

The carcinogenicity of metals in humans

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Epidemiologic evidence on the relation between exposure to metals and cancer is reviewed. Human exposure to metals is common, with wide use in industry and long-term environmental persistence. Historically, the heaviest metal exposures occurred in the workplace or in environmental settings in close proximity to industrial sources. Among the general population, exposure to a number of metals is widespread but generally at substantially lower levels than have been found in industry. The carcinogenicity of arsenic, chromium, and nickel has been established. Occupational and environmental arsenic exposure is linked to increased lung cancer risk in humans, although experimental studies remain inconclusive. Experimental studies clearly demonstrate the malignant potential of hexavalent^(VI) chromium compounds, with solubility being an important determining factor. Epidemiologic studies of workers in chromium chemical production and use link exposure to lung and nasal cancer. Experimental and epidemiologic data show that sparingly-soluble nickel compounds and possibly also the soluble compounds are carcinogens linked to lung and nasal cancer in humans. Some experimental and epidemiologic studies suggest that lead may be a human carcinogen, but the evidence is inconclusive. Although epidemiologic data are less extensive for beryllium and cadmium, the findings in humans of excess cancer risk are supported by the clear demonstration of carcinogenicity in experimental studies. Other metals, including antimony and cobalt, may be human carcinogens, but the experimental and epidemiologic data are limited. *Cancer Causes and Control* 1997, 8, 371-385

Key words: Arsenic, beryllium, cadmium, cancer, chromium, lead, metals, nickel.

Introduction

Human exposure to metals is common due to their ubiquity, wide use in industry, and environmental persistence.^{1,2} Historically, the heaviest metal exposures occurred in the workplace or in environmental settings in close proximity to industrial sources. Among the general population, exposure to a number of metals is widespread but generally the level of exposure is substantially lower. For this reason, epidemiologic evidence for the carcinogenicity of metals derives mainly from highly exposed occupational groups, with some studies of populations with unusual exposures. Here we review data on the carcinogenicity to humans of exposure to metals.

Arsenic

Arsenic is produced commercially as a byproduct of non-ferrous metal production, principally from copper smelting. It comprises greater than 10 percent of dust content in some smelter operations,³ and has been found at high levels near arsenic-emitting industries ($> 1 \mu\text{g}/\text{m}^3$).^{2,4} Surveys clearly showed elevated hair and urine arsenic levels among children living in United States towns with a copper smelter industry.^{5,6}

Experimental studies

Inorganic arsenic induces chromosomal aberrations and sister chromatid exchange. The compounds generally are not mutagenic, but may inhibit enzyme function and

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induce gene amplification and expression.⁷ *In vitro* studies indicate that direct oxidative damage of arsenic or its metabolites may play a role in cytotoxicity⁸ and pulmonary DNA single-strand breaks.⁹ There is limited direct evidence that arsenic causes cancer in animals.¹⁰

Epidemiologic studies

Although animal studies have been largely negative, there is substantial evidence that arsenic causes cancer in humans,^{10,11} by respiratory exposure (as reviewed here) or by ingestion in drinking water and pharmaceuticals (reviewed by Cantor, this volume). Following early case reports, Lee and Fraumeni¹² demonstrated, among Montana (US) copper smelters, a threefold increased risk of death due to respiratory cancer, and showed that risk increased in a dose-response fashion. This was confirmed in subsequent reports (Table 1) in Montana,¹³⁻¹⁶ Tacoma, Washington,^{17,18} in eight smaller US copper smelters,¹⁹ and in Japan,²⁰ Sweden,^{21,22} China,²³ and Chile.²⁴ Two studies

showed increased risk for lung cancer among workers involved in the manufacture of arsenical pesticides,^{25,26} but results were negative for orchardists using lead arsenate.²⁷ Epidemiologic studies from China,^{28,29} Canada,³⁰ and France³¹ found excesses of respiratory cancer among miners exposed to arsenic, but exposure to radon decay products, silica, and other potential carcinogens also may occur in these settings. One study,³² however, showed an increased risk for lung cancer with respect to both duration and level of arsenic exposure, after adjustment for radon exposure.

Analyses from the US,^{4,33,34} Quebec (Canada),³⁵ Sweden,³⁶ and China²³ showed increased lung cancer among residents near arsenic-producing industrial operations, although some investigations have been negative.^{37,38} There is evidence that combined exposure to arsenic and cigarettes may act synergistically to enhance risk.³⁹ The exposure-response curve appears to increase rapidly at lower levels of exposure, but increases proportionally less

Table 1. Selected epidemiologic studies of respiratory cancer in arsenic-exposed workers

Author (ref) Year	Location	Study population	Cases	Risk
Lee-Feldstein ¹⁴ 1986	Montana (USA)	8,045 copper smelter workers hired before 1925	302	2.9 ^a
		< 8.3 mg/m ³ .yrs	6	2.2
		8.3- < 208	100	4.8 ^a
		208 +	24	6.9 ^a
Enterline <i>et al</i> ¹⁸ 1995	Washington (USA)	2,802 copper smelter workers < 2 mg/m ³ .yrs	188	2.1 ^a
		2- < 20	52	1.7 ^a
		20 +	111	2.2 ^a
			25	2.9 ^a
Enterline <i>et al</i> ¹⁹ 1987	USA	6,078 copper smelter workers, 8 plants	93 ^b	1.2 ^a
Tokudome <i>et al</i> ²⁰ 1976	Japan	2,675 metal refinery, copper smelters	29	11.9 ^a
Jarup and Pershagen ²² 1991	Sweden	3,916 copper smelter workers < 5 mg/m ³ .yrs	102	1.4 ^a
		5- < 50	42	1.0
		50 +	42	1.5 ^a
			18	3.5 ^a
Xu <i>et al</i> ²³ 1989	Shenyang, China	Case-control, smelter workers	26	3.6 ^a
Mabuchi <i>et al</i> ²⁵ 1979	Maryland (USA)	1,393 arsenical pesticide manufacturers males employed 25+ yrs	24 ^b	1.6 ^a
			9 ^b	6.8 ^a
Sobel <i>et al</i> ²⁶ 1988	USA	611 arsenical pesticide manufacturers employed > 5 yrs	35	2.2 ^a
			5	3.1 ^a
Wicklund <i>et al</i> ²⁷ 1988	Washington (USA)	Case-control, orchardists and lead arsenate exposure	9	0.8

^a $P < 0.05$.

