[Review]

Cancer Risks of Hexavalent Chromium in the Respiratory Tract

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Abstract **:** Hexavalent chromium (Cr(VI)) compounds are recognized as carcinogens in the respiratory tract, giving rise to cancers of the lung, nose and nasal sinuses, especially in certain occupational environments. Inhalation exposure of Cr(VI)-containing particles, dusts and fumes commonly occurs in chromium-related occupational environments, such as chromium production, plating, welding of chromium-containing metals and alloys, electroplating, chromium-containing pigments and paints. Epidemiological surveys of chromium compounds have shown strong associations between exposure to Cr(VI) and mortality due to lung cancer, as well as positive associations with cancers of the nose and nasal cavity. Nasal symptoms, such as nasal irritation, ulceration and perforation of the nasal septum, nasal turbinate engorgement and hypertrophy, are important signs for the early diagnosis of lung cancer and cancers of the nose and nasal cavity in those with an occupational history of Cr(VI) exposure. Cr(VI) exposure in the workplace remains a serious problem as a cause of lung cancer and cancers of nose and nasal cavity, especially in relatively small enterprises that use chromium compounds. Appropriate protection for workers should be considered in occupations that involve exposure to chromium compounds.

Keywords **:** hexavalent chromium, cancer, inhalation exposure, respiratory tract.

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Introduction

Exposure to chromium compounds is common in several chromium-related occupations and can be quite hazardous to the health of workers in these environments, especially in relatively small enterprises. Hexavalent chromium (Cr(VI)) is the most hazardous of the several types of chromium, and numerous studies in both humans and animals have suggested a relationship between exposure to Cr(VI) and an increased risk of lung cancer, especially exposure in the work environment. In addition, numerous epidemiological studies have shown a positive association between Cr(VI) exposure and an increased risk of cancers of the nose and nasal sinuses in addition to non-cancerous effects on the nose and nasal sinuses, such as nasal irritation, nasal septum ulceration and perforation, nasal turbinate engorgement and hypertrophy.

We herein summarize the recent findings concerning exposure to Cr(VI) in the workplace and cancers of the respiratory tract, such as lung cancer and cancers of the nose and nasal sinuses, with a typical case presentation of a patient with both cancers (lung cancer and cancer of the upper pharynx) who worked in a small-industry chrome-plating factory for over 30 years without appropriate protection.

Case presentation of a complicated case of lung cancer and cancer of the nasal pharynx in a chromium plating worker

A 60-year-old Japanese man had observed bilateral neck lymph node swelling for 1 year. He then began to experience lightheadedness upon standing, dyspnea on exertion and melena for several months before finally visiting an internal medicine clinic. He had worked in a small chrome-plating factory as a plater for 31 years without wearing appropriate protection for chromium exposure. He was a current smoker with a smoking history of 45 pack-years and no remarkable medical history.

Chest X-ray showed pulmonary nodules in his lung field (Fig. 1A), and severe anemia (hemoglobin 6 g/d*l*) was observed in peripheral blood tests, so he was introduced to our hospital. After admission, red blood cell transfusion and upper and lower gastrointestinal fiberscopic examinations were performed, and the bleeding was diagnosed as being due to internal hemorrhoids. Head, neck and chest computed tomography and fluorodeoxyglucose-positron emission tomography revealed pulmonary nodules in the left lower lobe (Fig. 1C and 1D) and a tumor in the upper pharynx (Fig. 2A and 2B) with swelling of the bilateral lymph nodes (Fig. 2C and 2D), and a high uptake of fluorodeoxyglucose was seen in these tumors and lymph nodes. Rhinoscopic and endoscopic examinations revealed a large nasal septal perforation and an ulcerative tumor on the posterosuperior nasopharyngeal wall (Fig. 2E). Biopsies from the upper pharynx and endobronchial ultrasonography with a guide sheath-guided transbronchial biopsy of the tumor in the left lower lobe (Fig. 1B) were performed. Both biopsies revealed cancer of the upper nasopharynx (squamous cell carcinoma) (Fig. 3A and 3B), and lung cancer (squamous cell carcinoma) (Fig. 3C and 3D) was ultimately diagnosed. No Epstein-Barr virus-positive cells believed to be causative for the nasopharyngeal cancer were observed, supporting the hypothesis that the nasopharyngeal cancer in this patient was Cr(VI)-associated. The patient was diagnosed with both cancer of the nasopharynx and primary lung cancer in the left lobe, and left lower lobectomy was performed. Scanning electron microscopy and X-ray spectrometry of the pathological specimen obtained from the left lung cancer showed metal particles that had a peak for chromium (Fig. 4A and 4B). After lung surgery, systemic chemotherapy in combination with radiotherapy was started to treat the cancer of the nasopharynx.

Chemistry and biopersistence of chromium(VI)

Chromium is a naturally occurring metallic element found in rocks, soil and volcanic dust and gases and has oxidation states ranging from −2 to +6. The most stable forms are chromium(0), trivalent chromium (Cr(III)) and Cr(VI). Cr(VI) is the second-most stable oxidation state of chromium generally produced from anthropogenic sources but is rarely naturally formed, except in the rare mineral crocoite ($PbCrO_4$)[1]. In the presence of reducing agents, such as iron or oxidizable organic matter, most Cr(VI) compounds related to manufactured products can be reduced to the more

