

Role of chemical species and exposure characteristics in cancer among persons occupationally exposed to chromium compounds

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LANGÅRD S. Role of chemical species and exposure characteristics in cancer among persons occupationally exposed to chromium compounds. *Scand J Work Environ Health* 1993;19 suppl 1:81-9. Epidemiologic studies on chromate workers are considered with special reference to the valency of chromium compounds, carcinogenic potency, and water solubility. It is assumed that all hexavalent chromium compounds are carcinogenic to humans when inhaled but that there is no evidence that trivalent compounds are carcinogenic. It is suggested that zinc chromate is a highly potent carcinogen and also that calcium chromate may be carcinogenic. There are indications that chromates of low water solubility may be less potent carcinogens than compounds of greater solubility. Evidence is also presented for possible interactions with smoking and other factors involved in work-related cancers.

Key terms: calcium chromate, carcinogenic potency, chromium trioxide, lead chromate, interaction, lung cancer, prevention, valency state, zinc chromate.

Chromium (Cr) compounds are among the few established causes of work- or environment-related cancer that have been known for more than 100 years (1, 2).

Chromium occurs in the bivalent (chromous), trivalent [chromic = Cr(III)], hexavalent [chromate = Cr(VI)], or unstable tetra- and pentavalent states. Only exposure to compounds of Cr(III) and Cr(VI) appears to be of concern for human cancers (3), with the possible exception of the reduction of Cr(VI) to Cr(III) in biological material (3). The Cr(III) compounds are generally considered insoluble in water. Some Cr(VI) compounds (eg, Cr(VI) oxide) are very soluble in water, while calcium chromate and lead chromate are poorly soluble and zinc chromate is slightly more soluble.

Many workers are potentially exposed to chromium, and the use of its compounds is the most frequent source of exposure. Currently, the welding of stainless steel is a common source of occupational exposure; there are millions of stainless steel welders worldwide (4).

There is evidence that only Cr(III) compounds are capable of binding to deoxyribonucleic acid (DNA) and thus have the potential to cause DNA cross-links (3, 5-7). However, unlike Cr(VI) compounds, Cr(III) compounds are poorly absorbed in the human respiratory tract (5). Before becoming capable of

causing DNA damage therefore, Cr(VI) must be reduced to Cr(III) in human tissues (3, 5-7).

In this paper, the literature on epidemiologic studies on chromium-exposed cohorts and the evidence for carcinogenicity in humans have been reviewed. Case reports are included only when considered to be of significance for the elucidation of the carcinogenic potency of chromium compounds. One such significant case report is that by Lehmann (8) in 1932.

The study by Machle & Gregorius (9) was the first epidemiologic investigation to demonstrate elevated lung cancer mortality among chromium-exposed workers. Several epidemiologic studies have subsequently shown an association between Cr(VI) exposure and lung cancer; some of these investigations are considered in this review. Some studies have also indicated an elevated risk of cancer of the nasal sinuses and alimentary tract (1, 10).

Risk level

Table 1 presents a summary of the level of lung cancer risk found among Cr(VI)-exposed workers. Gafaer (11), in a study based on data on claims for compensation submitted to seven chromium manufacturing plants in the United States, showed a very high risk of lung cancer. The study population comprised active male workers employed between 1940 and 1950 who were members of sickness-benefit associations. Ten deaths from lung cancer occurred among white workers (expected 0.7, RR 14.3), and 16 (expected 0.2, RR 80.0) among black workers (2, 10). The latter is the highest relative risk (RR) ever observed for Cr(VI)-exposed workers.

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Table 1. Lung cancer risk among workers exposed to hexavalent chromium. (US = United States)

Study	Study population	Reference population	Cancer of respiratory system				Exposure
			Site	Number of cases	Relative risk	Estimated absolute risk	
Gafafer, 1953 (11)	Seven US chromate factories; active workers 1940–1948 included; 5522 person-years	US males White Black	Lung	10 16	14.3 80.0	—	—
Langård & Vigander, 1983 (13)	Chromium pigment manufacture since 1948; 133 workers in the cohort	Incidence of cancer in Norway 1953–1980	Lung	6	44	$150 \cdot 10^{-4}$	Hexavalent chromium level about $0.5 \text{ mg} \cdot \text{m}^{-3}$ in 1973
Sjögren et al, 1987 (16)	Stainless steel welders; 234 subjects	Incidence of cancer in Sweden	Lung	5	2	—	—
Simonato et al, 1991 (17)	Welders; multi-national study comprising 11 092 mild steel and stainless steel welders	Mortality rates in each participating country	Lung	116	1.3	—	—