^b Lung cancer only.

as cumulative exposures increase.⁴⁰ Other studies based upon mathematical modeling have suggested that arsenic acts primarily as a late-stage carcinogen.^{16,41}

Summary and conclusions

Although experimental studies of carcinogenicity of arsenic are limited, epidemiologic evidence strongly supports a causal relationship between respiratory exposure to inorganic arsenic and cancer in humans.¹⁰ Investigations also point to environmental risks for lung cancer due to atmospheric contamination with arsenic from industrial sources.

Beryllium

Most beryllium is used as an alloy or in specialty ceramics for electrical and electronic applications, while pure beryllium finds use in the nuclear industry, aircraft, and medical devices. Coal and fuel oil combustion are the major sources of atmospheric beryllium (average in US air: 0.03 ng/m³), while land disposal of coal and municipal ash and solid wastes generated from industry can contribute to soil contamination. Daily intake is about 10-20 µg, smokers of tobacco may be exposed to 35 ng per cigarette.⁴² At one facility for the extraction and production of beryllium metals in the 1960s to 1970s, daily exposures of > 30-50 µg/m³ (equivalent to about 600-1,000 µg per day) were encountered.⁴³

Experimental studies

Malignant lung tumors were produced in rats by inhalation or intratracheal instillation of beryllium ores, alloys, and a spectrum of beryllium compounds. Various beryllium compounds also produced osteosarcomas in rabbits, by implantation or injection.⁴⁴ Mechanistic studies indicate that beryllium, in addition to the promotion of an immune response, can interfere with gene expression and DNA repair.⁷

Epidemiologic studies

Beryllium is extremely toxic, resulting in acute and chronic respiratory disease.⁴³ A report⁴⁵ on mortality among 9,225 male workers employed at US beryllium processing facilities, expanding upon earlier investigations at some of these plants,^{46,47} found that death due to lung cancer was increased. Emphysema and the pneumoconioses and other non-malignant respiratory diseases also showed excesses. The excess of lung cancer was greatest among workers hired before 1950, when a 2 µg/m³ exposure standard went into effect (Table 2). Risk for lung cancer increased with time since initial exposure, but did not increase with duration of exposure. Short duration of employment in some facilities, however, may have correlated with heavy exposure. For example, 85 percent of the workers at the facility that showed the highest risk for lung cancer (risk = 1.7) were employed there for less than one year. Also, the workers at this facility had the greatest risk for death due to pneumoconiosis and other respiratory diseases.

Cases of acute and chronic beryllium disease in the United States have been registered in the Beryllium Case Registry since 1952. A lung cancer excess was found among 689 registrants.⁴⁸ Excess mortality also was found for the pneumoconioses and other respiratory diseases (34-fold risk) and for beryllium poisoning (36-fold risk). The lung cancer excess was greater for cases of acute beryllium disease, which is linked more strongly to high exposures, than for registrants with chronic beryllium disease (Table 2).

Summary and conclusions

Beryllium is carcinogenic in animals. Studies in US beryllium workers show excesses of lung cancer, coupled with excesses of beryllium induced non-malignant respiratory disease. Direct information on levels of exposure and potential confounders was not available,⁴⁹ but the greatest risks were found among those with presumptive high exposure, early workers, and those with acute

Table 2. Epidemiologic studies of lung cancer in beryllium-exposed workers

Author (ref) Year	Location	Study population	Cases	Risk
Ward <i>et al</i> ⁴⁵ 1992	USA	7 beryllium processing facilities (<i>n</i> = 9,225)	280	1.3 ^a
		Hired before 1950	177	1.4 ^a
		Hired 1950-59	85	1.2
		Hired 1960-69	18	0.6
Steenland and Ward, ⁴⁸ 1991	USA	Beryllium Disease Registry (<i>n</i> = 689)	28	2.0 ^a
		Acute disease	17	2.3 ^a
		Chronic disease	10	1.6

^a *P* < 0.05.

beryllium disease. The overall evidence indicates that beryllium and beryllium compounds are carcinogenic to humans.⁴⁴

Cadmium

Cadmium, which is produced primarily as a byproduct of extraction of zinc and other metals, is used principally in nickel-cadmium batteries, in pigments, as a chemical stabilizer, in metal coatings, and as an alloy. Industrial contamination of topsoil is likely the major source of human exposure, via uptake into food plants and tobacco. Human uptake from dietary sources is about 1-3 µg/day and absorption is approximately doubled in a one-pack per day smoker.⁵⁰ About 0.25-1.9 µg/day could be absorbed from air in the vicinity of cadmium-emitting industrial facilities.⁵¹ Levels reported in cadmium production and refining (> 1 mg/m³), alloy production (> 1 mg/m³), and battery manufacture (> 1 mg/m³) were substantial but have decreased in more recent years.⁴⁴ Cadmium oxide fumes, generated at high temperatures, are readily absorbed through the lung, while absorption of dusts of cadmium compounds are dependent upon particle size.⁵² Because of low excretion rates, cadmium accumulates in the body, particularly in the kidneys and liver, and has been linked to kidney dysfunction.⁴⁴