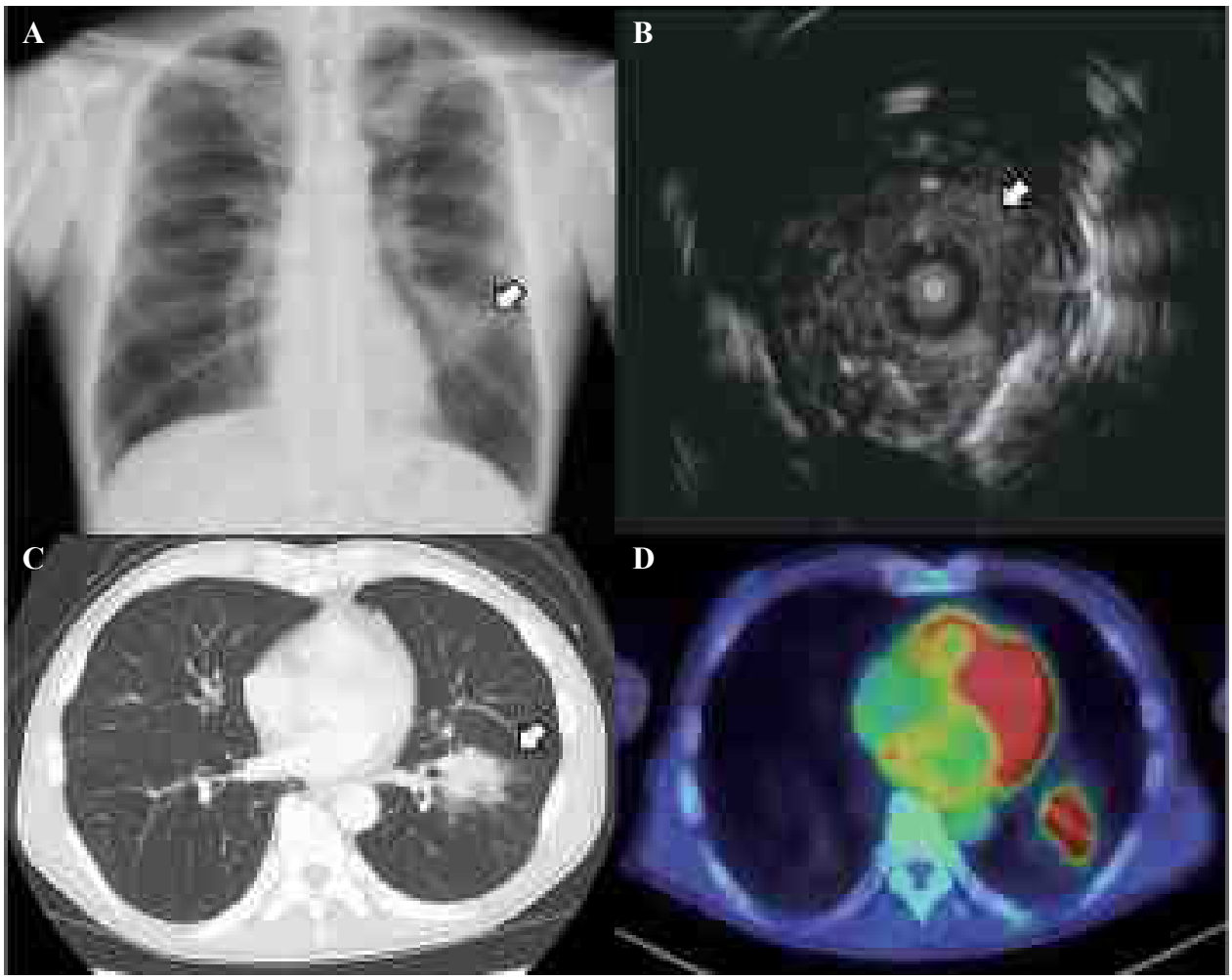

Fig. 1. Chest and intra-bronchial image findings on admission. A: Chest X-ray film on admission, showing mass lesions (white arrow) in the left lower lung field. B: Echography through an endobronchial ultrasonography-guided sheath, showing the echo probe was within the lung tumor (white arrow). C: Chest computed tomography on admission, demonstrating lung tumor with spiculations (white arrow) in the left lower lobe. D: Fluorodeoxyglucose positron emission tomography, showing the tumor in the left lobe with a high uptake of fluorodeoxyglucose (red area).

stable Cr(III) [2]. The valence state of the chromium atom and the nature of its ligands are determinants of its toxicity.

Inhaled chromium compounds can transfer across cell membranes in the lung. The entrance of a chromate anion into the cell through anion channels is seen in Cr(VI), which has higher absorption than Cr(III) in cells, as Cr(III) absorption is based on passive diffusion and phagocytosis, and chromium-containing particulate matter can persist in the lung for years after inhalation exposure. In the human body, Cr(VI) is unstable and is reduced to Cr(III), Cr(IV) and Cr(V) by ascorbate, glutathione and other substances. During these processes, free radical generation that can cause structural DNA damage occurs; this damage is believed to be the ultimate cause of Cr(VI) toxicity. Sustained high Cr(VI) exposure and the persistent deposition of Cr(VI)-containing particles in the bronchial bifurcations are reported to be causative of cytotoxicity of Cr(VI) [3, 4].

Most reported cases of carcinogenicity of Cr(VI) are seen in the chromate and pigment production industries, and occupational exposure to Cr(VI) in these production industries occurs due to the use of soluble calcium, zinc and strontium and lead chromate sprays [5−8]. Less soluble forms of Cr(VI) are likely to

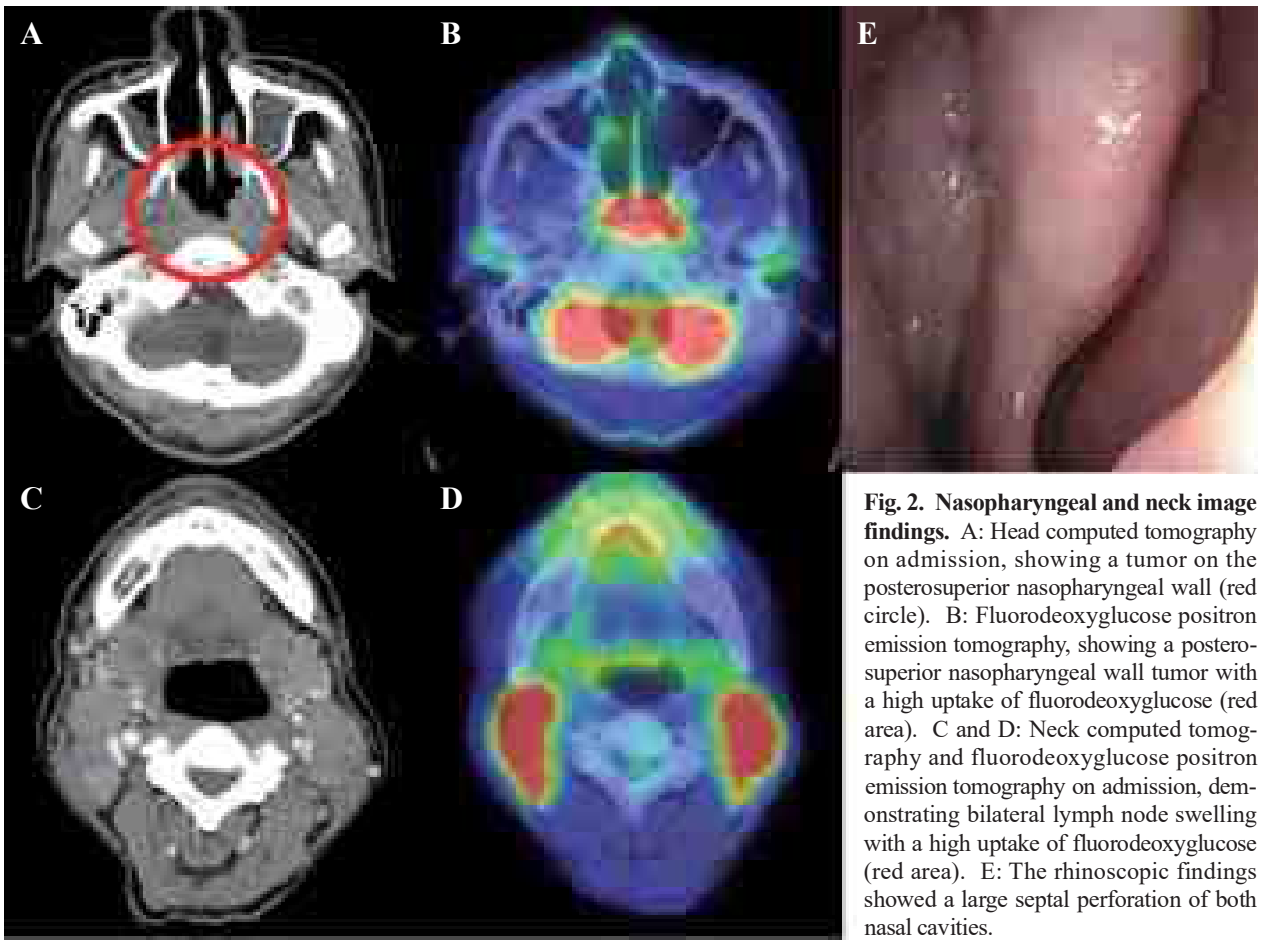

Fig. 2. Nasopharyngeal and neck image findings. A: Head computed tomography on admission, showing a tumor on the posterosuperior nasopharyngeal wall (red circle). B: Fluorodeoxyglucose positron emission tomography, showing a posterosuperior nasopharyngeal wall tumor with a high uptake of fluorodeoxyglucose (red area). C and D: Neck computed tomography and fluorodeoxyglucose positron emission tomography on admission, demonstrating bilateral lymph node swelling with a high uptake of fluorodeoxyglucose (red area). E: The rhinoscopic findings showed a large septal perforation of both nasal cavities.

have greater carcinogenic potential than more soluble forms, due to their longer biopersistence in the lung, as observed in rats [9−11]. Cr(VI) compounds can be water-soluble (sodium chromate, potassium chromate), slightly soluble or water-insoluble (barium chromate, lead chromate), and the water-solubility of zinc chromates varies widely [2]. For example, Cr(VI) oxide, chromic acid and the ammonium and alkali metal salts such as sodium and potassium of chromic acid are soluble in water. In contrast, the alkaline earth metal salts such as calcium and strontium of chromic acid are less soluble in water, and the zinc and lead salts of chromic acid are insoluble in cold water.

