleural administration. [116] Inhalation of calcium chromate produced in rats 1 keratinizing squamous cell carcinoma, 1 laryngeal squamous cell carcinoma with invasion of perineural spaces and adjoining cartilagenous rings, and 1 malignant peritruncal tumor of undetermined type and origin. At the same concentration of airborne calcium chromate, 1 hamster developed a squamous cell carcinoma of the larynx which was invading and destroying the cartilage. In terms of chromium(VI), this calcium chromate concentration was 670 μg/cu m. Animals received 589 exposures at this concentration over 891 days. In view of these findings, the investigators examined the larynges. Two rats showed laryngeal hyperplasia and 3 showed laryngeal squamous metaplasia. Effects in hamsters were more marked with 8 animals showing laryngeal hyperplasia. An additional 8 animals showed squamous metaplasia of which 5 were "atypical with downgrowth." Another hamster, dying after 611 days, showed a squamous papilloma in the larynx with hyperplasia and hyperkeratosis. [118]

One study [120] used calcium chromate with a solubility in water of 1,200-1,400 ppm ground in a ball mill after the solubility was determined. Approximately 136 C57BL/6 mice of each sex were exposed to 13 mg calcium chromate/cu m for 5 hours/day, 5 days/week for their lifetimes. Six males in the exposed group developed lung tumors; 3 of the unexposed had lung tumors. Eight females in the exposed group had lung tumors; 2 in the control group had lung tumors. The lung tumors in the calcium chromate-

exposed animals were generally not different from those in the control. All tumors were pulmonary adenomas or adenocarcinomas.

In 1 experiment, [113] mice were exposed by inhalation to a mixture of finely ground chromium roast material (13.7% chromium(VI) oxide, 9.3% sodium oxide, 6.9% chromium(III) oxide, 17.7% iron(III) oxide, 9.4% aluminum oxide, 8.7% magnesium oxide, 31% calcium oxide, 0.2% vanadium(V) oxide, and 2.4% silicon dioxide) to which was added 1% potassium bichromate. The concentration of airborne chromium(VI) to which the mice were exposed was 470-940 μg water-soluble chromium(VI)/cu m and 52-104 μg water-insoluble, acid-soluble chromium(VI)/cu m. No squamous cell carcinomas were produced in the mice. All lung tumors appeared to be the usual type of adenomas. Rats exposed to the same chromate material [113] did not develop bronchogenic carcinomas, but 4 of these 100 experimental rats developed lymphosarcomas and 1 developed a hepatoma. Three of the lymphosarcomas involved the lung and 1 appeared to originate in the lung. The concentration of airborne chromium(VI) to which the rats were exposed was 940-1,400 μg water-soluble chromium(VI)/cu m and 104-156 μg water-insoluble, acid-soluble chromium(VI)/cu m. Three of 85 control rats had malignancies, 1 had a subcutaneous fibrosarcoma, 1 had a mammary adenocarcinoma, and 1 had a lymphosarcoma involving the mesenteric lymph nodes. An additional experiment involved the study of 306 normal stock rats of the same strains as the 85 control rats. Final results indicated a total of 4 out of 100 experimental rats with fibrosarcoma and 2 out of 391 control rats with fibrosarcoma, a difference which was felt to be statistically significant. However, the authors mentioned that lymphosarcomas are not uncommon in rats and that, although this finding was

suggestive, it could not be ascribed to chromate exposure unless confirmed by other experiments.

In a later experiment with rabbits, guinea pigs, and rats, [114] a mixed inhalation exposure was used, consisting of (1) the above [113] roast dust plus the mist produced by atomizing a 5% solution of potassium dichromate for 2 days a week; (2) a mist produced by atomizing a 17.5% solution of sodium chromate for 1 day/week; and (3) "pulverized residue dust" which consisted of roast material from which the sodium chromate had been leached, for 1 day/week. Finely ground potassium dichromate was added in a concentration of 1% to the chromate roast and residue materials. Inhalation exposures continued 4-5 hours/day, 4 days/week. Average concentration of chromium(VI) was 1.5-2 mg/cu m and the average weekly exposures were 26, 22, and 24 mg-hr for rabbits, guinea pigs, and rats, respectively. None of the 8 rabbits developed lymphosarcomas from the mixed dust. One of 50 guinea pigs developed a lymphosarcoma, and 3 developed alveologenic adenomas. Of the 44 controls, 1 developed lymphosarcoma, and none developed alveologenic adenomas. Of the 78 rats, 4 developed lymphosarcomas and 3 developed alveologenic adenomas. Of the 75 controls, 4 developed lymphosarcomas and 2 developed alveologenic adenomas.