Experimental studies

Cadmium is a mutagen in mammalian but not in bacterial test systems. It binds to DNA, produces oxidative damage and strand breaks, and causes chromosomal aberrations.⁷ Malignant lung tumors have been induced in rats by respiratory exposure to cadmium compounds.⁴⁴ Zinc and metallothionein limit the carcinogenic effect of cadmium compounds; higher metallothionein levels in mice may result in lower cadmium-related tumor burdens in this species.⁵³

Epidemiologic studies

Following early reports,^{54,55} an excess of prostate cancer was found among workers with high exposure to cadmium oxide at UK nickel-cadmium (Ni-Cd) battery manufacturing in the United Kingdom.⁵⁶ Modest excesses also were noted for lung cancer, but risk did not increase with duration of high-level exposure.⁵⁷ A smaller study of nickel-cadmium battery workers from Sweden⁵⁸ found nonsignificant excesses of prostate and lung cancer, particularly among long-term workers followed for at least 20 years. Workers were exposed to nickel hydroxide and cadmium. Nickel exposures were not reported for the British nickel-cadmium battery facilities, but may also have occurred (Table 3).

Excesses of prostate and lung cancer were not found among UK copper-cadmium alloy workers, although

excesses of presumably cadmium-related emphysema and proteinuria were noted.^{59,60} An excess of lung cancer was identified among workers in the vicinity of these operations,⁶⁰ perhaps due to arsenic exposure. In 17 cadmium-producing or -using plants in the UK, there was evidence of increasing risk for lung cancer with increasing exposure to cadmium, but other exposures possibly to arsenic, nickel, beryllium, and chromium may have occurred.^{61,62} In a nested case-control study of 64 percent of these workers employed at a lead-zinc smelter, stronger effects were found for exposure to lead and arsenic than to cadmium.⁶²

Excess lung cancer was found among workers in a US cadmium recovery facility.^{63,64} The excess was limited to non-Hispanics, but the appropriate comparison rates for Hispanics were unavailable. Risk increased with estimates of increasing cadmium exposure⁶⁴ (Table 3) and among those hired after 1940,⁶⁵ when low-level arsenic exposures were believed to have been reduced to inconsequential levels. An analysis from this facility of cancer cases and a series of controls matched on age and date of hire⁶⁶ showed no link with cadmium exposure, but this result may have been due to overmatching on cadmium exposure,⁶⁷ as subsequently demonstrated by the identification of a lung cancer excess when controls were chosen based only upon survival to the same age as the case.⁶⁵ The exposure measures used in these studies continue, however, to be reviewed.⁶⁸ In population-based case-control investigations,^{69,70} no clear link was shown between cadmium exposure and prostate or lung cancer.

Summary and conclusions

Studies among workers exposed to cadmium have been hampered by generally small numbers of subjects with substantial exposure to cadmium, by limited information on cadmium speciation (CdO dust, fumes, or salts of Cd), and by the potential for exposure to other carcinogens, including nickel and arsenic. Nevertheless, increases in lung cancer risk have been identified, particularly from one study on cadmium recovery operators showing a dose-response for lung cancer among workers with minimal concomitant arsenic exposure. Investigations showing the formation of malignant lung tumors in experimental studies support the conclusion that cadmium is a human lung carcinogen.⁴⁴ Epidemiologic studies have not consistently supported the early reports of excesses of prostate cancer in cadmium-exposed workers.

Chromium

The naturally occurring mineral chromite contains chromic oxide [a trivalent^(III) chromium compound]. Chromite ores are used as refractory bricks; chromium^(VI) metal is used as ferrochromium in steel and other alloy produc-

Table 3. Epidemiologic studies of lung cancer in cadmium-exposed workers

Author (ref) Year	Location	Study population	Lung cancer		Prostate cancer	
			Cases	Risk	Cases	Risk
Sorahan and Waterhouse ⁵⁶ 1985	UK	Ni-Cd battery workers (<i>n</i> = 2,466) > 1 year, high exposure (<i>n</i> = 458)			15 8	1.4 ^a 4.0 ^a
Sorahan, ⁵⁷ 1987	UK	Ni-Cd battery workers (<i>n</i> = 3,025) Early workers: < 2 yrs 2-4 yrs 5-14 yrs 15 + yrs	110 5 5 5 4	1.3 ^a 0.6 2.0 1.7 1.4	— — — — —	— — — — —
Elinder <i>et al</i> ⁵⁸ 1985	Sweden	522 nickel-cadmium battery workers > 5 yrs, 20 + yrs latency	8 7	1.3 1.8	4 4	1.1 1.5
Sorahan <i>et al</i> ⁶⁰ 1995	UK	347 copper-cadmium alloy workers 624 vicinity workers (arsenic)	18 55	1.0 1.6 ^a	2 —	0.7 —
Kazantzis <i>et al</i> ⁶² 1992; Kazantzis and Blanks, ⁶¹ 1992	UK	6,910 workers at 17 Cd processing facilities Exposure: Always low Ever medium Ever high	270 55 14	1.1 1.2 1.6	36 0 1	0.8 — 1.0
Stayner <i>et al</i> ⁶⁴ 1992	USA	602 cadmium recovery workers Non-Hispanic < 585 mg/m ³ .days 585-1460 mg/m ³ .days 1461-2920 mg/m ³ .days 2921+ mg/m ³ .days	24 21 1 7 6 7	1.5 2.1 ^a 0.3 ^a 2.6 ^a 3.7 ^a 2.9 ^a	— — — — — —	— — — — — —

^a *P* < 0.05.

tion; while chromium^(III) and chromium^(VI) chemicals are used for chrome plating, the manufacture of dyes and pigments, leather tanning, and wood preserving.