Carcinogenicity of chromium(VI)

Chromium(VI) compounds can damage chromosomes and DNA in humans, and Cr(VI) is also genotoxic in vivo and in vitro. The carcinogenicity of Cr(VI) compounds in mammalian cells in vitro and also in animals in vivo has been consistently observed. Based on an increase in the lung cancer incidence following occupational exposure, Cr(VI) has been classified by The International Agency for Research on Cancer (IARC) as carcinogenic in humans (Group 1) since the first evaluation in 1973, and this classification was reconfirmed in the recent IARC 2012 report [2]. The WHO Air Quality Guideline for Europe Second Edition for Cr(VI) is based on the risk assessment of lung cancer in humans, and the excess lifetime lung cancer risk is estimated to be 4×10^{-2} ($\mu g/m^3$) unit risk/lifetime (unit risk: the excess risk of dying from cancer following lifetime exposure) at an air concentration of Cr(VI) of 1 $\mu g/m^3$, indicating that 4 people in a population of 100 will die from cancer following a lifetime Cr(VI) exposure of 1 $\mu g/m^3$ of Cr(VI) [12]. Regarding the threshold of carcinogenetic risk of chromium in the United States, the thresholds for work and general environments are 50 ng/m^3 according to the

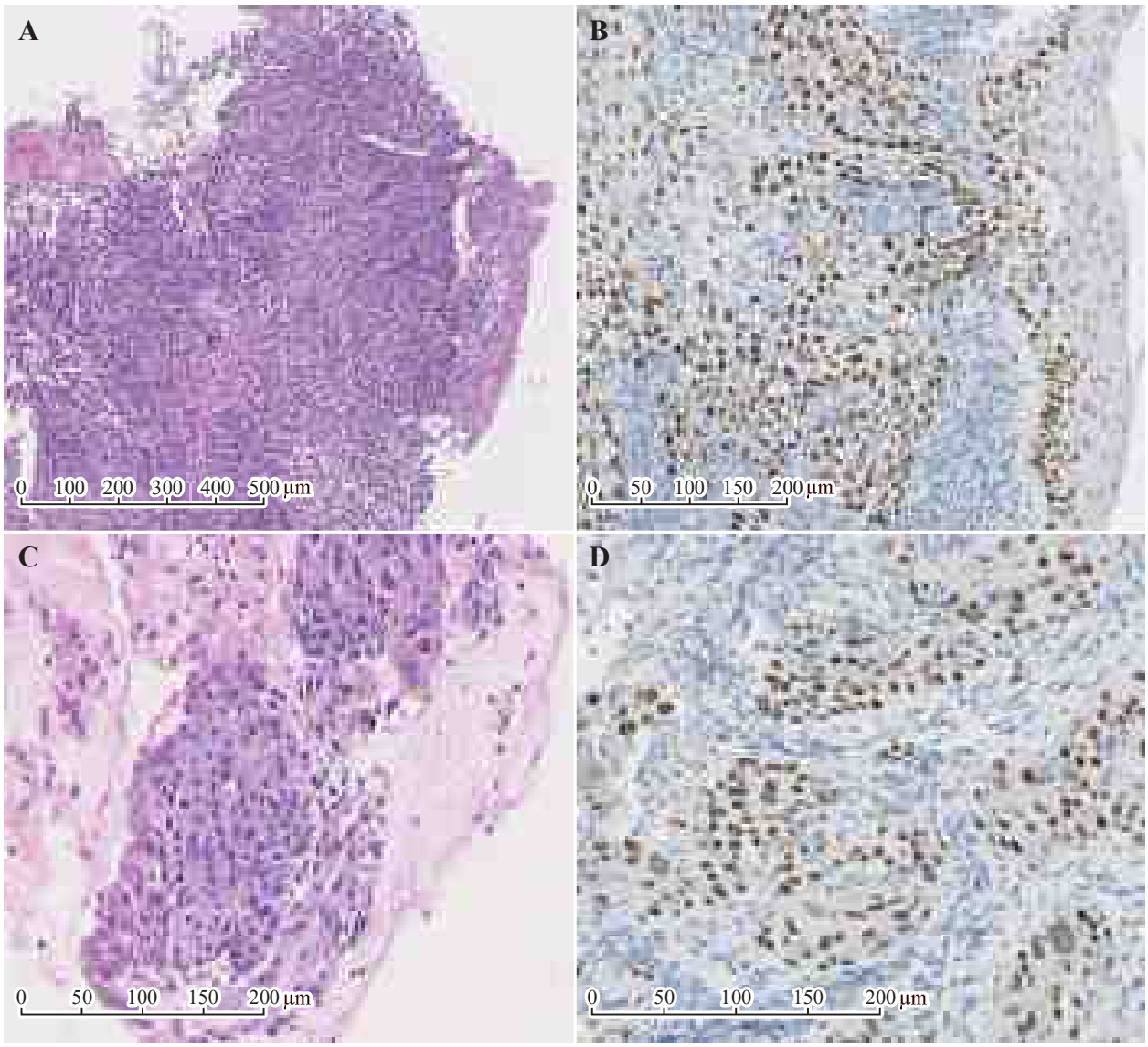

Fig. 3. Pathological findings of cancer in nasopharynx and lung. Pathological findings of the cancer of nasopharynx (A and B) and lung cancer surgically obtained from the left lower lobe (C and D). Hematoxylin eosin staining shows that both nasopharyngeal cancer (A) and lung cancer (C) are nonkeratinizing squamous cell carcinoma. Immunohistochemistry for p40 demonstrated that both cancer lesions were positive (B and D, brown).

Association Advancing Occupational and Environmental Health and 12 ng/m^3 according to the Environmental Protection Agency (EPA), respectively. In addition, the non-carcinogenic risk threshold and inhalation reference concentration of general environmental chromium for atrophy of the nasal mucosa is 5 ng/m^3 as the lowest observed adverse effect level (LOAEL) according to the Agency for Toxic Substances and Disease Registry (ATSDR) and 8 ng/m^3 according to the EPA, respectively.

Inhalation exposure to Cr(VI) may irritate and damage the upper respiratory tract (nose, throat) as well as the lower respiratory tract (lung) [13]. The IARC classifies Cr(VI) as a Group 1 compound (carcinogenic in humans) with a predisposition to lung cancer [5]. Increased risks of sinonasal cancer in workers exposed to Cr(VI) have also been reported by several epidemiological studies among workers occupationally exposed to chromate production, chromate pigment production and plating using chromate [2, 14]. Regarding other

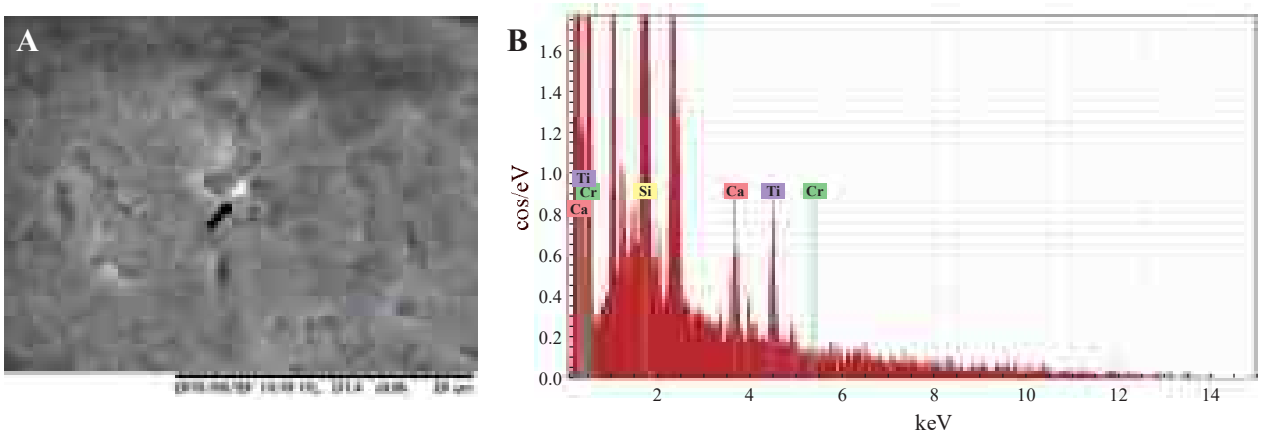

Fig. 4. The findings of scanning electron microscopy and X-ray spectrometry. A: Scanning electron micrograph of the lung cancer specimen obtained from the left lower lobe. Small metal particle was observed (arrow) and X-ray spectrometry revealed the particles to contain a chromium peak (B). Ca: calcium, Ti: titanium, Cr: chrome, Si: Silicon.

chromium compounds, Cr(III) and metallic chromium are classified as Group 3 compounds (not classifiable concerning [their] carcinogenicity in humans) according to the IARC [5].

