2. Studies of Cancer in Humans

2.1 Hard-metal industry

Four mortality studies have been carried out in two cohorts of workers from the hard metal industry in Sweden and France. The key findings are summarized in Table 11.

Hogstedt and Alexandersson (1990) reported on 3163 male workers, each with at least 1 year of occupational exposure to hard-metal dust at one of three hard-metal manufacturing plants in Sweden in 1940–82 and who were followed during the period 1951–82. There were four categories of exposure (with estimated concentrations of cobalt in ambient air prior to 1970 given in parentheses for each category): occasionally present in rooms where hard metal was handled (< 2 $\mu g/m^3$ cobalt); continuously present in rooms where hard metal was handled, but personal work not involving hard metal (1–5 $\mu g/m^3$ cobalt); manufacturing hard-metal objects (10–30 $\mu g/m^3$ cobalt); and exposed to cobalt in powder form when manufacturing hard-metal objects (60–11 000 $\mu g/m^3$ cobalt). The workers were also exposed to a number of other substances used in the production of hard metal, such as tungsten carbide. There were 292 deaths among persons under 80 years of age during the study period (standardized mortality ratio [SMR], 0.96; 95% confidence interval [CI], 0.85–1.07) and 73 cancer deaths (SMR, 1.05; 95% CI, 0.82–1.32). Seventeen deaths from lung cancer were observed (SMR, 1.34; 95% CI, 0.77–2.13). Comparing the high versus low categories of exposure intensity, SMRs were similar. With regard to latency (time since first exposure), the excess was higher in the subcohort with more than 20 years since first exposure. Among workers with more than 10 years of employment and more than 20 years

Table 10. Occupational exposure limit values and guidelines for cobalt

Country or region	Concentration (mg/m^3)[a]	Interpretation[b]	Carcinogen category[c]
Australia	0.05	TWA	Sen
Belgium	0.02	TWA	
Canada			
Alberta	0.05	TWA	
	0.1	STEL	
Ontario	0.02	TWA	
Quebec	0.02	TWA	A3
China	0.05	TWA	
	0.1	STEL	
Finland	0.05	TWA	
Germany	0.5[d]	TWA (TRK)	2; Sah
Ireland	0.1	TWA	
Japan	0.05	TWA	2B; Aw1S1
	0.2	STEL	
Malaysia	0.02	TWA	
Mexico	0.1	TWA	A3
Netherlands	0.02	TWA	
New Zealand	0.05	TWA	A3
Norway	0.02	TWA	Sen
Poland	0.05	TWA	
	0.2	STEL	
South Africa	0.1	TWA	
Spain	0.02	TWA	
Sweden	0.05	TWA	Sen
Switzerland	0.1	TWA	Sen; K
United Kingdom	0.1	TWA (MEL)	
USA[e]			
ACGIH	0.02	TWA (TLV)	A3
NIOSH	0.05	TWA (REL)	
OSHA	0.1	TWA (PEL)	

From Deutsche Forschungsgemeinschaft (2002); Health and Safety Executive (2002); ACGIH Worldwide® (2003a,b,c); Suva (2003)

[a] Most countries specify that the exposure limit applies to cobalt 'as Co'.

[b] TWA, 8-h time-weighted average; STEL, 10–15-min short-term exposure limit; TRK, technical correct concentration; MEL, maximum exposure level; TLV, threshold limit value; REL, recommended exposure level; PEL, permissible exposure level

[c] Sen, sensitizer; A3, confirmed animal carcinogen with unknown relevance to humans; 2, considered to be carcinogenic to humans; Sah, danger of sensitization of the airways and the skin; 2B, possibly carcinogenic to humans: substance with less evidence; Aw1S1, airway sensitizer; K, carcinogenic

[d] Cobalt metal used in the production of cobalt powder and catalysts, hard metal (tungsten carbide) and magnet production (processing of powder, machine pressing and mechanical processing of unsintered articles); all other uses have a TRK of 0.1 mg/m^3.