No cohort studies among workers exposed to chromium pigments were carried out before 1975. For members of a small Norwegian cohort of workers (12), zinc chromate was the main exposure. Three lung cancer cases (expected 0.08) occurred between 1951 and 1972 in a subgroup ($N = 24$) with three years or more of employment before December 1972. Measurements indicated that exposure levels to Cr(VI) had been up to $1.0\text{--}1.5 \text{ mg} \cdot \text{m}^{-3}$ during the six to eight years of employment of the subjects. Follow-up to 1980 (13) showed six (expected 0.135) cases of lung cancer (absolute risk $1.5 \cdot 10^{-2}$) in the same subgroup. Only one case had occurred among the 109 workers employed at the plant before 1972 for three years or less. No study among Cr(VI)-exposed workers has shown a higher absolute risk of lung cancer.

In a study from Japan on 276 chromate-producing workers employed in 1947 or later and observed from January 1960 through December 1982, Watanabe & Fukuchi (14) found 25 (expected 1.36) lung cancer deaths (RR 18.3). No data were presented on exposure levels.

The absolute risk of lung cancer experienced by workers in old study cohorts (11) was probably lower than in the study of chromium pigment exposure (12, 13). Although the absolute risk was relatively low, due to low reference risks in the 1940s and 1950s as compared with the 1970s, relative risks as high as 80 (11) (table 1) may reflect the most significant cancer hazard observed for Cr(VI) workers.

The presentation of absolute cancer risks in epidemiologic studies permits a direct comparison of results from one study to another, but such a comparison is not possible if relative risks only are used. For many cohort studies on chromium and cancer the

absolute cancer risks cannot be calculated. Among the studies for which it is possible, a small study on zinc chromate workers (13) gives the highest risk, namely, 1.5 cases per 100 observation years.

Among the groups of chromium-exposed workers, stainless steel welders appear to be at the low end of the range of cancer risks. Only a few studies have been conducted on "pure" stainless steel welders. They include the study by Sjögren (15), who identified a group of 234 welders who had welded stainless steel for five years or more between 1950 and 1965. The smoking habits of these welders were similar to those of the general male population, which was used as reference. Three pulmonary tumors were found (expected 0.8). Potential attenuation of the results was avoided by the exclusion of low-risk subjects. The same group was followed, and a slightly reduced incidence was found, namely, five cases (expected 2.5) (16).

The International Agency for Research on Cancer (IARC) has carried out a multinational study on a population comprising 11 092 mild steel and stainless steel welders from nine European countries (17). There were 116 lung cancer deaths (expected 86.8). By the year of first employment, the standardized mortality ratio for lung cancer among the stainless steel welders was 157, a value indicating that stainless steel welders are more likely to die from lung cancer than welders as a whole.

Significance of the valency state of chromium

The significance of the valency of chromium for carcinogenicity in humans has been a subject of debate

for 60 years (8). The results presented by Baetjer (18) in 1950, the statement by Hueper (19) that Cr(III) compounds were carcinogenic in humans, and the study by Mancuso (20) in 1975 are milestones in the understanding of the causes of chromium-related cancer (2, 10) (table 2). According to this study (20), Cr(III) compounds are as potent as carcinogens to humans as Cr(VI) compounds are.