Proctor *et al*. reported four key events in the mode of action and threshold mechanisms for lung cancer by inhalation exposure to Cr(VI) [15]. Key event 1 is the deposition and accumulation of chromium-containing particles in the bifurcations of the lung. Key event 2 is the entrance of dissolved Cr(VI) or chromate particles into cells through transporters and phagocytosis after exceeding the clearance mechanisms and detoxification by reduction at the bronchial bifurcation in the lung. Key event 3 is tissue irritation, inflammation and cytotoxicity and DNA damage by the generation of reactive oxygen species as well as binary and ternary chromium ligands inside the cell after the reduction of dissolved Cr(VI). Key event 4 is changes in the DNA sequences or methylation status caused by increased cell proliferation that may lead to tumorigenesis [15].

Environmental exposure to chromium(VI)

Although human exposure to Cr(VI) typically occurs in the general population through the inhalation of ambient air or tobacco smoke, according to the public health statement on chromium by the ATSDR, 2012, drinking chromium-laden water and eating chromium-laden vegetables can also cause cancers of the gastrointestinal tract [16, 17]. The emission of chromium into the air can occur from anthropogenic sources, such as fuel combustion and emission from metal industries, as well as natural sources, including forest fires. In the presence of large amounts of organic matter, Cr(VI) can be reduced to Cr(III) and then absorbed by airborne particulate matter. Chromium in soil is present mainly as an insoluble oxide, and compared to Cr(III), Cr(VI) may be much less strongly adsorbed into soils, and the mobility of soluble chromium in soil may depend on the absorption of the soil. The atmospheric concentrations of total chromium are < 10 ng/m^3 in rural areas and 10−30 ng/m^3 in urban areas, and concentrations more than 10 times higher can be seen near anthropogenic sources. The ambient air concentration of chromium (< 0.01−0.03 μg/m^3) has been used to estimate the average daily inhalation intake of chromium (< 0.2−0.6 μg).

Occupational exposure to chromium(VI)

Chromium(VI) compounds are usually yellow or lemon-yellow, orange or dark red in color, and these colors are related to the color of chromium used in painting [2]. Occupational exposure to airborne Cr(VI) compounds may include upper and lower respiratory tract and eye irritation, and nasal septum ulceration and perforation can also occur. Regarding the non-cancerous respiratory effects, short- and long-term occupational Cr(VI) exposure may cause pulmonary edema,

lung tissue fibrosis and hyperplasia of the bronchial epithelium, immunological sensitization and reaction in the respiratory tract and the development or exacerbation of bronchial asthma [18, 19].

Occupational exposure to Cr(VI) by the inhalation of dust, mist or fumes containing Cr(VI) can occur in the workplace in fields such as Cr(VI) production (sodium, potassium, calcium and ammonium chromates and dichromates), chrome plating (chromium trioxide), pigment production and spray painting (zinc and lead insoluble chromates) and stainless steel smelting and welding (water-soluble alkaline chromates). Cr(VI) exposure may occur in other industries as well, such as in the manufacture of dyes and pigments, surface coatings, inks, plastics, corrosion inhibitors, wood preservatives, metal finishing, leather-tannin, catalysts, chromic acid, tanning agents and pesticides as well as in printing, metal manufacturing, agricultural fields, construction, mining machinery and container manufacturing (e.g. boilers and tanks), auto repair, aluminum production, metal ore mining and coating. Welders may be the largest group of occupational exposed workers [20]. Regarding Cr(VI) exposure, the National Institute for Occupational Safety and Health (NIOSH) recommended an exposure limit of 1 $\mu g/m^3$ for a 10 h period and reported ranges of personal exposure to Cr(VI) of 3−16 $\mu g/m^3$ at electroplating facilities and 2−55 $\mu g/m^3$ at painting and coating facilities [21].

In the past, much higher exposure levels of Cr(VI) than at present (several hundred-fold higher) were observed in chromium-related industries and their workers. Recent exposure levels are generally below 20 $\mu g/m^3$. However, animal studies have shown that intermittent inhalation exposure to Cr(VI) at 1.81 mg/m^3 as chromium trioxide for 12 months induced pulmonary emphysema and perforation of nasal septum in mice, so the risk associated with exposure has not markedly decreased [22, 23].

Despite the large number of small-scale factories involved in the chromium industry, only a few investigations into chromium-induced cancer in workers at such facilities have been conducted. Prospective cohort studies in Japanese chromium platers in Tokyo including 1,193 male metal platers with a chromium plater subgroup (n = 623) and non-chromium plater subgroup (n = 567) from 1976 to 1992 showed a significant trend in the risk of lung cancer in the chrome-plating subgroup (standardized mortality ratio (SMR) 1.2; 95% confidence interval (CI) 1.0−3.0) [24]. Other reports from our institution with a follow-up study of the same cohort as well as epidemiological studies among chromium platers in other countries have shown that occupational chromium exposure in chromium-plating workplaces may be a risk factor for malignant lymphoma and brain tumor in addition to lung cancer mortality [25]. They also showed that the age at initial exposure to chromium may be a more important risk factor for lung cancer and malignant lymphoma than the duration of exposure [25]. As with the Japanese patient described above, physicians should consider occupational exposure to Cr(VI) as a potential cause of cancers in the respiratory tract, especially in workers employed at small-scale chromium-related factories.

Chromium(VI) exposure and risk of lung cancer

A report of the IARC found sufficient evidence supporting the carcinogenicity of Cr(VI) compounds in humans, concluding that Cr(VI) compounds cause lung cancer [2]. The risk of Cr(VI) compounds (potassium chromate, sodium chromate, calcium chromate, and strontium chromate) for inducing lung cancer has been shown in epidemiological studies. Studies using animals as well as in vitro studies have suggested that the tolerable concentration limit for Cr(VI) is < 1 mg/m^3 in the workplace [26]. This threshold is supported by epidemiological estimations with the best exposure information in chromate production workers (6×10^{-3}) with a first employment age of 20 years old, working 8 h/day, 5 days/week for 45 years; the estimated lifetime risk of lung cancer due to environmental exposure to 0.001 $\mu g/m^3$ of Cr(VI) for 24 h/day, 365 days/year for 70 years is 4×10^{-5}.

Among cancers in the human body, the carcinogenicity of Cr(VI) for inducing lung cancer has the strongest evidence at present, with less consistent evidence available for its role in inducing gastrointestinal (mainly stomach) [27, 28], pancreas, prostate, bladder and sinonasal cavity (nose and sinus) cancers. The relative risk for any type of cancer in 38 studies exceeded 1 [2]. The estimated relative risks for lung cancer in

almost all of the previous reports have exceeded 1 among chromate production workers, and similar trends are seen in chromate pigment production workers. Chromium electroplating workers showed particularly excessive risks in most studies. In a few cohort studies that documented smoking history data, elevated risks independent of smoking for lung cancer tended to be shown. While estimating the types and levels of Cr(VI) exposure is difficult, a meta-analysis including 47 studies of workers with possible Cr(VI) exposure showed a SMR of 1.4 (95% CI: 1.4−1.5) for lung cancer [29].

Epidemiology of chromium(VI)-induced lung cancer

There have only been two cohort studies providing quantitative estimates of lung cancer risk based on actual exposure measurements of Cr(VI) in populations working in chromate production; these studies were conducted in Baltimore (Maryland, USA) and Painesville (Ohio, USA) [6, 26, 30]. The data showed a nonlinear exposure-response [8, 30−32], but quantitative occupational risk assessments of Cr(VI) have primarily been based on a default linear approach, hampering understanding of the risk assessment. As such, Proctor *et al*. recently reported risk as a linear Cox proportional hazard model and exponential Cox proportional hazard models of lung cancer mortality by unlagged cumulative exposure to Cr(VI) in the Baltimore cohort [33].

The Baltimore chromate production facility started chromate production in 1824, and lung cancer mortality among chromate production workers has been reported [34, 35]. The study evaluated the mortality of 2,354 workers employed for the first time at a Baltimore chromate production plant between 1950 and 1974; it involved 91,186 person-years of observation, and 217 lung cancer deaths were observed. Cumulative Cr(VI) exposure was found to be significantly related to an increased risk of lung cancer death. In that study, cancer of the larynx was observed in 10 cases, compared to the expected number of 5.3, and the SMR was 1.9 (95% CI: 0.9−3.5), but cancer deaths were not significantly elevated. Gibb *et al*. recently reported the mortality of the same cohort, and cumulative Cr(VI) exposure was still a risk factor for lung cancer death. They also showed that nasal irritation, nasal perforation, nasal ulceration, and other forms of irritation such as skin symptoms due to Cr(VI) exposure were associated with lung cancer mortality [36]. However, the rates of deaths due to cancer other than lung cancer – including cancers of the nose and nasal sinuses – were not significantly elevated by cumulative Cr(VI) exposure [36].

