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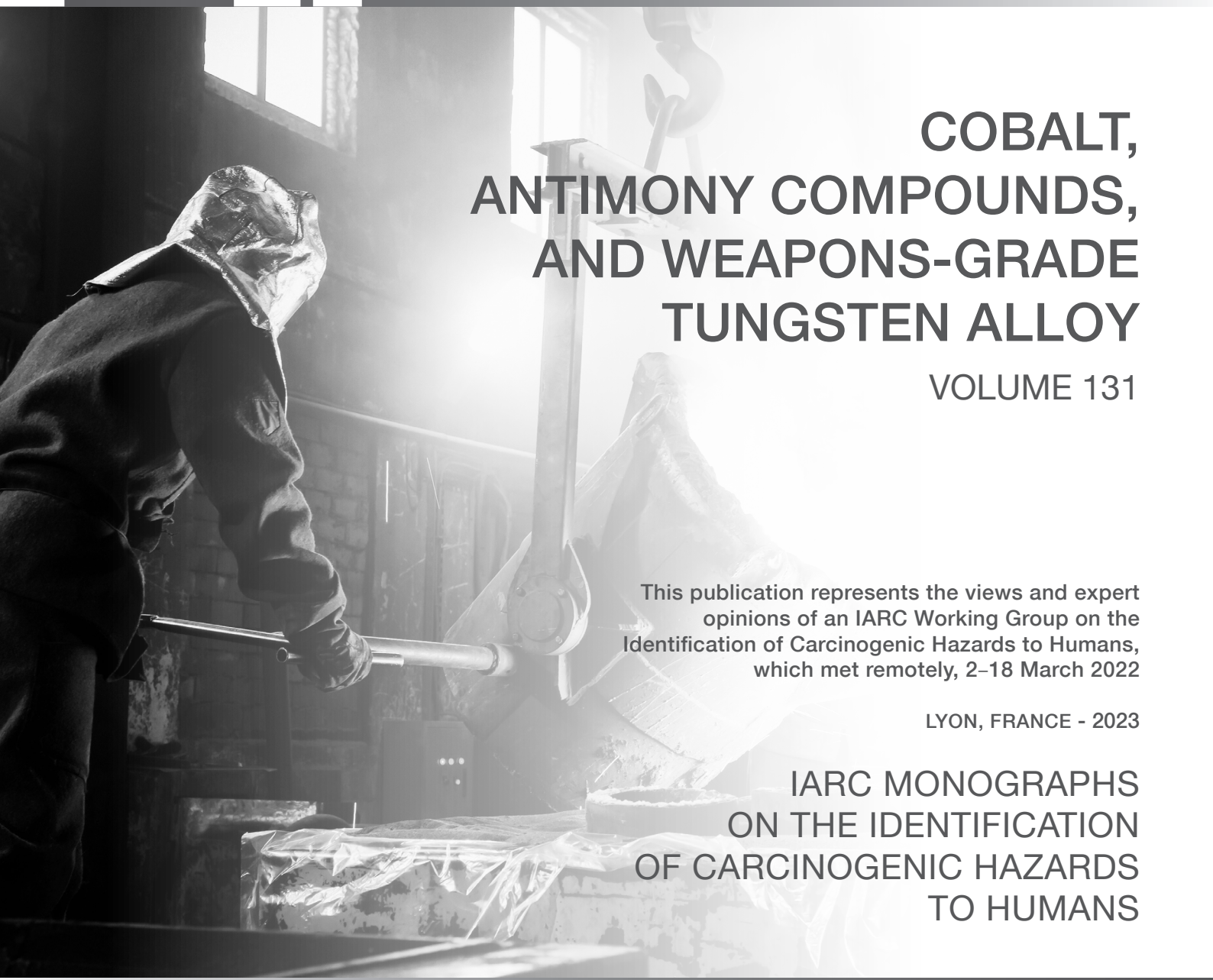

COBALT, ANTIMONY COMPOUNDS, AND WEAPONS-GRADE TUNGSTEN ALLOY

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International Agency for Research on Cancer

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Table S2.6 Epidemiological studies on cancer of other sites, including all sites combined, and exposure to cobalt