A finely powdered chromate roast was mixed with extracted sheep fat and implanted into the pleural cavities of 25 male rats. [107] Thirty-one female rats received implants into the muscle tissue of the right thigh. Control groups of 15 females received sheep fat implants in the thighs and pleural cavities. Pulmonary squamous cell carcinomas were found in 2 rats with intrapleural deposits of chromite roast in sheep fat. One of these rats had a metastatic carcinomatous nodule in 1 kidney. The 3 injection-

site tumors that were found in the rats given chromium-bearing sheep fat were fibrosarcomas. One of these rats had mesenteric metastases. Seven of the control rats had tumors, 3 of which were large round cell sarcomas involving the ileocecal and mesenteric lymph nodes. In a later experiment, [108] 2 groups of 35 rats received thigh and pleural implants, respectively, of sintered calcium chromate, the composition of which was not determined. Eight of those with thigh implants and 17 of those with pleural implants with this material developed injection-site spindle cell sarcomas or fibrosarcomas. Sintered chromium(VI) oxide (sintered chromic acid anhydride) implanted in the thighs and pleural cavities of 2 groups of 35 rats, respectively, produced injection-site sarcomas. Of these 70 rats, 29 developed injection-site sarcomas. Sintered chromium(VI) oxide has an indefinite composition, containing both chromium(III) and chromium(VI). This material has been referred to as chromic chromate in some instances. [116,108]

In a study by Payne, [109] sintered calcium chromate was mixed with sheep fat and implanted into muscle tissue of the thighs of 52 mice. At the end of 14 months, a total of 9 implantation-site sarcomas were found.

Animal experiments have recently (March 1975) been completed, according to a written communication from LS Levy, which distinguish between the chromium(VI) compounds which are carcinogenic and those which are not. In this study, sodium dichromate and chromate were tested and found to lack carcinogenicity. The less soluble chromium(VI) compounds tested, ie, chromic chromate in silica, calcium chromate, and zinc chromate, were found to be potent carcinogens.

While the animal data leave much to be desired, there is sufficient information to support the conclusion that chromium(VI) compounds are implicated in the production of cancer, regardless of the mode of administration.

From the information available, it appears that a chromium(VI) material generated by the alkaline roasting of chromite ore, has carcinogenic characteristics when inhaled. [5,33,90,118-120] It is not conclusive that the carcinogen is any discrete, identifiable material, although it is apparently a chromium(VI) material of only slight solubility. [33,90] It is not reasonable, on the basis of the epidemiologic and animal studies, to exclude chromium(VI) materials of only slight solubility from those which are potentially carcinogenic.

There is a group of chromium(VI) materials which have been used for pigments. [5,6,124] Pigments are generally materials having very low water solubilities. Examples of pigments most widely used containing chromium(VI) are lead chromate, [88,89,124] zinc chromate, [70,75,88,89,124] strontium chromate, [124] and cadmium chromate, all of which are poorly soluble. [124] Various shades of pigments may contain other substances in addition to these compounds. There are 2 studies [88,89] implicating pigments in lung carcinogenicity.

In 1943, Gross and Kolsch [88] reported lung cancer in workers involved with the production of lead chromate and zinc chromate. Lead chromate was prepared from lead acetate and potassium dichromate. Zinc chromate was prepared from zinc oxide and bichromate. It was noted that in these processes there was not much dust, but in the subsequent mixing with shading components, milling, grinding, and casking, a great deal of dust

was evolved. From the 3 firms engaged in this manufacturing, 8 deaths from lung cancer were reported. The number of workmen involved was given for 2 of the 3 firms which reported 7 of the 8 deaths from lung cancer. The number of men involved in the 2 plants was probably less than 50, 7 of whom died from lung cancer. The 7 had worked in the industry for 5-17 years. No estimates of the degrees of exposure were given. It was noted that 7 of the 8 were exposed to zinc chromate and lead chromate, and the eighth was exposed only to zinc chromate.