Daily intake of chromium from food, air, and water is estimated, respectively, as 60, < 0.2-0.6, and < 4.0 µg. High air concentrations have been reported for some cities (0.5 µg/m³ in Steubenville, Ohio [US], 1977; 0.2 µg/m³ in Baltimore, Maryland [US], 1980).⁷¹ In the US, releases to the air from anthropogenic sources are approximately 35 percent in the hexavalent^(VI) form.⁷² Potential industrial sources of chromium release to surface water include electroplating, leather tanning, and textile industries, while ground contamination may derive from disposal of slag from chromite ore processing, chromium-containing commercial products, and coal ash from electric utilities and other industries. In chromate production, high exposures to chromium^(III) were reported for the dry end mixing and roasting operations (> 1 mg/m³), while high levels of chromium^(VI) predominated in the end product filtering and shipping areas (0.08-8.8 mg/m³). High levels of hexavalent chromium (> 1 mg/m³) have also been found in chrome plating and in some types of chrome steel welding operations. In ferrochromium operations, chro-

mium^(III) predominates, but chromium^(VI) has also been recovered at low levels, while tanning operations involve only chromium^(III) exposures.

Experimental investigations

Chromium is a strong clastogen and produces both chromosome aberrations and sister chromatid exchanges. DNA strand breaks, oxidized base damage, and DNA-DNA and DNA-protein crosslinks are formed.⁷ Chromium^(III) compounds and materials and chromite ore have been negative in animal carcinogenicity assays, while studies of chromium metal have largely been inadequate. Various hexavalent chromium-bearing substances are capable of inducing administration-site tumors. Lead chromate yields renal tumors [see: Lead]. Exposures via the respiratory route have yielded positive results for strontium chromate, zinc chromate, and lead chromates, while weaker results were found for chromium trioxide (chromic acid) and sodium dichromate.⁷³

Epidemiologic investigations

Following reports of lung cancer cases in the German chromium chemical industry, epidemiologic studies

Table 4. Epidemiologic studies of lung cancer in chromium-exposed workers

Author (ref) Year	Year	Location	Study population	Cases	Risk
Chromate production					
Gafafer ⁷⁴	1953	USA	Before 1948 (<i>n</i> = 3,522)	26	29 ^a
Mancusco and Hueper ⁷⁵	1951	Ohio (USA)	1 plant, 1931-48 (<i>n</i> = 33 deaths)	6	15 ^a
Taylor ⁷⁸	1966	USA	3 plants, 1937-60 (<i>n</i> = 1,212)	71	8.6 ^a
Hayes <i>et al</i> ⁷⁷	1979	Maryland (USA)	1 plant, 1945-77 (<i>n</i> = 1,201)	59	2.0 ^a
			3 + years exposure	25	3.2 ^a
Pastides <i>et al</i> ⁷⁸	1994	North Carolina (USA)	1 plant, 1971-89 (<i>n</i> = 398)	2	1.0
Ohsaki <i>et al</i> ⁷⁹	1978	Japan	1 plant, 1936-73 (<i>n</i> = 554)	14	~ 49 ^a
Davies <i>et al</i> ⁸⁰	1991	UK	3 plants, 1950-88 (<i>n</i> = 2,298)	187	1.9 ^a
			Before process change		
			< 5 yrs exposed	47	1.5 ^a
			5 - 19	81	2.3 ^a
			20 +	47	2.1 ^a
			Postchange, no-lime	14	1.0
Korallus <i>et al</i> ⁸¹	1993	Germany	2 plants, 1948-88 (<i>n</i> = 1,417)		
			Before process change	66	2.3 ^a
			Postchange, no lime	9	1.3
Chromate pigment manufacture					
Langard and Vigander, ⁸⁴	1983	Norway	1 plant, 1948-77 (<i>n</i> = 24)	6	44 ^a
Equitable Environmental Health, Inc. ⁸⁵	1976	USA	US plants, before 1960	6	2.5 ^a
Hayes <i>et al</i> ⁸⁷	1989	New Jersey (USA)	1 plant, 1940-82 (<i>n</i> = 1,879)	24	1.4
			30+ years latency	12	2.2 ^a
Davies ⁸⁸	1978	UK	3 UK plants, 1930s-81 (<i>n</i> = 646)	29	1.8 ^a
Haguenoer <i>et al</i> ⁸⁹	1981	France	1 plant, 1958-80 (<i>n</i> = 251)	11	4.6 ^a
Frentzel-Beyme ⁹⁰	1983	Germany and Netherlands	5 plants, hired < 1956 (<i>n</i> = 978)	19	2.0 ^a
Kano <i>et al</i> ¹¹⁰	1993	Japan	5 plants, 1950-89 (<i>n</i> = 666)	3	1.0
Chromium plating					
Royle ⁹¹	1975	UK	54 UK plants	24	1.8
Sorahan <i>et al</i> ⁹²	1987	UK	1 plant, 1946-83 (<i>n</i> = 2,689)	72	1.5 ^a
			Chrome bath work	52	1.8 ^a
			Other chrome work	20	1.0
Franchini <i>et al</i> ⁹³	1983	Italy	9 plants, 1951-81 (<i>n</i> = 178)	3	3.3
Okubo and Tsuchiya ⁹⁴	1979	Japan	Tokyo plants (<i>n</i> = 952)	0	< 1.0
Ferrochromium production					
Axelsson <i>et al</i> ⁹⁹	1980	Sweden	1 plant, 1930-75 (<i>n</i> = 1,876)	5	0.7
Langard <i>et al</i> ¹⁰⁰	1990	Norway	1 plant, 1953-77 (<i>n</i> = 325)	10	1.6
Moulin <i>et al</i> ¹⁰¹	1990	France	1 plant, 1952-82 (<i>n</i> = 2,269)	11	2.0 ^a

^a *P* < 0.05.

showed elevated risks for lung cancer in the US, Japanese, UK, and German chromate production industries⁷⁴⁻⁸¹ (Table 4). Workers⁷⁷ in the 'wet end' of the chromium chemical production process, where hexavalent compounds predominate, tended to have the highest risks, as did workers with a history of skin conditions and nasal perforations, which are related primarily to hexavalent

exposure.⁸² Methods to limit exposure to calcium chromate probably lead to reduced risk.^{80,81} In one study,⁸³ risk increased with exposure to soluble and insoluble chromium, but these exposures were highly correlated. Excesses of respiratory cancer now have been found among chromate pigment workers in Norway,⁸⁴ the US,⁸⁵⁻⁸⁷ Great Britain,⁸⁸ France,⁸⁹ and Germany and the Netherlands⁹⁰

(Table 4). Zinc chromate exposure was common to most of the workers studied and is a likely respiratory carcinogen in this industry. No excess of respiratory cancer was noted among small subgroups exposed only to lead chromate.