In the extended follow-up study from the first date of employment of this cohort until 1992 [37], settled dust samples were collected and analyzed for Cr(VI) and Cr(III) following closure of the plant in 1985. The cumulative Cr(III) exposure for each individual in the study cohort was estimated using the concentration ratios of Cr(III)/Cr(VI) in the plant areas in combination with historic air-sampling data, and cumulative Cr(VI) exposure showed a strong dose-response relationship with lung cancer. The calculated cumulative Cr(VI) exposure in the plant from 1950 to 1985 was 0.1 mg/m^3·years as the mean and 0.009 mg/m^3·years (range: 0.0−5.3 mg/m^3·years) as the median. Based on the data for Cr(VI) and Cr(III) obtained from settled dust samples, the estimated cumulative Cr(III) exposure was 2 mg/m^3·years as the mean and 0.1 mg/m^3·years (range: 0.0−64.7 mg/m^3·years) as the median per individual. In this cohort, the cumulative Cr(VI) exposure was associated with an increased risk of lung cancer with a dose-response relationship, but cumulative Cr(III) exposure was not associated with lung cancer risk [37]. Using age-, calendar- and race-specific mortality rates for the USA and Maryland, the SMR for lung cancer for the entire cohort was calculated to be 180 (95% CI: 149−214), and the group with the highest chromium exposure showed an SMR of 224 (95% CI: 160−303) under exposure of 0.08−5.3 mg/m^3·years. In a proportional hazards model that included the variables of cumulative Cr(VI) exposure, cumulative Cr(III) exposure and smoking, only cumulative Cr(VI) exposure and cigarette smoking were statistically significant predictors of a risk of lung cancer[37].

Regarding the Ohio study, Luippold *et al*. [38] conducted a retrospective cohort mortality study of former employees for at least 1 year from 1940 in a chromate production plant in Painesville, Ohio, USA. The airborne Cr(VI) concentrations between 1943 and 1971 were used until the plant closed (1972), but Cr(II) concentrations were not included in their data.

In their study, the mean cumulative Cr(VI) exposure was higher for the workers who died from lung cancer (3 mg/m^3·years, standard deviation (SD): 5 mg/m^3·years, range: 0.06−23 mg/m^3·years) than for the total cohort (1.6 mg/m^3·years, SD: 2.5 mg/m^3·years, ranged: 0.003−23.0 mg/m^3·years). Based on the population of the USA and the population of Ohio, the observed/expected ratio for lung cancer was 51/21 for Ohio (SMR=241, 95% CI: 180−317). The greatest increase in lung cancer SMRs was associated with workers hired between 1940 and 1949 (SMR=326, 95% CI: 220−465), and increased SMRs (497, 95% CI: 328−723) were observed in employees working ≥20 years. In addition, the SMRs increased with time, especially among workers employed working ≥20 years since their first exposure.

In the same cohort, using relative risk and additive risk dose-response models, a linear dose-response relationship for cumulative exposure with a five-year lag was estimated [39]. Assuming 45 years of occupational exposure (8 h/day exposure on 240/365 days/year from the age of 20 to 65 years), they calculated that the estimated lifetime additional lung cancer mortality risk associated with 1 μg/m^3 Cr(VI) exposure was 0.00205 for the relative risk model and 0.00216 for the additive risk model. For environmental exposure to Cr(VI) at a concentration of 1 μg/m^3 for 24 h/day over a lifetime, the corresponding excess risks were 0.0098 (90% CI: 0.0064−0.014) and 0.013 (90% CI: 0.0083−0.018) for the relative and additive risk models, respectively[39].

A decrease in the average Cr(VI) concentrations in the air measured in the Painesville plant areas and a reduction in the lung cancer mortality was observed from 1940−1965, and the average concentrations in 1940−1949, 1950−1964 and 1965 were 720 mg/m^3, 270 mg/m^3 and 39 mg/m^3, respectively [7, 38]. In addition, in this cohort, no increase in the lung cancer risk was observed for workers with the highest monthly average exposures of 27 mg/m^3 [8]. Using the same cohort of Painesville, Proctor *et al*. recently reported an extended cohort study until 2011 with even lower values than reported in a previous study [33]. To provide quantitative lung cancer risk using exposure-response modeling with Poisson and Cox regressions, the estimated SMR was 186 (95% CI: 145−228) for workers hired before 1959 with the average length of follow-up was 34.4 years with 24,535 person-years at risk estimates and cumulative exposure 41 mg/m^3·years or highest monthly exposures 40 mg/m^3 [33]. After adjusting for smoking habit and age, the occupational and environmental unit risks were 0.0017 (95% CI: 0.00071−0.0035) and 0.0083 (95% CI: 0.0036–0.017), respectively, which are 20% and 15% lower than the respective values developed in a previous study using the same cohort [33].

Classifying automotive and painting industries as separate or same industries differs by country, so few epidemiological data are available regarding the incidence of lung cancer in automotive painters. Sabty-Daily *et al*. reported on lung cancer in these workers, and 72% of the Cr(VI) inhaled during spray painting had accumulated in the upper respiratory system, whereas 1% and 2% accumulated in the bronchus and alveoli, respectively [40]. Air concentrations of Cr(VI) as high as 118 mg/m^3 while spray painting with yellow paint have been reported [41]. Cumulative data of previous reports have described a latency period of chromium-related lung cancers of approximately 20−35 years [38, 42−45]. In a Korean epidemiological study of occupational lung cancers in workers compensated under the Industrial Accident Compensation Insurance Law between 1994 and 2011, 179 recognized cases were reported, and the major causative carcinogens were asbestos (87 cases, 49%; median latency 24 years), crystalline silica (42 cases, 24%; median latency 22 years) and Cr(VI) (26 cases, 15%; median latency 21 years). Twelve (46%) of 26 cases of chromium-related lung cancer occurred in painters, and 8 (19%) occurred in platers, mainly in shipbuilding and the manufacture of special-purpose machinery [45].

Among chrome plating workers, a positive dose-response relationship of chromium exposure for lung cancer has been observed among workers involved in chrome electroplating [6]. Among chrome platers in England employed from 1946 to 1983, exposure of soluble Cr(VI) as chromic acid (CrO_3) mist caused significant elevation of lung and bronchial cancers compared to the general population of England and Wales [46]. Limited evidence supports an increase in the rate of lung cancer among ferrochromium production workers [2, 6], and a study in Norway reported higher-than-expected rates of lung cancer among ferrochromium arc-furnace workers from 1928 to 1977 employed for at

least one year at a plant that manufactured ferrosilicon and ferrochromium [47]. However, that study did not include ambient concentration measurements of Cr(VI) in the workplace. No increases in the respiratory tumor incidence were observed in a Swedish study among ferrochromium plant workers, even among heavily exposed workers assigned to the arc-furnaces, although nasal irritation and perforation cases were reported [48].

Regarding the increased lung cancer risk among chromate production workers, there have been several reports showed an increased risk of lung cancer at levels ≥25 mg/m^3 [37, 38, 49−51]. For lung cancer, the observed/expected (O/E) ratio among the entire cohort was 1.8 (95% CI: 1.5−2.1) [37]. High cumulative exposure to Cr(VI) over a short period of time was associated with a significantly greater risk of lung cancer mortality than the same cumulative exposure spread over a longer duration, and a significant dose-rate effect was shown in a follow-up study of the Baltimore cohort [52]. Among cases with higher exposure to chromium, the SMRs of chromium for lung cancer were 365 (1.1−2.7 mg/m^3·year) and 463 (3−23 mg/m^3·year), but 60% of the 482 workers included in the mortality study had an estimated exposure 1 mg/m^3·year, and no significant increase in lung cancer risk was observed in cases exposed at these levels [38].