Mancuso (20) reported on the mortality experience of a group recruited from a Cr(VI) manufacturing plant. He used industrial hygiene data from 1949 as a basis for estimating the assumed exposure to total, insoluble, and water-soluble chromium. The study comprised 41 lung cancer deaths between 1931 and 1974. The standardized mortality ratios for a sub-cohort recruited in 1931–1937 were calculated for “dose”-related strata. High ratios were found for lung cancer in workers with 27–36 years since first employment. The ratio for lung cancer increased from 144.6 to 649.6 with increasing exposure, which ranged from 0.25–0.49 to $>4.0 \text{ mg} \cdot \text{m}^{-3}$ and from 80.2 to 998.7 at air levels ranging from <0.25 to $>2.0 \text{ mg} \cdot \text{m}^{-3}$ for insoluble Cr(III) and soluble Cr(VI), respectively. The corresponding standardized mortality ratio increased from 225.7 in the 0.50–0.99 $\text{mg} \cdot \text{m}^{-3}$ exposure group for total chromium to 741.5 in the $>6.0 \text{ mg} \cdot \text{m}^{-3}$ group. For a given exposure to what was assumed to be insoluble chromium,

an increase in exposure to total chromium was associated with an increased standardized mortality ratio in four of the five exposure categories. For total chromium, increasing exposure to insoluble chromium resulted in a decreased standardized mortality ratio from lung cancer in three of the five categories. The author concluded that the “carcinogenic potential extends to all forms of chromium [p 255].” However, the possible relationship between a given exposure to total chromium and increased exposure to soluble chromium was not analyzed, and therefore the author’s conclusion may not have been fully warranted.

Ferrochromium (FeCr) manufacturing involves the melting of chromite ore and might be thought not to involve exposure to Cr(VI) compounds. For this reason, a study was designed to scrutinize the possibility that exposure to chromium compounds other than those of Cr(VI) could result in cancer in exposed workers (21). Among 976 men qualifying for participation, seven (expected 3.1) (absolute risk $9.2 \cdot 10^{-4}$) of the nine observed (expected 9.45) lung cancer cases occurred in the FeCr subgroup. Industrial hygiene monitoring in the plant in 1975 showed, however, that there was Cr(VI) in the workplace air [0.01 – $0.29 \text{ mg} \cdot \text{m}^{-3}$ total chromium, 11–33% water-soluble Cr(VI)]. The study could therefore not answer the question addressed. It was concluded that,

Table 2. Epidemiologic studies on the significance of the valency state of chromium. (US = United States)

Study	Study population	Reference population	Cancer of respiratory system				Exposure
			Site	Number of cases	Relative risk	Estimated absolute risk	
Mancuso, 1975 (20)	US chromate workers employed for one or more years 1931–1937	No separate reference group	Lung	41	Crude rate $37 \cdot 10^{-4}$	<15 years observation; $9.7 \cdot 10^{-4}$ to a high of $55 \cdot 10^{-4}$	—
Langård et al, 1990 (22)	Ferrochromium and ferrosilicon workers; 1235 subjects employed 1928–1965	(A) general population; (B) local reference	Lung (ferrochromium workers)	10	A 1.5 B 2.6	$9.5 \cdot 10^{-4}$	Trivalent and hexavalent chromium
Axelsson et al, 1980 (23)	Swedish ferroalloy workers; 1876 workers employed for one or more years 1930–1975	Classification of work areas by trivalent and hexavalent chromium; comparison with county or national statistics	Mortality, all workers	5	<1	—	Trivalent chromium higher than hexavalent chromium; 0 – $2.5 \text{ mg} \cdot \text{m}^{-3}$ and 0 – $0.5 \text{ mg} \cdot \text{m}^{-3}$, respectively
			Maintenance workers	4	4.0	—	
Korallus et al, 1974 (24, 25)	German chromate workers; 1140 male workers employed for more than one year between 1934 and 1975 in two production plants	Local mortality rates in North Rhine-Westphalia	Lung	51	1.9	$15.4 \cdot 10^{-4}$	Exposure not given

although there was evidence for an elevated lung cancer risk among FeCr workers, concomitant exposure to Cr(VI) made it impossible to determine whether chromium compounds other than those of Cr(VI) were human carcinogens.

An additional eight years of follow-up (1978–1985) was added to this study group (22). Although the relative risk was reduced, the lung cancer incidence was still high in the FeCr subgroup, namely, 10 cases (expected 5.7).