Chromium platers, exposed to soluble chromium oxide (CrO_3), also show evidence of an increased risk for lung cancer.⁹¹⁻⁹⁴ (Table 4). One study found increased relative risk (RR) with time since first exposure⁹² and showed that the excess was not due to exposure to nickel.⁹⁵ There is also evidence that welders of stainless steel who are exposed to chromium^(VI) have an excess of lung cancer, but asbestos and other exposures may play a significant role.⁹⁶⁻⁹⁸ Ferrochromium workers are exposed to metallic and chromium^(III), but possibly also to some chromium^(VI), benzo(a)pyrene, and asbestos. In a Swedish study,⁹⁹ no excess of respiratory cancer was found, while a study in Norway¹⁰⁰ showed an excess only compared with lung cancer rates in the local population. In a French study,¹⁰¹ lung cancer was in excess, but the link was stronger for polycyclic aromatic hydrocarbons (PAH) than for chromium exposure (Table 4). Studies of workers in leather tanneries, where exposure is also primarily to chromium^(III), showed no lung cancer excess, but numbers of chromium-exposed workers were small.¹⁰²⁻¹⁰⁴ Chromium chemicals also were suspected of causing nasal and nasal sinus cancer since a case report was published in 1890.¹⁰⁵ Nasal cancers have been identified in several studies of workers exposed to chromium.^{80,84,106-108} Recently, a greater than fivefold risk for nasal cancer was found among chromium chemical workers.¹⁰⁹ Cytogenetic effects have been observed among residents living in chromium-contaminated areas.¹¹⁵

Summary and conclusions

Workers in chromate production, chromate pigment production, and chrome plating exhibit excess risk for lung cancer. While epidemiologic studies^{77,84,108} point to increased risk associated with longer-term employment, there is a lack of quantitative data on the exposure-response relationship.¹¹¹ Experimental studies demonstrate the carcinogenicity of a number of chromium^(VI) compounds encountered in these industries, but there is a lack of evidence that chromium^(III) or metallic chromium cause cancer in animals. Chromium^(VI) readily passes cell membranes, while chromium^(III) does not. *In vitro* studies of mutagenic and cytogenetic effects also support the carcinogenicity of chromium^(VI).⁷³ Intracellularly, the reduction of chromium^(VI) likely provides the reactive oxidative species required for chromium genotoxicity.¹¹²⁻¹¹⁴ A possible role for intracellular chromium^(III) in chromium carcinogenesis has also been suggested,⁷ but the evidence indicates that exposure to chromium^(VI) is the cause of cancer in man, with carcinogenic potency being likely a function of compound solubility.^{73,116}

Lead

Lead is used industrially either pure or alloyed with other metals, or in chemical compounds, primarily oxides. The production of tetra-alkyl lead as a gasoline additive is diminishing, and use of lead-based paints has also been curtailed. Total use of lead, however, has not declined substantially, due to increased production of batteries and other uses. In the US, about 50 percent of the lead requirements are met by recycled lead products; in 1990, more than 97 percent of all spent lead-acid batteries were recycled.¹¹⁷

Recent US air emissions of lead to the atmosphere from anthropogenic sources were estimated to be 7.2×10^3 metric tons, but have decreased substantially from earlier levels. High air levels have been found near smelters ($> 10 \mu\text{g}/\text{m}^3$), in soil adjacent to smelters (60 mg/g) and houses with exterior lead-based paints (10 mg/g), and in groundwater at hazardous waste sites (20 $\mu\text{g}/\text{L}$). In urban areas, motor vehicle exhaust from leaded gasoline has been a major source of soil contamination near roadways. Young children may consume 25 μg of lead per day from contaminated soil, while adults generally experience lower exposures through air and dietary sources.¹¹⁷ In 1978, average lead concentrations in air were reported for a number of occupational settings, including lead iron pouring (19.5 mg/m³), storage battery manufacture (0.15-0.75 mg/m³), lead smelting (0.35 mg/m³), paint mixing (1.75 mg/m³), paint spraying (red lead) (1.8 mg/m³), paint sanding and scraping (0.32 mg/m³), and printing linotyping (0.07 mg/m³) and stereotyping (0.26 mg/m³).¹¹⁸

Experimental investigations

Lead is not an effective genotoxin in mammalian cells, but shows co-mutagenic activity in combination with ultraviolet light (UV) and N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), possibly due to the inhibition of DNA repair.¹¹⁹ Several lead-soluble salts, including lead acetate and lead subacetate, produced renal tumors by several routes of administration in rats and mice. Metallic lead, lead oxide, and lead tetra-alkyls have not been tested adequately.¹⁰ Studies in mammalian test systems indicate that lead acetate does not consistently induce DNA-strand breaks or somatic mutations,¹⁰ but one investigation showed that lead exposure can interfere with the repair of UV-induced DNA damage, perhaps by interference with repair enzymes.¹²⁰