[e] ACGIH, American Conference of Governmental Industrial Hygienists; NIOSH, National Institute for Occupational Safety and Health; OSHA, Occupational Health and Safety Administration

Table 11. Cohort studies of lung cancer in workers in the hard-metal and cobalt industry

Reference, plants	Cohort characteristics	No. of deaths	Exposure categories	Observed/ expected or cases/ controls	Relative risk (95% CI)	Comments
Hard-metal industry						
Hogstedt & Alexandersson (1990) 3 factories in Sweden	3163 male workers; follow-up, 1951–82	17 deaths		Obs/Exp	**SMR**	No information on smoking
			Whole cohort	17	1.34 [0.77–2.13]	
			Low exposure	11/8.4	1.31 [0.65–2.34]	
			High exposure	6/4.3	1.39 [0.51–3.04]	
			≥ 10 years of exposure and > 20 years since first exposure	7/2.5	2.78 [1.11–5.72]	
			High exposure			
			< 20 years latency	2/2.6	0.77 [0.09–2.78]	
			≥ 20 years latency	4/1.7	2.35 [0.64–6.02]	
Lasfargues *et al*. (1994) 1 factory in France	709 male workers employed > 1 year; follow-up, 1956–89; vital status, 89.4%; cause of death, 90.7%	10 deaths	Whole cohort	10/4.69	2.13 [1.02–3.93]	National reference. Proportion of smokers comparable with a sample of the French male population
			Duration of employment (years)			
			1–9	7/2.07	3.39 [1.36–6.98]	
			10–19	1/0.81	1.23 [0.03–6.84]	
			≥ 20	1/0.40	2.52 [0.06–14.02]	
			Time since first employment (years)			
			1–9	1/0.54	1.86 [0.05–10.39]	
			10–19	5/1.37	3.65 [1.19–8.53]	
			≥ 20	3/1.38	2.17 [0.45–6.34]	
			Degree of exposure			
			Non-exposed	1/0.66	1.52 [0.04–8.48]	
			Low	0/0.71	0.00 [0.00–5.18]	
			Medium	3/2.08	1.44 [0.30–4.21]	
			High	6/1.19	5.03 [1.85–10.95]	

Table 11 (contd)

Reference, plants	Cohort characteristics	No. of deaths	Exposure categories	Observed/ expected or cases/ controls	Relative risk (95% CI)	Comments
Moulin *et al*. (1998) 10 factories in France	7459 workers (5777 men, 1682 women); follow-up, 1968–91; vital status, 90.8%; cause of death, 96.8%	63 deaths	Whole cohort	Obs/Exp 63/48.59	1.30 [1.00–1.66]	Information on smoking for 80% of participants but no adjustment for smoking. Includes the factory studied by Lasfargues *et al*. (1994)
	Nested case–control study; 61 cases (59 men, 2 women) and 180 controls (174 men, 6 women) followed-up at the time the case died and employed > 3 months, matched by gender and age		**Cobalt with tungsten carbide**	Cases/ controls	**Odds ratio**	
			Levels 2–9/levels 0–1	35/81	1.9 (1.03–3.6)	
			Levels			
			0–1	26/99	1.0	
			2–3	8/12	3.4 (1.2–9.6)	
			4–5	19/55	1.5 (0.8–3.1)	
			6–9	8/14	2.8 (0.96–8.1)	
			p for trend		0.08	
			Duration of exposure (levels ≥ 2)			
			Non-exposed	26/99	1.0	
			≤ 10 years	19/52	1.6 (0.8–3.3)	
			10–20 years	12/20	2.8 (1.1–6.8)	
			> 20 years	4/9	2.0 (0.5–8.5)	
			p for trend		0.03	
			Unweighted cumulative dose[a]			
			< 32	6/46	1.0	
			32–142	16/43	2.6 (0.9–7.5)	
			143–299	16/45	2.6 (1.5–11.5)	
			> 299	23/46	4.1 (1.5–11.5)	
			p for trend		0.01	

Table 11 (contd)