In 1975, a study [89] of cancer in Norwegian workers in a similar pigment manufacturing process was published. Three workers in a cohort of 24 developed lung cancer; 2 had exposure to both zinc chromate and lead chromate. The third worker had exposure to zinc chromate. The authors calculated that the ratio of the observed number of lung cancers for this cohort was 38. The total number of man-years-at-risk was 244. The airborne concentration of chromium in this plant (probably in 1972) was 0.19-0.43 mg/cu m. Although these determinations were made 16-23 years after the workers began their employment, interviews by the authors led them to conclude that airborne chromium(VI) concentrations at the time of the study (1972) were of the same magnitude as those in prior years.

The development of lung cancer following exposure to only slightly soluble chromium(VI) materials appears to be better documented in the chromate-production industry than in the pigment industry. Nevertheless, a reasonably good correlation can be made based on the findings in the studies of both the chromate-producing industry, [5,33,79] and the chrome-pigment-producing industry. [88,89] Other industries might be expected to exhibit excess lung cancer mortality if examined. Among these are

manufacturers who use chromium(VI) in the production of pyrotechnics, matches, certain fungicides and seed sterilants, and dry batteries.

Several chromium(VI) materials which fall into this group of chromium(VI) materials which have been implicated in lung cancer production also have caused dermatitis. Sixty-five men [75] in a population of 250 who were involved in the wet-sanding of automobile primer paint containing zinc chromate developed dermatitis. Lesions were generally red, scaly or vesicular dermatitis involving the hands, fingers, and forearms. Some had areas of patchy eczema, some had erythema or scattered papules, and others had a dyshidrotic pompholyx type of eruption, nummular eczema, or a follicular irritative dermatitis. Fifty-eight of the patients were patch-tested with an aqueous 0.5% solution of potassium dichromate and 91% had positive reactions. It is likely that the chromium(VI) in the primer was responsible for the dermatitis. Zinc has been implicated [125] in allergic dermatitis only on rare occasions. The concentration of chromium(VI) in quasi-equilibrium with zinc chromate was [108] 610 μg/ml water and 830 μg/ml Ringer's solution. The concentration of 610 μg chromium(VI)/ml corresponds to a 0.17% aqueous solution of potassium dichromate. It is therefore not surprising that 91% of these men reacted to a solution of 0.5% potassium dichromate. As mentioned earlier, [11] persons who have become sensitive to chromium(VI) yield positive skin reactions to 0.1%, 0.01%, and 0.001% solutions of potassium dichromate.

Hall [70] reported numerous cases of dermatitis in aircraft workers who worked with a zinc chromate primer, among other compounds. Ninety workers were patch-tested with a mixture of zinc chromate and calcium carbonate and 68% yielded positive reactions.

Although there have been reports of skin ulcers, nasal mucous membrane irritation, and nasal septal perforations in workers in the chromate-producing industry, [5,33,41] it is inappropriate to attribute these effects solely to the products of the roasting and leaching operations; rather, these effects have been found throughout many segments of the industry.

Tables III-3 and III-4 summarize, respectively, the results of epidemiologic studies of cancer mortality in chromium(VI)-producing and chromium(VI)-using plants, and the results of animal toxicity studies of chromium(VI) materials. Table III-5 classifies the various chromium(VI) materials as noncarcinogens and carcinogens. In Table III-5 evident noncarcinogens are those for which there is evidence of their lack of carcinogenicity; inferred noncarcinogens are those that have chemical and physical properties similar to the evident noncarcinogens. The evident carcinogens in Table III-5 are those chromium(VI) materials for which there is strong evidence of their carcinogenicity; inferred carcinogens are those materials for which either there is no evidence to suggest they are not carcinogens or they have chemical and physical properties sufficiently similar to those of the carcinogens that they are reasonably inferred to be carcinogens.