Epidemiologic investigations

Following earlier reports of a potential excess of digestive tract cancers at lead acid battery factories in Great Britain,^{121,122} a more recent report¹²³ found no significant excess (The statistical analysis, however, was open to question). A recent update¹²⁴ to earlier US studies¹²⁵⁻¹²⁷ of

Table 5. Cancer risk among selected populations with occupational lead exposure

Author (ref) Year	Location	Study population	Blood lead $\mu\text{mol/L}$	Cancer site					
				Stomach		Respiratory		Kidney	
				Cases	Risk	Cases	Risk	Cases	Risk
Cooper <i>et al</i> ¹²⁴ 1985	USA	4,519 battery workers	3.0	34	1.7 ^a	116	1.2 ^a	3	0.4
		2,300 lead smelters	3.9	9	1.5	43	1.2	2	0.8
Steenland <i>et al</i> ¹²⁸ 1992	USA	1,990 lead smelters	NA	15	1.4	72 ^b	1.2	9	1.9
		High exposure only	NA	10	1.3	49 ^b	1.1	8	2.4 ^a
Gerhardsson <i>et al</i> ¹³⁰ 1995	Sweden	664 secondary lead smelters	1.6-3.0	3	1.9	6	1.3	1	0.8
		Hired < 1970		3	2.4	4	1.2	1	1.1
Anttila <i>et al</i> ¹³² 1995	Finland	20,700 workers, mixed occupations							
		Level: Low	< 1.0	11	1.0	30	0.8	4	0.6
		Moderate	1.0-1.9	11	1.4	40	1.4 ^a	5	1.0
		High	2.0-7.8	1	0.3	13	1.2	0	—
Lundstrom <i>et al</i> ¹²⁵ 1997	Sweden	1,005 lead-only smelter workers							
		Level: ^d Low	< 2	6 ^c	0.5	14 ^b	3.1	0	—
		Moderate	2-10			0	—		
		High	> 10			7	4.5 ^a		
						7	5.1 ^a		
Cocco <i>et al</i> ¹²⁷ 1997	Sardinia	1,388 smelter workers		14	1.0	31 ^b	0.8	4	1.8

^a $P < 0.05$.^b Includes only lung cancer.^c Includes all gastrointestinal cancer.^d Cumulative blood lead level ($\mu\text{mol/L}$ -years).

NA = not available.

lead battery and smelting facilities showed excess deaths for all malignant neoplasms, largely due to increased risk of stomach and respiratory cancer (Table 5), but no association was shown by date of initial employment or duration of exposure.

Among workers at a Utah (US) primary lead smelter,^{128,129} where overall arsenic and cadmium exposure was determined to be relatively low, an excess of kidney cancer was observed, with a statistically significant excess in the high lead exposure subgroup (Table 5). In an internal comparison, total cancer (RR = 1.4, CI = 1.1-1.7) and lung cancer (RR = 1.8, CI = 1.1-2.9) were elevated among workers who ever had blood lead levels ≥ 1.0 $\mu\text{mol/L}$ as compared to lead-exposed workers who had lower blood lead levels. A small Swedish study of secondary lead smelters,¹³⁰ where minimal co-contamination with other metals such as arsenic and cadmium occurs, showed some excess for stomach, but no further pattern was seen with examination by dose or latency period. Another study¹³¹ of workers with heavy lead exposure at the Ronnskar (Sweden) copper smelter (see above: Arsenic) found a nonsignificant excess for lung cancer, but approximately 40 percent of these workers had also been

employed in arsenic-exposed jobs. A more recent report¹²⁶ on workers employed only in lead-exposed departments of this facility showed increased risks for lung cancer (RR = 3.1, CI = 1.7-5.2), particularly among those employed before 1950 (RR = 3.7, CI = 1.8-6.6) and among those who had the highest cumulative blood lead levels. Workers at a Sardinia, Italy primary lead smelter¹²⁷ had no excess of stomach or lung cancer, but showed some evidence of an increase in kidney cancer, particularly among long-term workers (> 20 years employment, two cases, RR = 10.9, CI = 1.0-1.2).

Workers monitored for blood lead in Finland¹³² showed an excess risk for lung cancer among moderately exposed subjects, but a dose-response was not evident (Table 5). Further analyses, including a nested case-control study on a subset of the lung cancer cases ($n = 53$), tended to confirm the excess. Based upon a smaller number of cases ($n = 16$), glioma also was linked to greater blood-lead levels.¹³³ Because of the wide variety of workplaces included in this study, other exposures including asbestos, other metals, silica, and engine exhaust also were considered, with a finding that co-exposure to lead and engine exhaust may have been important in determining the lung

cancer excess. Studies in the printing trades, where exposure to lead was common in the past, are inconclusive.^{134,135} [For lead chromate, see above: Chromium.]

In community-based case-control studies, occupational lead exposure has been linked to bladder cancer,¹³⁶ and stomach, lung, bladder, and kidney cancer,⁷⁰ but concomitant exposures were not ruled out. Glass workers may be at excess risk for cancer, but it is not possible to separate risk due to lead exposure from that due to other suspect carcinogens.⁴⁴ Studies of workers exposed to organic lead are inconclusive.¹³⁷⁻¹³⁹ Investigations of chromosomal aberrations in workers exposed to lead have provided inconsistent results.^{10,140}

Summary and conclusions

Experimental studies provide evidence that at least some highly soluble lead compounds cause kidney cancer. In humans exposed to lead, one study shows an excess at this site but others do not. Further experimental studies are needed of a broader group of lead species of relevance for human exposures, including elemental lead, lead oxide, and tetraethyl lead, to determine the range of lead exposures associated with kidney cancer and tumors at other sites. A pattern of excess risk for stomach and respiratory cancer is found among workers with established heavy exposure to lead.¹⁴¹ The excess risks, however, are generally moderate and could be due, at least partially, to other factors, including concomitant occupational exposures, demographic factors, and tobacco use. Continued follow-up of these cohorts, particularly of one large and relatively young group,¹³² will provide more substantial evidence regarding carcinogenic effects of lead in humans.