A parallel study carried out in a comparable cohort in Sweden (23) found no excess lung cancer; five (expected 7.2) bronchogenic cancers were observed. Exposure to Cr(III), ranging from 0.0 to $2.5 \text{ mg} \cdot \text{m}^{-3}$, had been higher than to Cr(VI) (0.0 – $0.25 \text{ mg} \cdot \text{m}^{-3}$). Maintenance workers formed the only subgroup with excess bronchogenic cancer, namely, four cases (expected 1.0), of which two were mesotheliomas.

Korallus et al (24, 25) carried out a study on workers in two Cr(III) oxide and Cr(III) sulfate manufacturing plants. The workers were exposed mainly to Cr(III) compounds. However, workers at the chromium sulfate manufacturing plant were also engaged in Cr(III) oxide production, possibly resulting in exposure to dichromates. Three deaths from lung cancer had occurred, indicating that Cr(III) did not cause cancer in the workers. Among 17 lung cancer cases reported by Zober (26), 11 had worked in alkali-chromate production, and three were said to be exposed to Cr(III) only. However, no proof of the absence of Cr(VI) exposure was provided.

Significance of the solubility of chromium compounds

Alderson et al (27) presented data from a study on a cohort comprising 2715 workers with more than one year of work between 1948 and 1977 at one of three chromate manufacturing plants. The same group had previously been studied by Bidstrup & Case (28). The “low-lime” process was introduced in one of the plants (which closed in 1967) in 1957–1959. One of the plants, still in operation in 1981, was modified in 1957–1961 by the introduction of the “nonlime” process. The “high-lime” process was used in the third plant until closure in 1966. There were 116 lung cancer deaths (expected 48.0), of which 75 (expected 26.3) were in a subgroup at one plant (2, 10).

There is therefore some evidence that the high-lime process might pose a greater hazard to workers than the low-lime one (18, 27, 29). In the former, Cr(III) oxide is converted to sodium chromate, and poorly soluble calcium chromate may be formed and discharged into the air. The evidence from these studies, however, is insufficient to prove that calcium chromate alone was responsible for the cancer hazard in the study groups.

A case report by Ohsaki et al (30) indicated that exposure to sodium and potassium chromates, which have a relatively high solubility in water, may result in cancer. Zober's results (26) indicated that work in the high-lime process could be a prime factor in the causation of the cases that he observed. Nishiyama et al (31) also indicated that both sodium and potassium chromate could be the causative agents in four of the 11 reported cases.

Davis (32) followed a group of chromium pigment workers at three plants in the United Kingdom from the 1930s or 1940s through December 1981. Among workers in one of the plants, most probably exposed only to lead chromate (poorly soluble), seven deaths (expected 6.45) by lung cancer had occurred. In a subgroup of 33 highly exposed workers, three lung cancer deaths (expected 0.84) were found. Among workers highly or moderately exposed to lead chromate and followed for less than 30 years, the relative risk for lung cancer varied from unity to 5.5, the latter applying to 31 highly exposed workers first employed between 1932 and 1945.

Davies (33) also identified a group of 57 lead chromate workers who had been poisoned by lead between 1930 and 1945. She followed the group from the time of poisoning up to 1981 and found four deaths (expected 2.8) from bronchogenic carcinoma.

In a New Jersey cohort of 1296 white and 650 nonwhite men employed for more than one month between 1940 and 1969 in the production of lead and zinc chromates, Sheffet et al (34) found 16 lung cancer deaths among white men (relative risk 1.6) and seven (relative risk 1.6) among nonwhite men. It was claimed that there had been nine times more lead than zinc chromate in the workplace air. Among the white subjects with more than 10 years of work, the relative risk was 1.7 as compared with 2.6 among the nonwhite men. The same recruitment cohort was followed from 1940 to 1982 (35). Chromium in the workplace air was monitored, and the total chromium concentration was $0.5 \text{ mg} \cdot \text{m}^{-3}$ for exposed jobs and more than $2 \text{ mg} \cdot \text{m}^{-3}$ for highly exposed jobs. Of 41 lung cancer deaths (expected 35.3), 24 had occurred among workers in Cr(VI)-exposed jobs. The absolute risk for lung cancer deaths in the whole cohort was $8.1 \cdot 10^{-4}$.

An association between chromium exposure in chromium electroplating and lung cancer has been indicated in case reports (25, 26, 36–40). The very young age of some of the subjects may support causation by the exposure of concern.