TABLE III-3

RESULTS OF EPIDEMIOLOGIC STUDIES IN CHROMIUM(VI) PRODUCING AND USING PLANTS

Plant	Materials	Concentration	Summary	Reference
A1 Chromate-producing; alkaline oxidation of chromite ore with lime	Calcium and chromium(III) chromates and bichromates; trace amounts of other metals	10-500 μg/cu m	4.86 deaths from lung cancer/1000 man-years. Controls: 0.09 deaths from lung cancer/1000 man-years.	33
B1 Chromate-producing; alkaline oxidation of chromite ore with lime	Chromite, soda ash, fused mixture, sodium chromate, sodium bichromate, sodium sulfate, sulfuric acid, (calcium and chromium(III) chromates and bichromates; trace amounts of other metals)	20-2,300 μg/cu m	1.61 deaths from lung cancer/1000 man-years. Controls: 0.09 deaths from lung cancer/ 1000 man-years.	33
E Chromate-producing; alkaline oxidation of chromite ore with lime	Calcium and chromium(III) chromates and bichromates, trace amounts of other metals	1.5-11,500 μg/cu m	2.52 deaths from lung cancer/ 1000 man-years. Controls: 0.09 deaths from lung cancer/ 1000 man-years.	33
D2 Chromate-processing; no alkaline oxidation of chromite ore	Sodium bichromate, chromic acid, basic chrome sulfate, sulfuric acid	No exposure estimate	No deaths from lung cancer/ 1853 man-years.	33
Baltimore, Md, Chromate-producing; alkaline oxidation of chromite ore with lime	Chromite, soda ash, lime, fused mixture, sodium chromate, sodium bichromate, sulfuric acid	Unreported	7 of 198 lung cancer cases in one plant and 3 of 92 in another plant were in chromate plant workers. Control group had significantly lower incidence of lung cancer.	94
Painesville, Ohio, Chromate-producing, alkaline oxidation of chromite ore with lime	Chromite ore, soda ash, lime, fused mixture, chromium(III). Sodium sulfate, sodium chromate, sodium bichromate.	0-500 μg/cu m	18.2% of deaths in chromate plant population were from lung cancer; 1.2% of deaths in control group were from lung cancer.	90
6 study plants, other than the one in Painesville, Ohio, including the Baltimore, Md, plant. Chromate-producing, alkaline oxidation of chromite ore with lime	Chromite ore, soda ash, lime, fused mixture, chromium(III), sodium sulfate, sodium chromate, chromium(VI) oxide, potassium bichromate, chrome tan	0-432 μg "water-soluble" Cr(VI)/ cu m, 0-312 μg acid-soluble water-insoluble Cr(VI)/cu m.	Death from cancer of respiratory system occurred at a rate of 470.8/100,000 in chromate plants; rate was 16.7/100,000 in the population of the United States.	5
3 study plants, comprising 70% of the chromate-producing industry (1,212 workers) Alkaline oxidation of chromite ore with lime	Unmentioned but probably same as above	Unreported	263 deaths occurred; 71 were due to cancer of respiratory system, 8 deaths from cancer of respiratory system were expected.	99
British chromate-producing, alkaline oxidation of chromite ore with limestone	Chromite ore, soda ash, limestone, sodium chromate, sodium dichromate, sulfuric acid, sodium sulphate, potassium chloride, potassium dichromate, potassium chromate, chromium(VI) oxide, chrome tan	0.4-17,000 μg Cr(VI)/cu m	1 case of lung cancer in 724 chromate workers; 3.6 times as many workers died of lung cancer as would have been expected in the male population of England and Wales.	100,101
Chromium pigment production; chromate-using plant	Lead acetate, potassium dichromate, lead chromate, zinc oxide, potassium dichromate, zinc potassium chromate, barium sulfate, iron(III) hexacyanoferrate(II)	Unreported	7 deaths from lung cancer in fewer than 50 workers.	88
Chromium pigment production; chromate-using plant (A)	Sodium bichromate, zinc oxide, lead chromate, zinc chromate	190-430 μg Cr/cu m	3 cases of cancer of the bronchus; expected cases was 0.079.	89