Chromium compounds are widely used in the production of vivid color pigments [6]. Among pigment production workers, the Cr(VI) forms of calcium, lead, zinc, barium and strontium chromate are slightly soluble or insoluble in water. Chromate pigment production workers have an increased risk of lung cancer in association with a high concentration of exposure (ATSDR, 2012). Concentrations of chromate higher than the current Occupational Safety and Health Administration (OSHA) permissible exposure limit of 5 mg/m^3, such as >2,000 mg/m^3 [6], have been reported, but data are insufficient to assess the relationship between the exposure concentration and lung cancer incidence. Exposure duration had a significant trend for increased incidence of lung cancer [53], and older pigment plants in Norway were reported to have relatively high chromium levels of 40 to 1,350 mg/m^3 from 1948 to 1972 [54], while newer plants in 1972 showed levels from 10 to 80 mg/m^3 [55].

Interestingly, despite the significant exposure to Cr(VI) among workers in stainless steel welding and aerospace industries, no marked increase in the risk of lung cancer induced by Cr(VI) has been reported [56−59]. Indeed, in contrast to the significantly increased risk of lung cancer in chrome production workers [37, 38], no marked increase in the risk of lung cancer has been noted among welders, even those with extremely high cumulative exposure (>1.5 mg/m^3·year). In a meta-analysis, the relative risk of lung cancer for mild-steel welders with minimal to no Cr(VI) exposure was the same as the relative risk for stainless steel welders with much higher Cr(VI) exposure, so the 30%−40% increased relative risk of lung cancer in welders cannot be explained by Cr(VI) exposure alone [58].

The IARC (1990) provided a summary of Cr(VI) exposure among stainless steel welders, and the concentrations ranged from 1 to 1,500 mg/m^3. Evidence concerning the association of Cr(VI) exposure and an increased risk of lung cancer incidence among aerospace workers is insufficient at present [56, 59]. Compared to exposure in chromate production and pigment production workers, the concentrations of Cr(VI) (average 15 mg/m^3) exposure were much lower among workers in aerospace industries [56, 60]. Occupational environment, exposure concentration, particle size and solubility (large particles in aerospace workers) and the forms of chromium used (zinc and strontium chromate and CrO_3) may affect the carcinogenicity of Cr(VI). Further studies are therefore necessary to clarify the difference in the carcinogenicity of Cr(VI) exposure for respiratory tract cancers among different occupational environments.

Limits of chromium(VI) exposure for lung cancer

Based on a LOAEL of 2 μg Cr(VI)/m^3 for non-cancerous upper respiratory effects in humans, a concentration limit for chromium trioxide/chromic acid of 0.005 μg Cr(VI)/m^3 was calculated. Seidler *et al.* reported results of a comprehensive literature search of studies with risk estimates for more than one level of cumulative exposure to occupational Cr(VI) with adequate consideration of smoking as a potential confounding factor and direct measurements of ambient exposure to Cr(IV) [26]. They proposed the absolute excess

risk of Cr(VI) as "acceptable" (less than 4 per 10,000 according to the German Committee on Hazardous Substances (AGS)) at a Cr(VI) concentration of 0.1 μg/m^3, and "intolerable" (more than 4 per 1,000) beyond a concentration of 1 μg/m^3, according to their review and calculations based on previous observations [26]. Several factors, such as changes in the methods for precisely determining airborne Cr(VI) concentrations in the low-dose range and insufficient statistical power to identify the shape of the dose-response relationship of Cr(VI) exposure and lung cancer risk, should be considered in attempting to understand these issues, as 0.1 μg/m^3 may be lower than the analytical limit of quantitation, even with current methods used [61]. While the estimation of exposure (1 μg/m^3) is uncertain, the available evidence leads to an estimated excess lung cancer incidence of 2.3 to 4.9 per 1,000 workers, suggesting that adequate health protection among workers in related work environments using proper measurement tools and controlling Cr(VI) levels should be considered [26].

Chromium(VI)-induced nose and nasal sinus cancer

Cancers of the nose and sinuses have been observed among workers exposed to high levels of airborne Cr(VI), such as those involved in chromate and pigment production, chromium plating and ferrochromium production [5, 6], and sufficient evidence supports positive associations between exposure to Cr(VI) compounds and cancer of the nose and nasal sinuses. However, Cr(VI)-induced cancer of the upper respiratory tract (nose and nasal sinus) is extremely rare, and most Cr(VI)-exposed cohort studies have not reported data on such cases [62]. In total, there have been 10 cohort studies reporting nasal cancers; as such, epidemiological evidence remains controversial, and the effects of Cr(VI) for inducing cancers of the nose and nasal sinuses remain inconclusive.

Estimating the risk based on cohort studies is difficult, and the SMR was calculated to be 8.0, given an aggregation of 12 observed and 1.5 expected cases [63]. Of three case-control studies on nose and nasal sinus cancer, two reported excess risk among workers with possible exposure to Cr(VI) compounds, but one noted no excess risk for Cr(VI)-exposed workers when the best exposure assessment protocol was applied [64]. A case-control study involving 207 cases and 409 controls in France noted a significant elevation in occupational risk factors for sinonasal cancer for male cabinet-makers (odds ratio [OR] 35.4, 95% CI: 18.1−69.3), male carpenters and joiners (OR 25.2, 95% CI: 14.6−43.6) and wood-working machine operators (OR 7.4, 95% CI: 3.4−15.8) in adenocarcinoma [65]. In addition, a significantly increased risk for squamous cell carcinoma (OR 9.5, 95% CI: 1.7−54.1) and a moderately increased for adenocarcinoma (OR 4.0, 95% CI: 0.7−23.5) were observed for textile workers. Binazzi *et al*. reported the outcomes of workers with nickel and chromium compounds (pooled relative risk of 18.0, 95% CI: 14.6−22.3) in their meta-analysis of 28 studies (11 cohort, 17 case-control) [66]. In the Baltimore cohort study, a recent report of Gibb *et al*. showed that mortality due to pharynx and larynx cancers was observed in 9/1,613 (5.1 expected, SMR 1.8, 95% CI: 0.8−3.3) and 10/1,613 (expected 5.3, SMR 1.9, 95% CI: 0.9−3.5), respectively, and the risks for pharynx and larynx cancer were not significantly increased [36]. In an old study from the 1940s in Painsville with very-high airborne concentration of Cr(VI) (720 μg/m^3), 92 of 100 workers had nasal septum ulceration, 65% had nasal septum perforation, 98% had nasal turbinate engorgement and 93% had hypertrophy of nasal turbinate. Nasal septum perforation was also reported in chromate pigment production workers with lung cancer [55].

Chromium(VI)-induced non-cancer disease of nose and nasal sinus

Highly acidic CrO^3 is a potent irritant and causes nasal irritation at exposures as low as 2 mg/m^3 [67], and chrome platers are reported to be at risk of ulceration and perforation of the nasal septum [68]. A close relationship between exposure to chromium and perforated nasal septum has been reported [47, 49, 68, 69]. Even with short-term exposure, the ambient concentrations of Cr(VI) are sufficient to induce the nasal irritation and ulceration observed in more than 60% of the cohort in the Baltimore study, and the median exposure to Cr(VI) at the time of symptomatic

occurrence (nasal septum perforation and bleeding, nasal irritation and ulceration) was approximately 25 mg Cr(VI)/m^3 [49]. In addition, nasal irritation, nasal perforation, nasal ulceration, and other forms of irritation (e.g. skin irritation) were associated with lung cancer mortality. A few cases of perforated nasal septum induced by Cr(VI) exposure have also been reported, with 11 of 2,869 welders afflicted in a Korean study [70]. Perforated nasal septum is less common in welders than in workers involved in chromate production, and the exposure concentration or particle size may be possible reasons explaining their differences. Exposure to chromium has also been associated with perforated nasal septum [47, 49, 68, 69], and the non-carcinogenic risk threshold for atrophy of the nasal mucosa is 5 ng/m^3 for the LOAEL according to the ATSDR, with an inhalation reference concentration of general environmental chromium of 8 ng/m^3 according to the EPA. Nasal symptoms, such as nasal irritation, septum ulceration and perforation, should be checked in workers in Cr(IV)-exposed environments and may be good symptom markers for the early detection of lung cancer [36].