Nickel

Background

Nickel is used primarily as an alloy with stainless steel being the major product. Nickel is also used in nickel plating, battery production, and other uses. The average daily intake of nickel in food is about 168 µg/day. The daily intake from drinking water is about 2 µg/day, although intake of about 140 µg/day was estimated for the Sudbury, Ontario (Canada), municipal area, where a nickel production facility is located.¹⁴² Occupational exposures in excess of 1 mg/m³ have been found in nickel-related industries, and historical exposures may have been substantially higher.

Experimental studies

Nickel produces DNA strand breaks, DNA-protein crosslinks, and inhibits DNA repair. Nickel complexes with certain amino acids, peptides, and proteins which can facilitate the production of reactive oxygen spe-

cies.^{7,112,143} Respiratory exposure to metallic nickel, and the sparingly soluble nickel monoxide and nickel subsulfide, induced malignant tumors of the lung in rats. Intraperitoneal injections have produced localized malignant tumors from powdered nickel alloys and the soluble nickel sulfate, nickel chloride, and nickel acetate. Intravenous injection of nickel carbonyl has resulted in an increase in overall incidence of neoplasms at several organ sites.^{73,144}

Epidemiologic studies

In 1990, the International Committee on Nickel Carcinogenesis in Man (ICNCM) reported the results of nine cohort studies and one case-control study among workers in nickel mining, smelting, refining, and specialty use.¹⁴⁵ These investigations included workplaces previously studied, with several now including enlarged cohorts, extended follow-up, and additional statistical analyses. Major reviews of nickel carcinogenicity in humans also were carried out at about that time.^{73,146}

The largest cohort in the ICNCM report included about 55,000 workers at INCO (Ontario, Canada) nickel mining, smelting, and refining facilities. Approximately threefold and 50-fold risks were found, respectively, for lung and nasal cancer among workers in sinter plant operations (leaching, calcining, sintering), where oxidic and sulfidic nickel are the primary exposures (Table 6). Marginal increases for lung (cases = 547, standardized mortality ratio [SMR] = 1.1, 95 percent confidence interval [CI] = 1.0-1.2) and nasal cancer (cases = 6, SMR = 1.4, CI = 0.5-3.1) were observed among the large number of other employees with no work experience in the sinter plants. Electrolysis work, where exposure to soluble nickel occurs, was weakly linked to lung cancer, but an excess of nasal cancer was identified among workers with mixed electrolysis and sinter plant exposure.

Exposure to soluble nickel at the Ontario facility was considered to be lower than at the Norwegian electrolysis operation (see below).¹⁴⁵ At the Clydach Mond/INCO facility in Wales, risks were increased substantially for lung and nasal cancer, particularly among men hired before 1930 (Table 6). The majority of these workers was employed in operations where exposure to insoluble oxidic and sulfidic nickel was high. A role for soluble nickel is also indicated by excess lung cancer (cases = 5, expected [Exp] = 1.5, SMR = 3.3) and nasal cancer (cases = 4, Exp = 0.01, SMR = 364) found among workers who had been employed in these high oxidic and sulfidic nickel-exposure jobs for less than one year, but who had long-term (five or more years) employment in hydrometallurgy, where exposure to soluble nickel occurs in combination with only low-level oxidic and sulfidic species. At a Norwegian nickel refinery, exposure in electrolysis to soluble nickel and in calcining and related

Table 6. Selected epidemiologic studies of lung cancer in nickel-exposed workers evaluated by the International Committee on Nickel Carcinogenesis in Man (ICNCM)¹⁴⁵

Location	Study population	Lung cancer		Nasal cancer	
		Cases	Risk	Cases	Risk
Ontario, Canada	Refining, 3 sinter plants (<i>n</i> = 3,769)	148	2.6 ^a	25	51 ^a
	15 year latency, 5 + years exposure	77	4.9 ^a	19	173 ^a
	Electrolysis (<i>n</i> = 2,747)				
	15 year latency, < 5 yr in sinter plants	49	1.4 ^a	4	14 ^a
South Wales, UK	Refining, 1 plant (<i>n</i> = 2,521)				
	Hired < 1930	172	3.9 ^a	74	211 ^a
	Hired 1930+	44	1.2	1	5.6
Norway	Refining, 1 plant (<i>n</i> = 3,250)	77	2.6 ^a	3	4.5
	Electrolysis only, 15 year latency	30	3.8 ^a	2	—
	5 + years exposure	19	4.8 ^a	2	—
	Refining, no electrolysis, 15 year latency	14	2.2 ^a	5	—
	5 + years exposure	8	2.5 ^a	5	—
West Virginia (USA)	Refining				
	Hired < 1947 (<i>n</i> = 1,855)	72	1.0	2	2.2
	Hired 1947 + (<i>n</i> = 1,353)	19	1.0	0	—
Falconbridge, Canada	Mining, smelting, 2 facilities (<i>n</i> = 11,594)	114	1.4 ^a	1	1.3
Oregon, USA	Mining and smelting, 1 facility (<i>n</i> = 1,510)	27	1.5 ^a	0	—

^a *P* < 0.05.^b 15 or more years since initial exposure in this exposure category.

operations was linked to lung cancer (Table 6). In a recent update,¹⁴⁷ risk was correlated more strongly with estimated cumulative exposure to soluble nickel than to nickel oxide. No excess risk was identified among workers at a West Virginia (US) refinery (Table 6), but only a small number of these workers was employed in calcining operations.