TABLE III-4

RESULTS OF ANIMAL TOXICITY STUDIES OF CHROMIUM(VI) MATERIALS

Material	Route of Administration	Animal	Number	Results	Reference
Chromite ore lime roast and benzene-extracted sheep fat	Implantation in thigh muscle	Rats (female)	31	3 fibrosarcomas, thigh 2 round cell sarcomas, mesenteric lymph nodes 3 carcinomas, uterus 1 cholangiomacarcinoma, liver	107
Sheep fat	"	"	15	2 round cell sarcomas, mesenteric lymph nodes 1 cholangioma, liver	"
Chromite ore lime roast and benzene-extracted sheep fat	Implantation in pleural cavity	Rats (male)	25	2 squamous cell carcinomas, implant site 1 adenoma, adrenal 1 cholangiomacarcinoma, liver	107
Sheep fat	"	Rats (female)	15	1 adenoma, implant site 2 adenofibroma, breast 1 round cell sarcoma, mesenteric lymph nodes	"
Finely pulverized calcium chromate in sheep fat	Pellet implanted in pleural cavity	Rats	35	21 sarcomas, implant site	107
Sintered calcium chromate in sheep fat	"	"	"	17 sarcomas, implant site	108
Sintered chromium(VI) oxide in sheep fat	"	"	"	14 sarcomas, implant site	"
Barium chromate in sheep fat	"	"	"	No tumors	"
Sheep fat	"	"	"	No tumors	"
Finely pulverized calcium chromate in sheep fat	Pellet implanted in thigh muscle	Rats	35	8 sarcomas, implant site 1 squamous cell carcinoma, implant site	108
Sintered calcium chromate in sheep fat	"	"	"	8 sarcomas, implant site	"
Sintered chromium(VI) oxide in sheep fat	"	"	"	15 sarcomas, implant site	"
Barium chromate in sheep fat	"	"	"	No tumors	"
Sheep fat	"	"	"	"	"
Calcium chromate in extracted sheep fat	Pellet implanted in thigh muscle	Mice	52	2 sarcomas, implant site	109
Sintered calcium chromate in extracted sheep fat	"	"	"	9 sarcomas, implant site	"
Sheep fat	"	"	"	No tumors	"
Calcium chromate in tricaprylin	Injection into nape of neck	Mice	52	1 sarcoma, injection site	109
Sintered calcium chromate in tricaprylin	"	"	"	No tumors	"
Sintered chromium(VI) oxide in tricaprylin	"	"	"	"	"
Tricaprylin	"	"	"	"	"
Calcium chromate in gelatin capsules	Implanted intramuscularly in thigh	Rats	6	2 sarcomas, implant site	109
Calcium chromate in gelatin capsules	Implanted intrapleurally	"	"	3 sarcomas, implant site	"
Water-extracted residue from alkaline lime roasting and leaching operation in chromate-producing industry	Subcutaneous injection into nape of neck	Mice	52	3 sarcomas, injection site	110

TABLE III-4 (CONTINUED)

RESULTS OF ANIMAL TOXICITY STUDIES OF CHROMIUM(VI) MATERIALS

Material	Route of Administration	Animal	Number	Results	Reference
Roast residue in sheep fat	Pellet implanted intrapleurally	Mice	35	3 sarcomas, implant site	110
Sheep fat	"	"	"	No tumors	"
Roast residue in sheep fat	Pellet implanted in thigh	Mice	52	No tumors	110
Sheep fat	"	"	"	"	"
Sodium bichromate in gelatin	16 monthly intrapleural injections, each	Rats	39	1 adenocarcinoma, injection site 2 reticulum cell sarcomas, liver	111
"	16 monthly intramuscular injections, each	"	"	1 adenofibroma, breast 1 cystadenoma, ovary 1 adenoma, renal cortex 1 cholangioma 1 round cell sarcoma, ileocecal lymph nodes 1 squamous cell carcinoma, uterine mucosa	"
Untreated	None	"	60	4 unspecified tumors, remote 12 unspecified malignant tumors, remote	"
Calcium chromate in gelatin	Intratracheal instillation every 2 months	Rats	85	1 unspecified malignant tumor, remote 2 fibrosarcomas, injection site	111
Strontium chromate in gelatin	"	"	60	1 unspecified benign tumor, remote 1 fibrosarcoma, injection site 1 adenofibroma, breast	"
Zinc chromate in gelatin	"	"	73	1 unspecified malignant tumor, remote	"
Untreated	"	"	35	4 unspecified malignant tumors, remote	"
Calcium chromate in gelatin capsule	Implantation in pleural cavity	Rats	14	8 unspecified malignant tumors, implant site	111
Calcium chromate in gelatin capsule	Implantation in thigh muscle	"	8	2 unspecified malignant tumors, remote 4 unspecified malignant tumors, implant site	" "
Roast dust from alkaline lime roasting process in chromate producing plant with 1% potassium dichromate added to it.	Inhalation of dust; 0.47-0.94 mg/cu m water-soluble chromium(VI) and 0.052-0.104 mg/cu m water-insoluble, acid-soluble chromium. Solubilities were undefined.	Mice	500	241 survivors, 114 with lung adenomas	113
Control	None	"	448	353 survivors, 160 with lung adenomas	"
Roast dust from alkaline lime roasting process in chromate producing plant with 1% potassium dichromate added to it.	Inhalation of dust; 0.94-1.4 mg/cu m water-soluble chromium(VI) and 0.104-0.156 mg/cu m water-insoluble, acid-soluble chromium(VI). Solubilities were undefined.	Rats	110	3 lymphosarcomas, lung 1 hepatoma 1 lymphosarcoma appeared to originate in lung	113
Control	None	"	100	1 subcutaneous fibrosarcoma 1 mammary adenocarcinoma 1 lymphosarcoma	"
"	"	"	306	1 lymphosarcoma 2 unspecified malignancies	"