Reference Location Enrolment/ follow-up period Study design	Population size, description Exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Moulin et al. (1993) France Enrolment, 1950–1980/ follow-up, 1988 Cohort	1148 men employed in an electrochemical plant producing cobalt and sodium for ≥ 12 mo between 1950 and 1980. Exposure assessment method: exposure to cobalt via all routes (indirectly) was assessed qualitatively and semiquantitatively using company job history records; Exposure metrics: employed ≥ 12 mo between 1950 and 1980, occupational categories, time since first employment (man-years), and duration of employment	Stomach, mortality	Employed in cobalt production (SMR):			Age, calendar period	*Exposure assessment critique*: Key limitations include: non-differential exposure misclassification likely (broad exposure categories). Possible co-exposures identified could not be fully accounted for in analyses. *Other strengths*: clearly defined exposure groups. Analyses in subgroup without loss to follow-up. *Other limitations*: causes of death before 1968 assessed by physicians. Incomplete follow-up among non-French-born.
			All workers	3	0.39 (0.08–1.14)		
			French-born workers	3	0.56 (0.12–1.64)		
		Intestine (except rectum), mortality	Employed in cobalt production (SMR):				
			All workers	2	0.33 (0.04–1.19)		
			French-born workers	1	0.23 (0.01–1.29)		
		Rectum, mortality	Employed in cobalt production (SMR):				
			All workers	0	0 (0–1.12)		
			French-born workers	0	0 (0–1.29)		
		Pancreas, mortality	Employed in cobalt production (SMR):				
			All workers	2	0.59 (0.07–2.12)		
			French-born workers	1	0.41 (0.01–2.30)		
		Urinary bladder, mortality	Employed in cobalt production (SMR):				
			All workers	0	0 (0–1.27)		
			French-born workers	0	0 (0–1.77)		
		Prostate, mortality	Employed in cobalt production (SMR):				
			All workers	7	1.24 (0.50–2.56)		
			French-born workers	7	1.65 (0.67–3.41)		
		Lymphoma (type not specified), mortality	Employed in cobalt production (SMR):				
			All workers	3	1.07 (0.22–3.11)		
			French-born workers	3	1.47 (0.30–4.29)		
		Leukaemia, mortality	Employed in cobalt production (SMR):				
			All workers	2	0.69 (0.08–2.50)		
			French-born workers	1	0.48 (0.01–2.66)		

Table S2.6 (continued)

Reference Location Enrolment/ follow-up period Study design	Population size, description Exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Moulin et al. (1993) France Enrolment, 1950–1980/ follow-up, 1988 Cohort (cont.)		Osteosarcoma, mortality	Employed in cobalt production (SMR):			Age, calendar period	
			All workers	0	0 (0–3.19)		
			French-born workers	0	0 (0–4.51)		
		All cancers combined, mortality	Employed in cobalt production (SMR):				
			All workers	84	0.83 (0.66–1.03)		
			French-born workers	72	1.00 (0.78–1.26)		
		Brain, mortality	Employed in cobalt production (SMR):				
			All workers	5	3.57 (1.16–8.32)		
			French-born workers	4	3.98 (1.08–10.19)		

Table S2.6 (continued)