In above-mentioned patient with lung cancer and cancer of the upper nasopharynx complicated with large nasal perforation, large perforation of nasal septum may alter airflow in the nasal cavity with shunting of air from the higher resistance location to that with lower resistance that may lead to reallocation of Cr(IV) distribution and influence the location of cancer of the pharynx [71].

Conclusion

Chromium(VI) exposure in the workplace remains a social and medical problem, causing lung cancer and cancers of the nose and nasal cavity, especially in small-scale facilities that use chromium compounds. Appropriate protection from Cr(VI) exposure will require more precise measurements of chromium and dose-response data for carcinogenicity in the respiratory tract. Nasal symptoms are very important for the early diagnosis of lung cancer and cancers of the nose and nasal cavity in workers with Cr(VI) exposure, and the careful collection of the occupational history should be considered in these cases in the clinical setting.

Conflict of Interest

The authors declare that they have no conflicts of interest regarding the publication of this article.

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References

1. Hurlbut CS (1971): Dana's manual of mineralogy 18th edition. Wiley, New York pp 346−347
2. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans (2012): Chromium(VI) Compounds. *In*: Arsenic, metals, fibres, and dusts. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans; 100(Pt C). International Agency for Research on Cancer (IARC), Lyon pp 147−167
3. Ishikawa Y, Nakagawa K, Satoh Y, Kitagawa T, Sugano H, Hirano T & Tsuchiya E (1994): Characteristics of chromate workers' cancers, chromium lung deposition and precancerous bronchial lesions: an autopsy study. Br J Cancer 70: 160−166
4. Nickens KP, Patierno SR & Ceryak S (2010): Chromium genotoxicity: A double-edged sword. Chem Biol Interact 188: 276−288
5. IARC working group on the Evaluation of Carcinogenic Risks to Humans (1990): Chromium, nickel and welding. IARC monogrophs on the Evaluation of Carcinogenic Risks to Humans 49. IARC, Lyon 648 pp
6. Occupational Safety and Health Administration (OSHA), Department of Labor (2006): Occupational exposure to hexavalent chromium. Final rule. Federal Register 71. OSHA, Washington, DC pp 10099−10385
7. Proctor DM, Panko JP, Liebig EW, Scott PK, Mundt KA, Buczynski MA, Barnhart RJ, Harris MA, Morgan RJ & Paustenbach DJ (2003): Workplace airborne hexavalent chromium concentrations for the Painesville, Ohio, chromate production plant (1943−1971). Appl Occup Environ Hyg 18: 430−449
8. Proctor DM, Panko JP, Liebig EW & Paustenbach DJ (2004): Estimating historical occupational exposure to airborne hexavalent chromium in a chromate production plant: 1940−1972. J Occup Environ Hyg 1: 752−767

9. Levy LS & Venitt S (1986): Carcinogenicity and mutagenicity of chromium compounds: the association between bronchial metaplasia and neoplasia. Carcinogenesis 7: 831−835
10. Levy LS, Martin PA & Bidstrup PL (1986): Investigation of the potential carcinogenicity of a range of chromium containing materials on rat lung. Br J Ind Med 43: 243−256
11. Steinhoff D, Gad SC, Hatfield GK & Mohr U (1986): Carcinogenicity study with sodium dichromate in rats. Exp Pathol 30: 129−141
12. World Health Organization (WHO) (2000): Quantitative assessment of carcinogenicity based on human data. Air quality guidelines for Europe. 2nd *ed*. WHO, Copenhagen pp 24−25
13. Agency for Toxic Substances and Disease Registry (ATSDR) (2012): Toxicological profile for chromium. ATSDR, Atlanta 592 pp
14. N Home (2016): National toxicology program. Update. https://ntp.niehs.nih.gov/update/2016/10/hexavalent-chromium/index.html
15. Proctor DM, Suh M, Campleman SL & Thompson CM (2014): Assessment of the mode of action for hexavalent chromium-induced lung cancer following inhalation exposures. Toxicology 325: 160−179
16. Peralta-Videa JR, Lopez ML, Narayan M, Saupe G & Gardea-Torresdey J (2009): The biochemistry of environmental heavy metal uptake by plants: implications for the food chain. Int J Biochem Cell Biol 41: 1665−1677
17. Welling R, Beaumont JJ, Petersen SJ, Alexeeff GV & Steinmaus C (2015): Chromium VI and stomach cancer: a meta-analysis of the current epidemiological evidence. Occup Environ Med 72: 151−159
18. Adams RJ, Wilson DH, Taylor AW, Daly A, Tursan d'Espaignet E, Dal Grande E & Ruffin RE (2006): Coexistent chronic conditions and asthma quality of life: a population-based study. Chest 129: 285−291
19. Schneider BC, Constant SL, Patierno SR, Jurjus RA & Ceryak SM (2012): Exposure to particulate hexavalent chromium exacerbates allergic asthma pathology. Toxicol Appl Pharmacol 259: 38−44
20. Peters CE, Ge CB, Hall AL, Davies HW & Demers PA (2015): CAREX Canada: an enhanced model for assessing occupational carcinogen exposure. Occup Environ Med 72: 64−71
21. Blade LM, Yencken MS, Wallace ME, Catalano JD, Khan A, Topmiller JL, Shulman SA, Martinez A, Crouch KG & Bennett JS (2007): Hexavalent chromium exposures and exposure-control technologies in American enterprise: results of a NIOSH field research study. J Occup Environ Hyg 4: 596−618
22. Adachi S (1987): Effects of chromium compounds on the respiratory system. 5. Long term inhalation of chromic acid mist in electroplating by C57BL female mice and recapitulation of our experimental studies. Sangyo Igaku 29: 17−33 (in Japanese)
23. Adachi S & Takemoto K (1987): Occupational lung cancer. A comparison between humans and experimental animals. Sangyo Igaku 29: 345−357 (in Japanese)
24. Itoh T, Takahashi K & Okubo T (1996): Mortality of chromium plating workers in Japan–a 16-year follow-up study. J UOEH 18: 7−18 (in Japanese)
25. Hara T & Takahashi K (2012): Worldwide cancer mortality among chromium platers. J UOEH 34: 309−313 (in Japanese)
26. Seidler A, Jähnichen S, Hegewald J, Fishta A, Krug O, Rüter L, Strik C, Hallier E & Straube S (2013): Systematic review and quantification of respiratory cancer risk for occupational exposure to hexavalent chromium. Int Arch Occup Environ Health 86: 943−955
27. Proctor DM, Otani JM, Finley BL, Paustenbach DJ, Bland JA, Speizer N & Sargent EV (2002): Is hexavalent chromium carcinogenic via ingestion? A weight-of-evidence review. J Toxicol Environ Health A 65: 701−746
28. Beaumont JJ, Sedman RM, Reynolds SD, Sherman CD, Li LH, Howd RA, Sandy MS, Zeise L & Alexeeff GV (2008): Cancer mortality in a Chinese population exposed to hexavalent chromium in drinking water. Epidemiology 19: 12−23
29. Cole P & Rodu B (2005): Epidemiologic studies of chrome and cancer mortality: a series of meta-analyses. Regul Toxicol Pharmacol 43: 225−231
30. Haney JT Jr, Erraguntla N, Sielken RL Jr & Valdez-Flores C (2014): Development of an inhalation unit risk factor for hexavalent chromium. Regul Toxicol Pharmacol 68: 201−211
31. Haney JT Jr, Erraguntla N, Sielken RL Jr & Valdez-Flores C (2012): Development of a cancer-based chronic inhalation reference value for hexavalent chromium based on a nonlinear-threshold carcinogenic assessment.