TABLE III-4 (CONTINUED)

RESULTS OF ANIMAL TOXICITY STUDIES OF CHROMIUM(VI) MATERIALS

Material	Route of Administration	Animal	Number	Results	Reference
Roast dust from alkaline lime roasting process in chromate producing plant with 1% potassium dichromate added to it.	Inhalation of dust; 15-25 mg chromium/cu m (expressed as chromium(VI) oxide). Exposed 30 min/day	Mice	61	30 survivors, 14 with lung adenomas	113
Control	None	"	49	30 survivors, 13 with lung adenomas	"
Roast dust from alkaline lime roasting process in chromate producing plant with 1% potassium dichromate added to it.	Intratracheal injection, 5-6 doses at 4- to 6-week intervals	Mice	506	183 survivors, 112 with lung adenomas	113
Control	Intratracheal injection of 55 with saline	"	458	272 survivors, 155 with adenomas	"
Roast dust from alkaline lime roasting process in chromate producing plant with 1% potassium dichromate added to it. Suspended in olive oil.	Intratracheal injection, 15 doses at 2-week intervals	Rats	40	No tumors	113
Olive oil	Intratracheal injection	"	42	" "	"
Zinc potassium chromate	Intratracheal injection	Mice	106	62 survivors, 30 with lung adenomas	113
Saline	"	"	39	31 survivors, 14 with lung adenomas	"
Control	None	"	99	68 survivors, 38 with lung adenomas	"
Barium chromate	Intratracheal injection	Mice	52	38 survivors, 29 with lung adenomas	113
Control	None	"	49	31 survivors, 22 with lung adenomas	"
Roast dust from alkaline lime roasting process in chromate producing plant with 1% potassium dichromate added to it.	Intrapleural injection	Mice	55	41 survivors, 25 with lung adenomas	113
Control	None	"	41	30 survivors, 20 with lung adenomas	"
Basic potassium zinc chromate	Intravenous injection	Mice	27	20 survivors, 16 with lung adenomas	113
Saline	"	"	26	22 survivors, 14 with lung adenomas	"
Control	None	"	27	22 survivors, 14 with lung adenomas	"
Barium chromate	Intravenous injection	Mice	40	38 survivors, 29 with lung adenomas	113
Saline	"	"	"	34 survivors, 22 with lung adenomas	"
Control	None	"	45	30 survivors, 19 with lung adenomas	"

TABLE III-4 (CONTINUED)