Reference, plants	Cohort characteristics	No. of deaths	Exposure categories	Observed/ expected or cases/ controls	Relative risk (95% CI)	Comments
Moulin *et al*. (1998) (contd)			*Frequency-weighted cumulative dose*[a]	Cases/ controls		
			< 4	8/45	1.0	
			4–27	20/45	2.3 (0.9–6.1)	
			27–164	14/45	1.9 (0.7–5.2)	
			> 164	19/45	2.7 (1.0–7.3)	
			p for trend		0.08	
			Other exposure to cobalt (duration of exposure to levels ≥ 2)	15/30	2.2 (0.99–4.9)	Cobalt alone or simultaneously with agents other than tungsten carbide
Wild *et al*. (2000) 1 factory in France	2860 workers (2216 men, 644 women); follow-up, 1968–92; cause of death, 96%	46 deaths		Obs/Exp	**SMR** Men	Not adjusted for smoking
			Whole cohort	46/27.11	1.70 (1.24–2.26)	
			Hard-metal dust intensity score ≥ 2	26/12.89	2.02 (1.32–2.96)	
			Before sintering	9/3.72	2.42 (1.10–4.59)	
			After sintering	5/3.91	1.28 (0.41–2.98)	
			Per 10 years of exposure to unsintered hard-metal dust		1.43 (1.03–1.98)	Poisson regression adjusted for smoking and asbestos, PAH, silica, nickel and chromium compounds
			Sintered hard metal dust (yes/no)		0.75 (0.37–1.53)	

Table 11 (contd)

Reference, plants	Cohort characteristics	No. of deaths or cases	Exposure categories	Observed/ expected or cases/ controls	Relative risk (95% CI)	Comments
Cobalt production industry						
Moulin *et al*. (1993)	1148 male workers employed 1950–80;	8 deaths	Exclusively employed in cobalt production	3/2.58	1.16 (0.24–3.40)	Not adjusted for smoking
1 electro-chemical plant in France	follow-up until 1988; vital status, 99%		Ever employed in cobalt production	4/3.38	1.18 (0.32–3.03)	
Other cobalt compounds						
Tüchsen *et al*. (1996)	1394 female workers (874 exposed; 520 not exposed) employed in the plate underglazing departments 1943–92	15 cases (8 exposed; 7 not exposed)			**SIR**	No information on smoking
2 porcelain plants in Denmark			Exposed to cobalt	8/3.41	2.35 [1.01–4.62]	
			Not exposed to cobalt	7/3.51	1.99 [0.80–4.11]	

PAH, polycyclic aromatic hydrocarbon

[a] Cumulative doses expressed in months × levels

since first exposure, a significant excess of mortality from lung cancer was found (seven cases observed; SMR, 2.78; 95% CI, 1.11–5.72). In addition, there were four deaths from pulmonary fibrosis in this cohort (1.4% of all deaths, which the authors noted to be higher than the national proportion of 0.2%). A survey carried out at the end of the 1970s among hard-metal workers in Sweden showed that their smoking habits were not different from those of the male Swedish population in general (Alexandersson, 1979). [The Working Group noted the small number of exposed lung cancer cases, the lack of adjustment for other carcinogenic exposures and the absence of a positive relationship between intensity of exposure and lung cancer risk.]

A cohort mortality study was carried out among workers at a plant producing hard metals in France (Lasfargues *et al*., 1994). Seven hundred and nine male workers with at least 1 year of employment were included in the cohort and were followed from 1956 to 1989. Job histories were obtained from company records; however, before 1970 these histories were often missing. Using concentrations of cobalt measured in dust and in urine of workers in 1983, and taking into account improvements in working conditions over time, four categories of exposure were defined: not exposed directly to hard-metal dust; low exposure (cobalt in dust, < 10 μg/m^3; cobalt in urine, 0.01–0.02 μmol/L); medium exposure (cobalt in dust, 15–40 μg/m^3; cobalt in urine, 0.01–0.10 μmol/L); high exposure (atmospheric mean concentrations of cobalt, > 50 μg/m^3; cobalt in urine, 0.02–0.28 μmol/L). Workers who had been employed in jobs with different degrees of exposure were categorized according to their highest exposure and possible previous exposure at other plants was also considered. Of the 709 cohort members, 634 (89.4%) were alive and 295 were still employed at the end of follow-up. Smoking was ascertained for 81% of the workers and 69% of the deceased. The overall mortality did not differ from that expected (75 deaths; SMR, 1.05; 95% CI, 0.82–1.31) whereas mortality due to lung cancer was in excess (10 deaths; SMR, 2.13; 95% CI, 1.02–3.93). This excess was highest among workers employed in the areas with the highest exposures to cobalt (six deaths; SMR, 5.03; 95% CI, 1.85–10.95).