Cancer risk among several other groups of nickel-exposed workers was analyzed by the ICNCM.¹⁴⁵ Workers in mining and smelting at relatively low exposure levels (average < 1 mg/m³) at Falconbridge, Ontario, and in Oregon (US) showed excesses of lung cancer (Table 6). No excesses of respiratory cancer or nasal cancers were identified in mining and smelting operations in New Caledonia (Melanesia), among workers exposed to fine pure nickel powder at the Oak Ridge, Tennessee (US), Gaseous Diffusion Plant, or among workers at a Hereford, England, nickel alloy facility. One nasal sinus cancer was found among 129 men at a Finnish refinery.¹⁴⁵

Other studies provide limited additional support to the overall finding that nickel is, at least in some forms, a human respiratory carcinogen.^{73,95,148-152} A review suggests that nickel-related nasal cancer follows a similar histologic distribution as found in the general population, but that a preponderance of squamous cell lung cancers are

found.¹⁵³ Another consideration is possible interaction with tobacco use, as suggested by results from the Norwegian cohort.¹⁴⁷ Chromosomal abnormalities have been observed among workers exposed mainly to nickel oxide and subsulfide in crushing, roasting, and smelting, to nickel chloride and nickel sulfate in electrolysis, and to soluble nickel and chromium compounds in electroplating. Studies of sister chromatid exchange are negative.⁷³

Summary and conclusions

Although metallic nickel is an experimental carcinogen, there is inadequate data on workers exposed primarily to metallic nickel to evaluate its carcinogenicity in humans. The evidence from human and experimental studies indicates that exposure via the respiratory route to sparingly soluble compounds of nickel results in respiratory cancer. Because the epidemiologic studies included mostly mixed exposures, it is not possible to determine the relative effect of oxidic and sulfidic exposures in humans. Human studies also link lung cancer to soluble nickel, and experimental studies showed the production of local tumors, or initiation of renal tumors (promotable with sodium barbital) by intraperitoneal injection of this class of compounds.^{73,144,154} Also, soluble nickel acted as a trans-

placental carcinogen in rats.¹⁵⁵ Toxicologic studies^{7,112,143,156} indicate that sparingly soluble compounds are more efficiently processed, delivered, and maintained as reactive agents in the nucleus than occurs for the soluble compounds. An additional potential role for the soluble salts is indicated, however, by their ability to inhibit DNA repair.¹⁵⁷

Other metals

Antimony ore and antimony trioxide have been linked to lung cancer in female rats¹⁵⁸ and, in one study, lung cancer was in excess among US antimony smelter workers.¹⁵⁹ The risk increased with increasing duration of employment in the study facility and did not appear to be due to the relatively low-level presence of arsenic in the smelter feed stock. Cobalt metal powder and cobalt (II) oxide are experimental carcinogens; there is limited evidence in animals for the carcinogenicity of cobalt alloys (with chromium and molybdenum), cobalt (II) sulfide, and cobalt (II) chloride.^{160,161} Among workers at three Swedish cobalt-containing hard-metal manufacturing plants, 17 cases of lung cancer were identified *cf* 12.7 expected. Risk was significantly increased (RR = 2.8, CI = 1.1-5.7) among workers with 10 or more years of exposure and more than 20 years since first exposure.¹⁶² Other studies of cobalt-exposed workers could not exclude exposure to other established lung carcinogens.^{160,163} Some experimental studies suggest that iron, molybdenum, and mercury may be carcinogenic, but the risks have not been adequately evaluated in human populations.^{2,10,44}

Conclusions

The carcinogenicity of arsenic, chromium, and nickel has been established. Occupational and environmental arsenic exposure is linked to increased lung cancer risk in humans, although experimental studies remain inconclusive. Experimental studies clearly demonstrate the malignant potential of hexavalent^(VI) chromium compounds, with solubility being an important determining factor. Epidemiologic studies of workers engaged in chromium chemical production and use link chromium exposure to lung and nasal cancer. Experimental and epidemiologic data show that sparingly soluble nickel compounds and possibly also the soluble compounds are carcinogens linked to lung and nasal cancer in humans. Some experimental and epidemiologic studies suggest that lead may be a human carcinogen, but the evidence is not conclusive. Although epidemiologic data are less extensive for beryllium and cadmium, their activity as human carcinogens is supported by findings of cancer occurrence in experimental studies. Other metals including antimony and cobalt may be human carcinogens, but the experi-

mental and epidemiologic data are limited.

Experimental and epidemiologic studies have provided a firm basis for the assessment of metal carcinogenicity. There remain, however, substantive issues for evaluating human carcinogenicity: the relative importance of major metal species and compounds requires continued evaluation; knowledge about dose-response effects is limited; the impact of multiple exposures, to several metals and to other potential carcinogens, is only partially understood; and, monitoring of other metals as they come into more common industrial use is required. Early epidemiologic studies of exposure to potent carcinogens at presumably high levels of exposure established associations that would not likely be due to confounding by other risk factors. As efforts are made in studying weaker carcinogens and lower levels of exposure, it becomes increasingly challenging to account for metal-specific effects, independent of other occupational and behavioral risk factors. Advances are required in epidemiologic methods including improved exposure assessment and the incorporation of human toxicologic approaches in the overall epidemiologic study design.

Metals share certain physical and chemical features and it is reasonable to speculate that common mechanisms for carcinogenicity may operate. There are a number of potential pathways for metal carcinogenicity. In experimental systems, several metals induce DNA damage. DNA crosslinks may form directly or indirectly and metals may interfere with DNA repair. Some metals impact signal transduction by promoting alterations in gene expression and cellular communication and also may effect the immune response and cellular homeostasis.¹⁶⁴ Specific carcinogenic pathways, however, are determined by numerous factors including metal type, speciation, solubility, possible metal-metal interactions, and other factors.

Scientific investigations have established the carcinogenicity of several metals to which humans are exposed in industrial and environmental settings. Continued investigations of metals are needed to monitor their continued impact on the human cancer burden and to link experimental findings on mechanisms to their effects in humans.

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