Reference Location Enrolment/ follow-up period Study design	Population size, description Exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Tüchsen et al. (1996) Denmark Enrolment, factory 1: 1943–1987; factory 2: 1962–1987/ follow-up, 1992 Cohort	874 exposed/520 unexposed; all women working in one of two porcelain factories employed in the plate underglazing departments (exposed to cobalt) and a referent population (unexposed) working in cobalt-free departments in the same factories Exposure assessment method: exposure to cobalt aluminate spinel via all routes (indirectly) was assessed qualitatively using company administrative records Exposure metrics: ever/never employed	Stomach, incidence	Exposure group (SIR):			Age, calendar period	*Exposure assessment critique*: Key strengths include: exposure measurements from the two factories for several years. Key limitations include: non-differential exposure misclassification likely. Possible co-exposure to dusts (quartz?) and nickel at "insignificant" levels not accounted for in analyses. *Other strengths*: long follow-up period. *Other limitations*: the results were not adjusted for confounders, e.g. smoking. High number of emigrant workers. Information bias possible.
			All exposed	1	[1.00 (0.05–4.98)]		
			Factory 1, exposed	1	[1.64 (0.08–8.08)]		
			Factory 2, exposed	0	[0 (0–9.65)]		
			Referents	1	[0.55 (0.03–2.71)]		
		Colon, incidence	Exposure group (SIR):				
			All exposed	2	[0.64 (0.11–2.12)]		
			Factory 1, exposed	1	[0.54 (0.03–2.68)]		
			Factory 2, exposed	1	[0.78 (0.04–3.85)]		
			Referents	4	[0.93 (0.30–2.25)]		
		Rectum, incidence	Exposure group (SIR):				
			All exposed	2	[1.32 (0.22–4.35)]		
			Factory 1, exposed	2	[2.22 (0.37–7.34)]		
			Factory 2, exposed	0	[0 (0–5.92)]		
			Referents	1	[0.46 (0.02–2.25)]		
		Pancreas, incidence	Exposure group (SIR):				
			All exposed	2	[2.06 (0.35–6.81)]		
			Factory 1, exposed	1	[1.72 (0.09–8.50)]		
			Factory 2, exposed	1	[2.55 (0.13–12.65)]		
			Referents	1	[0.74 (0.04–3.63)]		
		Cervix/uterine cervix, incidence	Exposure group (SIR):				
			All exposed	12	2.31 (1.19–4.03)		
			Factory 1, exposed	6	[2.23 (0.91–4.67)]		
			Factory 2, exposed	6	[2.38 (0.93–4.93)]		
			Referents	4	[0.75 (0.24–1.82)]		
		Uterus/uterine corpus, incidence	Exposure group (SIR):				
			All exposed	3	[1.19 (0.30–3.24)]		
			Factory 1, exposed	1	[0.70 (0.04–3.47)]		
			Factory 2, exposed	2	[1.82 (0.30–6.01)]		
			Referents	9	3.02 (1.38–5.73)		

Table S2.6 (continued)

Reference Location Enrolment/ follow-up period Study design	Population size, description Exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Tüchsen et al. (1996) Denmark Enrolment, factory 1: 1943–1987; factory 2: 1962–1987/ follow-up 1992 Cohort (cont.)		Ovary, incidence	Exposure group (SIR):			Age, calendar period	
			All exposed	4	[1.37 (0.43–3.29)]		
			Factory 1, exposed	3	[1.88 (0.51–5.44)]		
			Factory 2, exposed	1	[0.75 (0.04–3.71)]		
			Referents	2	[0.61 (0.10–2.00)]		
		Kidney, incidence	Exposure group (SIR):				
			All exposed	1	[1.00 (0.05–4.98)]		
			Factory 1, exposed	0	[0 (0–6.44)]		
			Factory 2, exposed	1	[2.38 (0.12–11.74)]		
			Referents	1	[0.82 (0.04–4.04)]		
		Urinary bladder, incidence	Exposure group (SIR):				
			All exposed	0	[0 (0–3.46)]		
			Factory 1, exposed	0	[0 (0–6.01)]		
			Factory 2, exposed	0	[0 (0–8.15)]		
			Referents	0	[0 (0–2.76)]		
		Melanoma, incidence	Exposure group (SIR):				
			All exposed	2	[0.80 (0.13–2.65)]		
			Factory 1, exposed	0	[0 (0–3.03)]		
			Factory 2, exposed	2	[1.57 (0.26–5.16)]		
			Referents	4	[2.19 (0.69–5.27)]		
		Non-melanoma skin cancer, incidence	Exposure group (SIR):				
			All exposed	8	[1.33 (0.62–2.53)]		
			Factory 1, exposed	5	[1.55 (0.57–3.44)]		
			Factory 2, exposed	3	[1.08 (0.27–2.94)]		
			Referents	5	[0.83 (0.30–1.83)]		
		NHL, incidence	Exposure group (SIR):				
			All exposed	0	[0 (0–3.78)]		
			Factory 1, exposed	0	[0 (0–7.05)]		
			Factory 2, exposed	0	[0 (0–8.15)]		
			Referents	0	[0 (0–3.67)]		

Table S2.6 (continued)