The results from some cohort studies among chromium platers provide firm evidence of the carcinogenic action of Cr(VI) oxide fumes. Royle (41) studied 1056 male and 182 female chromium platers with three months or more of employment in one of 54 small plants in the United Kingdom. He found a significant excess of deaths from lung cancer, namely, 24 observed as compared with 13 expected.

Three (expected 0.7) lung cancer deaths were reported by Franchini et al (42) among 178 Italian chromium platers, of whom 62 were "bright" (thin plating) and 116 were "hard" (thick) platers. If allowance is made for a latency period of 10 years, three deaths from lung cancer (expected 0.6) were observed among the hard platers. In 1980, the air level of Cr(VI) in the hard-plating process averaged $7 \mu\text{g} \cdot \text{m}^{-3}$, but it was assumed that the level had been higher during previous years.

The results presented by Sorahan et al (43), who found 63 lung cancer deaths (expected 40) among men in a study among mainly thin-plating workers over the period 1946–1983, indicate a relationship between work at the chromium-plating baths and elevated lung cancer risk. A few air-level samples had been taken before 1973, giving Cr(VI) oxide levels of up to $8.0 \text{ mg} \cdot \text{m}^{-3}$, $1.6 \text{ mg} \cdot \text{m}^{-3}$, and $0.4 \text{ mg} \cdot \text{m}^{-3}$. After 1973, the air levels were mostly

below $50 \mu\text{g} \cdot \text{m}^{-3}$. Exposure to nickel chloride and sulfate had also taken place.

In all, several studies have provided evidence of a relationship between exposure to fumes from the relatively highly water-soluble Cr(VI) oxide and cancer of the respiratory system. Table 3 presents a summary of the studies concerning the significance of the water solubility of Cr(VI) compounds.

Cancer at other sites

After having observed five cases of cancer in the alimentary system among 44 deceased chromate workers, Teleky (44) suggested that there could be a connection between exposure to chromates and the occurrence of such cancers. With the aid of data reported in 1966 by Taylor (46), whose analysis covered the period 1941–1960, Enterline (45) reanalyzed

Table 3. Epidemiologic studies concerning the significance of the water solubility of the hexavalent chromium compounds. (UK = United Kingdom, US = United States)

Study	Study population	Reference population	Cancer of respiratory system				Exposure
			Site	Number of cases	Estimated relative risk	Estimated absolute risk	
Davies, 1984 (32, 33)	Three UK chromium pigment factories; the population followed to 1981	Mortality rates in the UK	Lung	—	—	—	In factory A and B zinc and lead chromate; in plant C only lead chromate
			A (1932–45) 158 workers	14	1.7	$35.2 \cdot 10^{-4}$	
			B (1946–54) 103 workers	9	2.2	$36.3 \cdot 10^{-4}$	
			C (1948–67) 118 workers	11	4.4	$49.8 \cdot 10^{-4}$	
Hayes et al, 1989 (35)	US zinc and lead chromate workers followed to the end of 1982; 1737 subjects	Expected deaths based on US white and non-white death rates	Lung cancer	24	1.4	—	Exposure estimated at $0.5 \text{ mg} \cdot \text{m}^{-3}$ for exposed; $2 \text{ mg} \cdot \text{m}^{-3}$ for highly exposed
			30-year latency and < 1 year exposure	3	1.4	—	
			1–9 years exposure	3	2.0	—	
			≥ 10 years exposure	6	3.2	—	
Royle, 1975 (41)	UK chromium-plating plants; 1056 male platers; 1099 male referents	Unexposed workers		24	1.8	—	Current exposure to less than $0.1 \text{ mg} \cdot \text{m}^{-3}$ chromium trioxide; also nickel exposure
Franchini et al, 1983 (42)	"Thick" and "thin" Italian platers; N = 178, of whom 116 were thick platers employed between 1951 and 1981	Italian national rates	Lung	3	4.3	$18.2 \cdot 10^{-4}$	Chromium trioxide, mean $7 \text{ mg} \cdot \text{m}^{-3}$ in 1980
Sorahan et al, 1987 (43)	UK chromium platers (2689) employed between 1946 and 1975; observed from 1946 to 1983	England and Wales	Lung, men	63	1.6	—	A few high air concentrations measured before 1973; later generally below $50 \mu\text{g} \cdot \text{m}^{-3}$
			Lung, women	6	1.2	—	

data on workers employed between 1937 and 1940 in three Cr(VI) production plants of the United States. In addition to excess deaths from lung cancer, he found an excess of 16 deaths (expected 10.4) from cancer of the alimentary system.