RESULTS OF ANIMAL TOXICITY STUDIES OF CHROMIUM(VI) MATERIALS

Material	Route of Administration	Animal	Number	Results	Reference
				Effects on Lung Tissue	
Sequence of exposures to (1) lime roast dust from an alkaline roasting process in chromate plant plus a mist of 1% potassium bichromate; (2) mist of 17.5% solution of sodium chromate; (3) pulverized residue dust consisting of lime roast material which had been leached with water to remove sodium chromate	Inhalation; water-soluble chromium(VI) concentration was 1.5-2 mg/cu m; acid-soluble, water-insoluble, chromium(VI) concentration was 1.5-2 mg/cu m. Animals were exposed 4-5 hours/day, 4 days/week.	Rabbits	8	1 alveolar hyperplasia	114
		Guinea pigs	50	11 alveolar hyperplasia 3 alveologenic adenomas 1 lymphosarcoma 5 alveolar hyperplasia	"
		Rats	78	3 alveologenic adenomas	"
Control	None	Rabbits	5		"
"	"	Guinea pigs	44	1 lymphosarcoma	"
"	"	Rats	75	2 alveolar hyperplasia 2 alveologenic adenomas 4 lymphosarcomas	"
Lime roast dust from alkaline roasting process in chromate producing plant with 1% potassium bichromate	3-5 intratracheal injections at 3-month intervals	Rabbits	10	2 alveolar hyperplasia	114
	6 intratracheal injections at 3-month intervals	Guinea pigs	19	"	"
Mixed lime roast chromate dust, potassium bichromate	16 intratracheal injections at 1-month intervals	Rats	38	" 2 lymphosarcomas	"
Zinc potassium chromate	6 intratracheal injections at 6-week intervals	Mice	62	28 alveolar hyperplasia 31 alveologenic adenomas 2 lymphosaromas	"
"	3-5 intratracheal injections at 3-month intervals	Rabbits	7	6 alveolar hyperplasia	"
"	6 intratracheal injections at 1-month intervals	Guinea pigs	21	13 alveolar hyperplasia 1 alveologenic adenoma	"
Lead chromate	3-5 intratracheal injections at 3-month intervals	Rabbits	7	1 alveolar hyperplasia	"
"	6 intratracheal injections at 1-month intervals	Guinea pigs	13	2 alveolar hyperplasia	"
Residue from water leaching of lime roast material produced by alkaline oxidation of chromite ore	3-5 intratracheal injections at 3-month intervals	Rabbits	7	"	"
"	6 intratracheal injections at 1-month intervals	Guinea pigs	19	1 alveolar hyperplasia	"
Saline	3-5 intratracheal injections at 3-month intervals	Rabbits	5	No hyperplasia	"
Control	None	"	2	"	"
Saline	6 intratracheal injections at 1-month intervals	Guinea pigs	18	5 alveolar hyperplasia	"
Control	None	Mice	"	2 alveolar hyperplasia 7 alveologenic adenomas 2 lymphosarcomas	"
Zinc carbonate (control)	6 intratracheal injections at 6-week intervals	"	12	1 alveolar hyperplasia 3 alveologenic adenomas	"
Lead titanate (control)	6 intratracheal injections at 1-month intervals	Guinea pigs	6	1 alveolar hyperplasia	"

TABLE III-4 (CONTINUED)

RESULTS OF ANIMAL TOXICITY STUDIES OF CHROMIUM(VI) MATERIALS

Material	Route of Administration	Animal	Number	Results	Reference
Calcium chromate in arachis oil	20 once-weekly intramuscular injections into right flank	Rats	24	11 spindle cell sarcomas, injection site 7 plemorphic sarcomas, injection site	115
Arachis oil	"	"	16	No tumors	"
Chromic chromate	Intramuscular injection	Rats	35	30 cancers, injection site	116
"	Intrapleural injection	"	"	34 cancers, injection site (1 carcinosarcoma of lung 1 osteogenic sarcoma with squamous cell nests in the lung)	"
Calcium chromate	Intramuscular injection	"	"	10 unspecified cancers, injection site	"
"	Intrapleural injection	"	"	28 unspecified cancers, injection site (2 cornified squamous cell carcinomas of lung)	"
Sintered calcium chromate	Intramuscular injection	"	"	13 unspecified cancers, injection site	"
"	Intrapleural injection	"	"	21 unspecified cancers injection site	"
Strontium chromate	Intramuscular injection	"	"	17 unspecified cancers injection site	"
"	Intrapleural injection	"	"	"	"
Barium chromate	Intramuscular injection	"	"	No cancers, injection site	"
"	Intrapleural injection	"	"	2 unspecified cancers injection site	"
Lead chromate	Intramuscular injection	"	"	3 unspecified cancers injection site	"
"	Intrapleural injection	"	"	3 unspecified cancers, injection site (1 adenocarcinoma with squamous cell transformations in lung)	"
Sodium bichromate	Intramuscular injection	"	"	No cancers, injection site	"
"	Intrapleural injection	"	"	2 unspecified cancers, injection site	"
Chromite roast residue	Intramuscular injection	"	"	1 unspecified cancer, injection site	"
"	Intrapleural injection	"	"	8 unspecified cancers injection site	"
Zinc yellow	Intramuscular injection	"	"	16 unspecified cancers, injection site	"
"	Intrapleural injection	"	"	22 unspecified cancers, injection site	"
Sheep fat	Intramuscular injection	"	"	No cancers, injection site	"
"	Intrapleural injection	"	"	"	"