Regul Toxicol Pharmacol 64: 466–480
32. Park RM & Stayner LT (2006): A search for thresholds and other nonlinearities in the relationship between hexavalent chromium and lung cancer. Risk Anal 26: 79–88
33. Proctor DM, Suh M, Mittal L, Hirsch S, Valdes Salgado R, Bartlett C, Van Landingham C, Rohr A & Crump K (2016): Inhalation cancer risk assessment of hexavalent chromium based on updated mortality for Painesville chromate production workers. J Expo Sci Environ Epidemiol 26: 224–231
34. Hayes RB, Lilienfeld AM & Snell LM (1979): Mortality in chromium chemical production workers: a prospective study. Int J Epidemiol 8: 365–374
35. Braver ER, Infante P & Chu K (1985): An analysis of lung cancer risk from exposure to hexavalent chromium. Teratog Carcinog Mutagen 5: 365–378
36. Gibb HJ, Lees PS, Wang J & Grace O'Leary K (2015): Extended followup of a cohort of chromium production workers. Am J Ind Med 58: 905–913
37. Gibb HJ, Lees PS, Pinsky PF & Rooney BC (2000): Lung cancer among workers in chromium chemical production. Am J Ind Med 38: 115–126
38. Luippold RS, Mundt KA, Austin RP, Liebig E, Panko J, Crump C, Crump K & Proctor D (2003): Lung cancer mortality among chromate production workers. Occup Environ Med 60: 451–457
39. Crump C, Crump K, Hack E, Luippold R, Mundt K, Liebig E, Panko J, Paustenbach D & Proctor D (2003): Dose-response and risk assessment of airborne hexavalent chromium and lung cancer mortality. Risk Anal 23: 1147–1163
40. Sabty-Daily RA, Harris PA, Hinds WC & Froines JR (2005): Size distribution and speciation of chromium in paint spray aerosol at an aerospace facility. Ann Occup Hyg 49: 47–59
41. Kim B, Yoon JH, Choi BS & Shin YC (2013): Exposure assessment suggests exposure to lung cancer carcinogens in a painter working in an automobile bumper shop. Saf Health Work 4: 216–220
42. Korallus U, Ulm K & Steinmann-Steiner-Haldenstaett W (1993): Bronchial carcinoma mortality in the German chromate-producing industry: the effects of process modification. Int Arch Occup Environ Health 65: 171–178
43. Rosenman KD & Stanbury M (1996): Risk of lung cancer among former chromium smelter workers. Am J Ind Med 29: 491–500
44. Langård S (1990): One hundred years of chromium and cancer: a review of epidemiological evidence and selected case reports. Am J Ind Med 17: 189–215
45. Ahn YS & Jeong KS (2014): Epidemiologic characteristics of compensated occupational lung cancers among Korean workers. J Korean Med Sci 29: 1473–1481
46. Sorahan T, Burges DC & Waterhouse JA (1987): A mortality study of nickel/chromium platers. Br J Ind Med 44: 250–258
47. Langård S, Andersen A & Gylseth B (1980): Incidence of cancer among ferrochromium and ferrosilicon workers. Br J Ind Med 37: 114–120
48. Axelsson G, Rylander R & Schmidt A (1980): Mortality and incidence of tumours among ferrochromium workers. Br J Ind Med 37: 121–127
49. Gibb HJ, Lees PS, Pinsky PF & Rooney BC (2000): Clinical findings of irritation among chromium chemical production workers. Am J Ind Med 38: 127–131
50. Grevatt PC (1998): 4. Hazard identification. Toxicological review of hexavalent chromium. support of summary information on the integrated risk information system (IRIS). US Environmental Protection Agency, Washington DC, US pp7–43
51. US Department of Health and Human Services (1991): 3.2.1.17 Cancer. Toxicological profile for chromium. Public Health Services Agency for Toxic substances and Diseases Registry, Washington, DC pp 102–112
52. Gibb H, Hoffman HJ & Haver C (2011): Biologic implications from an epidemiologic study of chromate production workers. Open Epidemiol J 4: 54–59
53. Hayes RB, Sheffet A & Spirtas R (1989): Cancer mortality among a cohort of chromium pigment workers. Am J Ind Med 16: 127–133
54. Langård S & Norseth T (1975): A cohort study of bronchial carcinomas in workers producing chromate pigments. Br J Ind Med 32: 62–65
55. Langård S & Vigander T (1983): Occurrence of lung cancer in workers producing chromium pigments. Br J Ind Med 40: 71–74
56. Boice JD Jr, Marano DE, Fryzek JP, Sadler CJ & McLaughlin JK (1999): Mortality among aircraft manufacturing workers. Occup Environ Med 56: 581–597
57. Gérin M, Fletcher AC, Gray C, Winkelmann R, Boffetta P & Simonato L (1993): Development and use of a welding process exposure matrix in a historical pro-

spective study of lung cancer risk in European welders. Int J Epidemiol 22 (Supple 2): S22−S28
58. Moulin JJ (1997): A meta-analysis of epidemiologic studies of lung cancer in welders. Scand J Work Environ Health 23: 104−113
59. Alexander BH, Checkoway H, Wechsler L, Heyer NJ, Muhm JM & O'Keeffe TP (1996): Lung cancer in chromate-exposed aerospace workers. J Occup Environ Med 38: 1253−1258
60. Marano DE, Boice JD Jr, Fryzek JP, Morrison JA, Sadler CJ & McLaughlin JK (2000): Exposure assessment for a large epidemiological study of aircraft manufacturing workers. Appl Occup Environ Hyg 15: 644−656
61. Seidler A, Jähnichen S, Hegewald J, Fishta A, Krug O, Rüter L, Strik C, Hallier E & Straube S (2013): Systematic review and quantification of respiratory cancer risk for occupational exposure to hexavalent chromium. Int Arch Occup Environ Health 86: 957−960
62. International Agency for Research on Cancer (IARC) (2007): Cancer incidence in five continents. Volume IX. (Curado MP, Edwords B, Shin HR, Storm H, Ferlay J, Heanue M & Boyle P, *eds*): IARC Press, Lyon 961 pp
63. Enterline PE (1974): Respiratory cancer among chromate workers. J Occup Med 16: 523−526
64. Luce D, Gérin M, Leclerc A, Morcet JF, Brugere J & Goldberg M (1993): Sinonasal cancer and occupational exposure to formaldehyde and other substances. Int J Cancer 53: 224−231
65. Luce D, Leclerc A, Morcet JF, Casal-Lareo A, Gérin M, Brugère J, Haguenoer JM & Goldberg M (1992): Occupational risk factors for sinonasal cancer: a case-control study in France. Am J Ind Med 21: 163−175
66. Binazzi A, Ferrante P & Marinaccio A (2015): Occupational exposure and sinonasal cancer: a systematic review and meta-analysis. BMC Cancer 15: 49
67. Lindberg E & Hedenstierna G (1983): Chrome plating: symptoms, findings in the upper airways, and effects on lung function. Arch Environ Health 38: 367−374
68. The National Institute for Occupational Safety and Health (NIOSH) (1988): III. Characteristics of welding processes. criteria for a recommended standard. Occupational exposure to chromium(VI). DHHS (NIOSH) 76−129. NIOSH, Washington DC pp 22−38
69. Miller JB (1953): Effect of chromates on nose, throat, and ear. AMA Arch Otolaryngol 58: 172−178
70. Lee CR, Yoo CI, Lee J & Kang SK (2002): Nasal septum perforation of welders. Ind Health 40: 286−289
71. Cannon DE, Frank DO, Kimbell JS, Poetker DM & Rhee JS (2013): Modeling nasal physiology changes due to septal perforations. Otolaryngol Head Neck Surg 148: 513−518

呼吸器系における六価クロムの発癌リスク

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要　　旨：六価クロム化合物は，呼吸器系における発癌物質として認識され，特に特定の職業環境下では肺や鼻，鼻腔の癌を引き起こす．クロム（Ⅵ）含有粒子や塵および煙の吸入曝露は，クロム生成，メッキ，クロム含有金属や合金の溶接，電気メッキ，クロム含有顔料や塗料などのクロム関連職業環境において，一般的に生じる．クロム化合物に関する疫学調査では，クロム（Ⅵ）曝露と肺癌による死亡率との間に強い関連があり，また，鼻や鼻腔の癌との間にも関連があることが示されている．鼻の炎症や潰瘍および鼻中隔の穿孔，鼻甲介の鬱血や肥大などの鼻症状は，クロム（Ⅵ）曝露の職歴を有する人において，肺癌や鼻・鼻腔癌の早期診断にとって重要な兆候である．職場におけるクロム（Ⅵ）の曝露は，特にクロム化合物を扱う比較的小規模の企業において肺癌や鼻・鼻腔癌の原因として深刻な問題となる．それゆえ，労働者の適切な保護はクロム化合物への曝露を伴う職業においては考慮されるべきである．

キーワード：六価クロム，癌，吸入曝露，呼吸器系．

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