Reference Location Enrolment/ follow-up period Study design	Population size, description Exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Tüchsen et al. (1996) Denmark Enrolment, factory 1: 1943–1987; factory 2: 1962–1987/ follow-up 1992 Cohort (cont.)		Leukaemia, incidence	Exposure group (SIR):			Age, calendar period	
			All exposed	2	[2.13 (0.36–7.03)]		
			Factory 1, exposed	2	[3.86 (0.64–12.71)]		
			Factory 2, exposed	0	[0 (0–8.73)]		
			Referents	3	[2.75 (0.70–7.49)]		
		All cancers combined, incidence	Exposure group (SIR):				
			All exposed	67	1.20 (0.94–1.52)		
			Factory 1, exposed	34	[1.12 (0.79–1.55)]		
			Factory 2, exposed	33	[1.29 (0.90–1.79)]		
			Referents	60	[0.99 (0.76–1.27)]		
		Brain/CNS, incidence	Exposure group (SIR):				
			All exposed	1	[0.50 (0.03–2.48]		
			Referents	3	[1.68 (0.43–4.59)]		
Sauni et al. (2017) Finland Enrolment, 1968–2004/ follow-up, 2013 Cohort	995 (26 093 person-years); men working at a Finnish cobalt plant 1986–2004 employed for ≥ 1 yr Exposure assessment method: exposure to cobalt via all routes (indirectly) assessed semiquantitatively using company administrative records Exposure metrics: duration and departmental exposure groupings	Stomach, incidence	Duration of employment (SIR):			Age, calendar period	*Exposure assessment critique*: Key limitations include: non-differential misclassification likely. Possible co-exposure to nickel not accounted for in analyses. *Other strengths*: identification of cohort members and follow-up for deaths and emigration were complete. *Other limitations*: the results were not adjusted for confounders beyond age and calendar period.
			> 1 yr	7	2.01 (0.81–4.15)		
			> 5 yr	5	1.83 (0.59–4.26)		
		Colon, incidence	Duration of employment (SIR):				
			> 1 yr	4	0.92 (0.25–2.34)		
			> 5 yr	4	1.16 (0.32–2.96)		
		Rectum, incidence	Duration of employment (SIR):				
			> 1 yr	4	1.05 (0.29–2.69)		
			> 5 yr	3	1.03 (0.21–2.99)		
		Pancreas, incidence	Duration of employment (SIR):				
			> 1 yr	2	0.58 (0.07–2.09)		
			> 5 yr	1	0.37 (0.01–2.07)		
		Melanoma, incidence	Duration of employment (SIR):				
			> 1 yr	1	0.30 (0.01–1.69)		
			> 5 yr	1	0.39 (0.01–2.20)		
		Non-melanoma skin cancer, incidence	Duration of employment (SIR):				
			> 1 yr	3	1.08 (0.22–3.15)		
			> 5 yr	3	1.35 (0.28–3.94)		

Table S2.6 (continued)

Reference Location Enrolment/ follow-up period Study design	Population size, description Exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sauni et al. (2017) Finland Enrolment, 1968–2004/ follow-up, 2013 Cohort (cont.)		Skin (basal cell carcinoma), incidence	Duration of employment (SIR):			Age, calendar period	
			> 1 yr	18	0.94 (0.56–1.48)		
			> 5 yr	12	0.80 (0.41–1.38)		
		Prostate, incidence	Duration of employment (SIR):				
			> 1 yr	33	1.35 (0.93–1.89)		
			> 5 yr	26	1.34 (0.87–1.96)		
		Kidney, incidence	Duration of employment (SIR):				
			> 1 yr	2	0.52 (0.06–1.89)		
			> 5 yr	2	0.67 (0.08–2.40)		
		Urinary bladder, incidence	Duration of employment (SIR):				
			> 1 yr	9	1.88 (0.86–3.56)		
			> 5 yr	6	1.60 (0.59–3.47)		
		Urinary bladder, incidence	Exposure group (SIR):				
			Variable exposure	0	0 (0–15.0)		
			Low	6	3.07 (1.12–6.67)		
			Moderate	0	0 (0–12.2)		
			High	3	1.30 (0.27–3.78)		
		NHL, incidence	Duration of employment (SIR):				
			> 1 yr	3	0.68 (0.14–1.97)		
			> 5 yr	3	0.88 (0.18–2.56)		
		Leukaemia, incidence	Duration of employment (SIR):				
			> 1 yr	3	1.42 (0.29–4.15)		
			> 5 yr	3	1.90 (0.39–5.54)		
		All cancers combined, incidence	Duration of employment (SIR)				
			> 1 yr	92	1.00 (0.81–1.22)		
			> 5 yr	77	1.08 (0.85–1.34)		