Among male chromium platers, Royle (41) found cancer of the alimentary system to be in excess; eight deaths were found versus four among the referents, four men having died of stomach cancer (expected 1.85). There were also 25 stomach cancer deaths (expected 16.2) among male British chromium electroplaters in the study conducted by Sorahan et al (43).

Two cases of laryngeal cancer (expected 0.6) were reported by Silverstein et al (47) in a study of workers in a die-casting and electroplating plant in the United States. Two deaths from nasal cancer (expected 0.15) were observed in a subcohort in the study by Alderson et al (27), but none were found in the other subcohorts.

Five of a total of nine kidney cancers occurred in a FeCr group (standardized incidence ratio 273) in a Norwegian study (22). However, the mean latency period was only two years longer than that for all kidney cancers in the study group, indicating that exposure to chromium was unlikely to explain the excess.

Carcinogenic potency

Gross & Kölsch (48) reported eight deaths from lung cancer among workers at three chromium pigment manufacturing plants in Germany. Five of these deaths occurred among workers producing zinc chromate, the other three were found among workers in plants producing chromates of both zinc and lead. Four of the deceased were only 33–37 years of age. The authors suggested that zinc chromate was the prime causative agent and should be considered to be a potent carcinogen. Letterer et al (49) reported two subjects (36 and 48 years of age) with lung cancer after 7 and 20 years of work in a chromium pigment plant. The youngest had been exposed to zinc chromate only.

In a study in the United Kingdom (32), excess deaths from lung cancer were found mainly among workers in plants where workers had been exposed to both zinc and lead chromates. The excess was not significant among those in plants reported to produce lead chromate only. The author concluded that exposure to zinc chromate was the probable cause of lung cancer among the workers exposed in both processes. She also suggested that the results indicated that lead chromate might be noncarcinogenic. However, a nonsignificant excess of lung cancer deaths was seen in a small subgroup of workers exposed to lead chromate only, as well as in a small group of lead chromate workers who had previously suffered from lead poisoning (33). The author did not discuss the possible protection that the monitor-

ing of these subjects for exposure to lead might have provided.

The high lung cancer risk found among zinc chromate workers (13) and the aforementioned case reports suggest that this pigment is a more potent human carcinogen by inhalation than are other Cr(VI) compounds. Lead chromate seems to be a less potent human carcinogen. Hayes et al (35) found lower relative risks for lung cancer than that in a Norwegian study (12, 13) at comparable levels of exposure to Cr(VI). If the measurements are comparable in the two studies, and the airborne chromium in the study by Hayes et al (35) was derived mainly from lead chromate, the results are not in conflict.

To date, no groups exposed to strontium chromate have been studied, and no information is available for review.

The carcinogenicity of calcium chromate is indicated by the possible differences in risks of lung cancer between workers in high- and low-lime production processes.

Interaction with smoking and other possible confounders

A cohort of 723 chromate-producing workers recruited from three different factories in the United Kingdom was studied by Bidstrup & Case (28), who found 12 lung cancer deaths (expected 3.3). The authors indicated that smoking could not explain the high death rates. In a follow-up of the same population (27), in which the lung cancer excess was low, heavy smoking was less prevalent than in the general population which served as reference. A total of 20 cases of lung cancer among the chromate-producing workers was reported by Abe et al (50), of whom all but five were found to be heavy smokers. Ohsaki et al (51, 52) reported 14 men with lung cancer among 133 workers, of whom 12 were smokers and one was a nonsmoker. Tsuneta (53) reported that smoking was confirmed for 20 of 24 subjects with lung cancer recruited from a chromate-producing plant.