Following the report by Lasfargues *et al.* (1994) described above, an industry-wide mortality study on the association between lung cancer and occupational exposure to cobalt and tungsten carbide was carried out in the hard-metal industry in France (Moulin *et al*., 1998). The cohort comprised 7459 workers (5777 men, 1682 women) from 10 factories, including the one previously studied by Lasfargues *et al.* (1994), from the time each factory opened (between 1945 and 1965) until 31 December 1991. The minimum time of employment was 3 months in nine factories and 1 year in the factory previously studied (Lasfargues *et al*., 1994). The mortality follow-up period was 1968–91. A total of 1131 workers were considered to be lost to follow-up; of these, 875 were born outside France. The causes of the 684 registered deaths were ascertained from death certificates (633 subjects) and from medical records (29 subjects), but were unknown for 22 subjects (3.2%). The SMR for all causes of mortality was 0.93 (684 deaths; 95% CI, 0.87–1.01), and mortality for lung cancer was increased (63 deaths; SMR, 1.30; 95% CI, 1.00–1.66) when compared with national death rates. [The loss to follow-up will underestimate the SMRs,

although analyses from the nested case–control study will probably be less affected by this bias.]

Sixty-one cases (i.e. deaths from lung cancer) and 180 controls were included in a nested case–control study (Moulin *et al*., 1998). Three controls per case were sampled among cohort participants: (a) under follow-up on the date that the case died, having completed 3 months of employment and known to be alive on that date; and (b) of the same gender and with the same date of birth ± 6 months. Job histories were drawn from administrative records and information on job histories was complemented by interviews with colleagues who were not aware of the case or control status of the subjects. Occupational exposure of cases and controls was obtained using a job–exposure matrix involving 320 job periods and semi-quantitative exposure intensity scores from 0 to 9. Exposure was assessed as (i) simultaneous exposure to cobalt and tungsten carbide specific to hard-metal manufacture and (ii) other exposure to cobalt resulting from other production activities. Exposure to cobalt with tungsten carbide was analysed using the maximum intensity score coded at any period of the job history, the duration of exposure at an intensity of ≥ 2 and the estimated cumulative exposure. Cumulative exposure was expressed as either an unweighted (intensity × duration) or a frequency-weighted (intensity × duration × frequency) score. The cumulative exposure scores were divided into quartiles of the exposure distribution among controls after exposure to cobalt had been classified as exposed versus unexposed. Exposure scores for each risk were based on information up to 10 years prior to the death of the case. Information on smoking habits (defined as never, former or current smokers) was obtained by interviewing colleagues, relatives and the subjects themselves. For analysis, each subject was classified as an ever versus never smoker. Information on smoking habits was available for 80% of the study population. The effect of possible confounders, including potential carcinogens listed in the job–exposure matrix (assessed as 'yes' or 'no'), socioeconomic level and smoking, was assessed using a multiple logistic model.

The odds ratio for workers exposed to cobalt and tungsten carbide was 1.93 (95% CI, 1.03–3.62) for exposure levels 2–9 versus levels 0–1. The odds ratio for cobalt with tungsten carbide increased with duration of exposure and unweighted cumulative dose, but less clearly with level of exposure or frequency-weighted cumulative dose. Exposure to cobalt and tungsten before sintering was associated with an elevated risk (odds ratio, 1.69; 95% CI, 0.88–3.27), which increased significantly with frequency-weighted cumulative exposure ($p = 0.03$). The odds ratio for exposure to cobalt and tungsten after sintering was lower (1.26; 95% CI, 0.66–2.40) and no significant trend was observed for cumulative exposure. Adjustment for exposure to known or suspected carcinogens did not change the results. Adjustment for smoking in the 80% subset with complete smoking data resulted in a slightly higher odds ratio (2.6; 95% CI, 1.16–5.82; versus 2.29; 95% CI, 1.08–4.88). The odds ratio for cobalt alone or with exposures other than to tungsten carbide was 2.21 (95% CI, 0.99–4.90) in a model with only indicators of duration of exposure to cobalt with tungsten carbide.