Table S2.6 (continued)

Reference Location Enrolment/ follow-up period Study design	Population size, description Exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sauni et al. (2017) Finland Enrolment, 1968–2004/ follow-up, 2013 Cohort (cont.)		All cancers combined, incidence	Exposure group (SIR):			Age, calendar period	
			Variable exposure	7	1.39 (0.56–2.87)		
			Low	42	1.11 (0.80–1.50)		
			Moderate	4	0.66 (0.18–1.70)		
			High	39	0.90 (0.64–1.22)		
		Brain/CNS, incidence	Duration of employment (SIR):				
			> 1 yr	2	0.71 (0.09–2.56)		
			> 5 yr	2	0.97 (0.12–3.49)		
Rodrigues et al. (2020) New York, Vermont, California, USA 1965–1999 Nested case–control	Cases: 120; cancer deaths (1965–1999) or incident cancer diagnoses (1976–1999) among a cohort of 126 836 employees at three facilities manufacturing semiconductors and electronic storage devices Controls: 1028; for each case 10 controls were selected by incidence density sampling and matched by year of birth, facility, sex, and race Exposure assessment method: exposure to cobalt through all routes (indirectly) was assessed quantitatively based on company records and using a JEM in employees at three US facilities engaged in semiconductor and electronic storage device manufacturing	Brain/CNS, incidence and mortality	Cumulative cobalt exposure, East Fishkill, New York, facility (OR):			Age, year of birth, sex, race	*Exposure assessment critique*: Key strengths include: JEM co-exposures were estimated. Key limitations include: non-differential misclassification likely. *Other strengths*: company records from three facilities producing semiconductors and electronic storage devices. *Other limitations*: both cases and controls should have worked for ≥ 5 yr before index date. Co-exposures not accounted for in analyses.
			0	22	1		
			> 0 to < 0.055 mg/m³-year	11	1.97 (0.90–4.29)		
			0.055–0.44 mg/m³-year	8	1.52 (0.63–3.65)		
			> 0.44 mg/m³-year	12	1.58 (0.73–3.42)		
			Trend-test *P*-value, 0.04				
		Brain/CNS, mortality	Cumulative cobalt exposure, Burlington, Vermont, facility (OR):				
			0	6	1		
			> 0 to < 0.055 mg/m³-year	2	1.76 (0.33–9.55)		
			0.055–0.44 mg/m³-year	5	1.79 (0.49–6.60)		
			> 0.44 mg/m³-year	4	1.01 (0.26–3.90)		
			Trend-test *P*-value, 0.49				

Table S2.6 (continued)

Reference Location Enrolment/ follow-up period Study design	Population size, description Exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Rodrigues et al. (2020) New York, Vermont, California, USA 1965–1999 Nested case–control (cont.)		Brain/CNS, incidence and mortality	Cumulative cobalt exposure, San Jose, California, facility (OR):			Age, year of birth, sex, race	
			0	30	1		
			> 0 to < 0.055 mg/m^3-year	10	0.94 (0.44–2.02)		
			0.055–0.44 mg/m^3-year	9	0.95 (0.43–2.10)		
			> 0.44 mg/m^3-year	0	NA		
			Trend-test *P*-value, 0.62				
Duan et al. (2020) USA Enrolment, 1999–2014/ follow-up, 2015 Cohort	26 056 participants age ≥ 20 yr, not pregnant; with full covariate, mortality, and metal data drawn from the NHANES 1999–2014 survey sample of 82 091 participants; followed for mortality through 2015 (mean follow-up 7.4 yr); mean age at baseline 45.9 yr. Exposure assessment method: exposure to cobalt through all routes was assessed quantitatively from a single urine sample; WQS estimates were made of the metal mixture (including urinary levels of barium, cadmium, caesium, molybdenum, lead, titanium, antimony, tungsten, and uranium, and blood levels of mercury, lead, and cadmium)	All cancers combined, mortality	Urinary cobalt level (RR):			Sex, age, age^2, ethnicity, urinary creatinine, education, PIR, cotinine category, BMI, physical activity, CVD, diabetes, 9 other metals (barium, cadmium, caesium, molybdenum, lead, antimony, titanium, tungsten, uranium)	*Exposure assessment critique*: Key strengths include: single urine samples were collected before the development of the outcomes. Key limitations include: urinary levels of cobalt have relatively short half-lives, and hence, reflect recent rather than long-term exposure, and non-differential exposure misclassification likely. Co-presence and relative weights of other metals were examined (however, other possible carcinogenic exposures were not assessed).
			Median, 0.35 µg/L; per 1 µg/L increase	560	1.05 (0.85–1.30)		
		All cancers combined, mortality	Urinary cobalt level (RR):			Sex, age, age^2, ethnicity, urine creatinine	
			Median, 0.35 µg/L; per 1 µg/L increase	560	1.23 (1.03–1.46)		