Five out of the six subjects with lung cancer were smokers in a Norwegian study of zinc chromate production workers (13).

de Marco et al (54) observed 20 deaths from respiratory cancer, including three cases of pleural cancer and three cancers of the larynx, in a group of Cr(VI) workers. The results indicated that asbestos could be a confounder for Cr(VI) exposure. In a study on FeCr workers (23), maintenance workers constituted the only group with excess cancer of the respiratory system; there were four cases (expected 1.0), which included two mesotheliomas. Asbestos may therefore also be of importance in chromium studies.

A cohort of 1224 stainless steel welders using different welding methods was reported in 1985 (55);

Becker et al (56) followed the group during 1983—1989 using 1694 turners as the reference population. When definite smokers and nonsmokers (ex-smokers excluded) were considered separately, a higher standardized mortality ratio (SMR 179) was found among the smoking welders than among the smoking turners (SMR 134). There were, however, three (probable) mesotheliomas in the welder group and none in the turner group, a finding indicating possible confounding by previous asbestos exposure among the welders.

Other exposure conditions influencing cancer hazard

To understand the mechanisms of the carcinogenicity of Cr(VI) compounds in humans, it should be appreciated that there is a series of "steps" between exposure to Cr(VI) compounds and definite damage to DNA (57). Between the exposure and the end point there is a definite possibility of reducing the cancer hazard (eg, by repair of DNA damage).

The uptake of chromium from Cr(VI)-containing particulates or droplet aerosols deposited in the airways depends on several factors, such as the overall size distribution of the particulate matter of the aerosol and interference from other exposure factors that may delay clearance from the bronchial tree. Such delayed clearance may result in a significantly prolonged internal exposure of the epithelial cells to chromium compounds, as demonstrated in humans for other particulates (58). This much longer exposure to insoluble Cr(VI) compounds compared with the shorter exposure to soluble Cr(VI) compounds could explain why it was concluded, possibly erroneously, that Cr(VI) compounds of low solubility are more potent carcinogens than compounds of intermediate or high solubility (19).

Petrilli et al (59) demonstrated that both alveolar macrophages and the epithelial lining fluid of the human bronchial tree are capable of reducing Cr(VI) to Cr(III) and that the rate of reduction depends on the abundance of macrophages. Thus, as little Cr(III) is taken up in the epithelial cells (57), the total uptake of chromium in the bronchial tree could be reduced as a result of an abundance of macrophages (57, 59). Their results (59) also indicate that alveolar macrophages from smokers could be more potent Cr(VI) reducers than those from nonsmokers. As suggested elsewhere (57), Cr(VI) reduction also takes place in the bronchial epithelial cells.

At high levels of exposure to Cr(VI) compounds, chromium is taken up in the cells of the bronchial lining membrane and later transported as Cr(VI) or Cr(III) via the blood stream to other organs (57). The capability of the red blood cells to reduce Cr(VI) compounds to Cr(III) is significant (60, 61). It thus seems unlikely, at low levels of exposure, that Cr(VI) compounds as such reach other target sites, because

Cr(VI) will be reduced before reaching other organs. This phenomenon could explain why Cr(VI) compounds are unlikely to reach distant sites and cause cancer there.

Efficient clearance of particles containing Cr(VI) from the bronchial tree could result in ingestion and subsequent exposure of the alimentary system to Cr(VI) and result in a cancer hazard to that system.

Discussion

Lung cancer was accepted in Germany as a work-related cancer among chromate workers in 1936. As judged by the numerous reports on lung cancer among such workers, prevention does not seem to have been very successful, but it is also possible that the necessary preventive measures were not taken by industry or required by the regulatory authorities. However, if the high rates of cancer, as found in German studies in the 1930s and 1940s, are compared with the much lower rates reported recently, some primary prevention must have been achieved.

In skilled hands, secondary prevention may prove to be useful among groups that have accumulated a very high cancer risk (eg, those with an *a priori* risk exceeding $80 \cdot 10^{-4}$) (62). The aim in the future should be to ensure primary prevention among exposed workers and secondary prevention among those already at high risk (62, 63). Exposure to chromium occurs in metal industries and during stainless steel welding, both of which are becoming increasingly important in developing countries. Thus a significant contribution to the prevention of future Cr(VI)-related cancers could be made by providing information on chromium-related health hazards and means of control to these countries.

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