A study in addition to that of Moulin *et al*. (1998) was conducted in the largest plant already included in the multicentre cohort and used the same job–exposure matrix but made

use of the more detailed job histories available (Wild *et al*., 2000). In this study, which included follow-up from 1968 to 1992, mortality from all causes among 2860 subjects was close to the expected number (399 deaths; SMR for men and women combined, 1.02; 95% CI, 0.92–1.13). Mortality from lung cancer was increased among men (46 deaths; SMR, 1.70; 95% CI, 1.24–2.26). The SMR for exposure to hard-metal dust at an intensity score ≥ 2 was increased (26 deaths; SMR, 2.02; 95% CI, 1.32–2.96). Lung cancer mortality was higher than expected in those working in hard-metal production before sintering (nine deaths; SMR, 2.42; 95% CI, 1.10–4.59); after sintering, the SMR was 1.28 (five deaths; 95% CI, 0.41–2.98). In a Poisson regression model (Table 11) including terms for smoking and other occupational carcinogens, the risk for lung cancer increased with duration of exposure to cobalt with tungsten carbide before sintering (1.43 per 10-year period); there was no evidence of risk from exposure to sintered hard-metal dust.

2.2 Cobalt production industry

Moulin *et al.* (1993) studied the mortality of a cohort of 1148 workers in a cobalt electrochemical plant in France which produced cobalt and sodium by electrochemistry, extending the follow-up of an earlier study (Mur *et al*., 1987; reported in IARC, 1991). The cohort included all the men who had worked in this plant for a minimum of 1 year between 1950 and 1980. The vital status of the members of the cohort was ascertained up to the end of 1988, and was obtained for 99% of French-born workers using information provided by the registry office of their place of birth. Due to difficulties in tracing workers born outside France, results are presented here only for French-born workers (n = 870).

The SMR for all causes of death was 0.95 (247 deaths; 95% CI, 0.83–1.08) and that for all cancer deaths was 1.00 (72 deaths; 95% CI, 0.78–1.26). The SMR for lung cancer mortality was 1.16 (three deaths; 95% CI, 0.24–3.40) among workers employed exclusively in cobalt production and 1.18 (four deaths; 95% CI, 0.32–3.03) for workers ever employed in cobalt production. For workers who worked exclusively as maintenance workers, the SMR for lung cancer was 2.41 (two deaths; 95% CI, 0.97–4.97) and, for those ever employed as maintenance workers, it was 2.58 (eight deaths; 95% CI, 1.12–5.09). There was evidence for an increased risk in this group of workers for those employed more than 10 years in cobalt production and for 30 years or more since first employment in cobalt production. [The Working Group noted that this might be explained by other carcinogenic exposures such as smoking or other occupational exposures such as asbestos.]

2.3 Other cobalt compounds

A study was conducted among 874 women occupationally exposed to poorly soluble cobalt–aluminate spinel and 520 women not exposed to cobalt in two porcelain factories in Denmark (Tüchsen *et al*., 1996). The period of follow-up was from 1943 (time of first employment) to 1992. Vital status was assessed through the national population register and incident cancer cases were traced through the national cancer register. The observed

deaths and incident cancer cases were compared with the expected numbers based on national rates for all Danish women. Cobalt concentrations in air in this plant were high (often > 1000 μg/m^3). During the follow-up period, 127 cancer cases were diagnosed in the cohort. The overall cancer incidence was slightly elevated among the exposed women (67 observed; standardized incidence ratio [SIR], 1.20; 95% CI, 0.93–1.52) and close to unity in the reference group (60 observed; SIR, 0.99 [95% CI, 0.76–1.27]). Compared with the national reference rate, both exposed women (eight observed; SIR, 2.35; 95% CI, 1.01–4.62) and the reference group (seven observed; SIR, 1.99; 95% CI, 0.80–4.11) had an increased risk for lung cancer. However, the exposed group had a relative risk ratio of 1.2 (95% CI, 0.4–3.8) when compared with the reference group.

No relation with duration or intensity of exposure was found. The influence of smoking could not be taken into account in this study. Among the eight cases of lung cancer identified in the exposed cohort, three had been exposed to cobalt spinel for less than 3 months. [This study did not provide evidence of an increased risk of lung cancer associated with exposure to cobalt spinel.]