TABLE III-4 (CONTINUED)

RESULTS OF ANIMAL TOXICITY STUDIES OF CHROMIUM(VI) MATERIALS

Material	Route of Administration	Animal	Number	Results	Reference
Roast residue in sheep fat	Pellet implanted in thigh	Rats	35	1 sarcoma, implant site	110
Sheep fat	"	"	"	No tumors	"
Residue, in cholesterol from alkaline lime roasting of chromite ore after leaching by water	Intrabronchial implant	Rats	100	1 squamous cell carcinoma 1 hepato-cell carcinoma atypical squamous metaplasia of bronchus	13
Calcium chromate in cholesterol	"	"	"	6 squamous cell carcinomas 1 hepato-cell carcinoma atypical squamous metaplasia of bronchus	"
Chromium(III) oxide in cholesterol	"	"	98	No carcinomas, atypical squamous metaplasia of bronchus	
Chromium(VI) oxide in cholesterol	"	"	100	2 hepato-cell carcinomas	"
Cholesterol	"	"	24	No carcinomas	"
Calcium chromate	Inhalation; 2 mg/cu m 589 exposures in 891 days	Rats	Unknown	1 keratinizing squamous cell carcinoma of lung 1 laryngeal squamous cell carcinoma with invasion of perineural spaces and adjoining cartilagenous rings 1 malignant peritruncal tumor 2 laryngeal hyperplasia 3 laryngeal squamous metaplasia	118
"	"	Hamsters	"	1 squamous cell carcinoma of larynx 8 laryngeal hyperplasia of larynx 8 squamous metaplasia of larynx 1 squamous papilloma of larynx with hyperplasia and hyperkeratosis	"
Calcium chromate	Inhalation; 13 mg/cu m 5 hours/day, 5 days/week	Mice (males)	136	6 lung tumors No bronchogenic tumors	120
Air	Inhalation control	"	"	2 lungs tumors No bronchogenic tumors	"
Calcium chromate	Inhalation; 13 mg/cu m 5 hours/day, 5 days/week	Mice (females)	136	8 lung tumors No bronchogenic tumors	120
Air	Inhalation control	"	"	2 lung tumors No bronchogenic tumors	"
Calcium chromate	15 weekly intratracheal injections	Hamsters	-	Frank bullous emphysema extensive goblet cell hyperplasia, bronchiolization of alveoli	120

TABLE III-5

NONCARCINOGENIC AND CARCINOGENIC CHROMIUM(VI)

Evident Noncarcinogens	Inferred Noncarcinogens (see text for basis for inferences)	Evident Carcinogens	Inferred Carcinogens
Sodium bichromate [33, LS Levy, written communication, 1975]	Lithium bichromate	Calcium chromate [3,5, 13,33,41,90,93,94, 98-102,107,119, LS Levy, written communication, 1975]	Alkaline earth chromates and bichromates
Sodium chromate [LS Levy, written communication, 1975]	Lithium chromate	Sintered calcium chromate [108]	Chromyl chloride
Chromium(VI) oxide [33]	Potassium bichromate	Alkaline lime roasting process residue [13]	t-Butyl chromate
	Potassium chromate	Zinc potassium chromate [88,89, LS Levy, written communication, 1975]	Other chromimum(VI) materials not listed in this table
	Rubidium bichromate	Lead chromate [88,89]	
	Rubidium chromate		
	Cesium bichromate		
	Cesium chromate		
	Ammonium bichromate		
	Ammonium chromate		