Table S2.6 (continued)

Reference Location Enrolment/ follow-up period Study design	Population size, description Exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Duan et al. (2020) USA Enrolment, 1999–2014/ follow-up, 2015 Cohort (cont.)		All cancers combined, mortality	Urinary cobalt level (RR): Median, 0.35 µg/L; per 1 µg/L increase	560	1.16 (0.97–1.39)	Sex, age, age^2, ethnicity, urine creatinine, education, PIR, cotinine category, BMI, physical activity	*Other strengths*: metals considered as single elements and as a mixture taking into account collinearity. participants drawn from the US general population. Relatively large sample size. *Other limitations*: the relatively short follow-up period yielded a small number of death outcomes. Potential for exposure misclassification because concentrations in the urine may not reflect the actual exposure. Most metals have a short half-life, which reflects recent exposure. All cancers combined is a heterogeneous outcome, mortality does not reflect incidence of cancers with low mortality rates.
		All cancers combined, mortality	Urinary cobalt level (RR): Median, 0.35 µg/L; per 1 µg/L increase	560	1.17 (0.98–1.41)	Sex, age, age^2, ethnicity, urine creatinine, education, PIR, cotinine category, BMI, physical activity, CVD, diabetes	

Table S2.6 (continued)

Reference Location Enrolment/ follow-up period Study design	Population size, description Exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Li et al. (2021) China Enrolment, 2008–2010/ follow-up, 2018 Cohort	4573 participants were from the DFTJ cohort, which comprised 27 009 retired workers of an automotive-manufacturing company; 5173 individuals with type 2 diabetes mellitus were enrolled at baseline; after exclusion 4573 participants were included in the study Exposure assessment method: exposure to cobalt through all routes was assessed quantitatively in blood in a sample of participants from the DFTJ cohort	All cancers combined, incidence	Plasma cobalt (μg/L) (HR): Quartile 1 Quartile 2 Quartile 3 Quartile 4 Trend-test *P*-value, 0.03	 NR NR NR NR	 1 0.96 (0.76–1.20) 0.79 (0.62–1.00) 0.8 (0.63–1.02)	Age, sex, BMI, smoking status, drinking status, education, physical activity, family history of cancer, use of antidiabetic, duration of diabetes	*Exposure assessment critique*: Key limitations include: non-differential exposure misclassification likely, as the timing of exposure measurement may be outside the relevant time window of exposure for cancer outcome under study. *Other strengths*: sociodemographic, lifestyle factors and traditional cancer risk factors were adjusted to minimize potential confounders. Modelling used to account for multiple plasma metals simultaneously. *Other limitations*: only one measurement of fasting plasma metals collected at baseline. The potential effect of diabetes itself on metal levels cannot be completely ruled out.

BMI, body mass index; CI, confidence interval; CNS, central nervous system; CVD, cardiovascular disease; DFTJ, Dongfeng-Tongji; HR, hazard ratio; JEM, job-exposure matrix; mo, month; NA, not available; NHANES, National Health and Nutrition Examination Survey; NHL, Non-Hodgkin lymphoma; OR, odds ratio; PIR, poverty-to-income ratio; RR, relative risk; SIR, standardized incidence ratio; SMR, standardized mortality ratio; US, United States; WQS, weighted quantile sum; yr, year.

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