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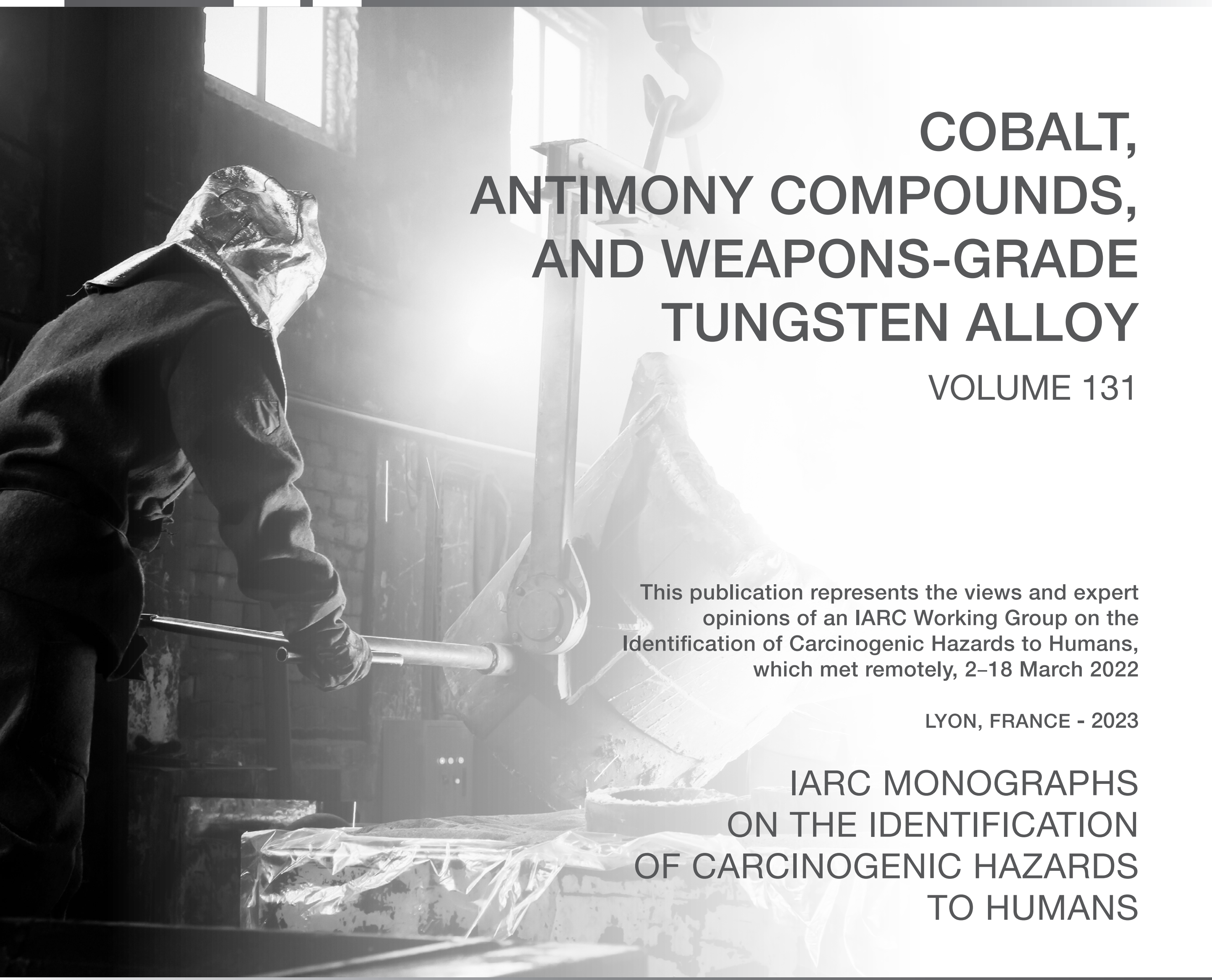

COBALT, ANTIMONY COMPOUNDS, AND WEAPONS-GRADE TUNGSTEN ALLOY

VOLUME 131

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International Agency for Research on Cancer

World Health Organization

Table S1.18 Exposure assessment review and critique for epidemiological studies on cancer and exposure to cobalt

Reference and outcome	What was the study design?	Relevant form(s) of cobalt in exposed population[a]	What methods were used for the exposure assessment? (including data source, environmental and biological measurements etc.)	What was the exposure context? Specify period over which exposure data gathered, and how historical exposures were accounted for (if relevant)	Was exposure assessment qualitative, semiquantitative, or quantitative?	Concerns noted on sampling and collection protocols for metal measurement	What routes of exposure were assessed?	What exposure metrics were derived for use in analyses (e.g. average exposure, exposure duration, cumulative exposure etc.)?	What was the timing of exposure relative to the outcome?	Was there potential for co-exposures to other carcinogens? If yes, were these accounted for in analyses?	Was there potential for differential or non-differential exposure misclassification?
Bai et al. (2019) Incidence: Lung	Nested case–control	Not specified	Plasma blood levels of cobalt	Work for a motor corporation; require detail on Dongfeng-Tongji cohort study; authors cite Wang et al. (2013d)	Quantitative	Timing of sample collection was after diagnosis and may not reflect exposure prediagnosis	All routes (indirectly)	Continuous blood cobalt levels (µg/L)	Exposure occurred before outcome	Occupational co-exposures not discussed Single- and multiple-metal models run for 10 essential metals	Differential misclassification: possible, as individuals with a diagnosis may have different exposures postdiagnosis than prediagnosis Non-differential misclassification: likely, as the timing of exposure measurement may be outside the relevant time window of exposure for cancer outcome under study
Cuckle et al. (1980) Mortality: Lung cancer	Retrospective cohort	Cobalt metal Cobalt oxides Cobalt salts	Company administrative records to assess job histories	Employment 12 months or more between 1933 and 1960 in departments manufacturing nickel and cobalt salts (wet treatment plant: nickel sulfate, copper sulfate, cobaltic hydrate, and precious metal concentrates; Chemical Products Department: range of compounds and salts of nickel, cobalt, and selenium) No exposure data collected	Qualitative for metric 1; semiquantitative for metrics 2 and 3	N/A: exposure not directly assessed	All routes (indirectly)	1. Employment for 12 months or more 2. Time since first exposure (employment) (man-years): < 20 ≥ 20 3. Duration of employment (years) 1–5 ≥ 6	Exposure occurred before outcome	Yes Nickel, “precious metals” Not accounted for in analyses (exposure metrics not specific to a particular contaminant)	Differential misclassification: unlikely Non-differential misclassification: likely (broad exposure categories)
Duan et al. (2020) Mortality: Overall cancer	Cross-sectional (NHANES 1999–2014)	Not intended to be specified (general population study)	Cobalt metal in urine measured by ICP-MS	Heavy metals (including cobalt) assessed for a sample of 26 056 participants drawn from the NHANES 1999–2014 survey (US general population)	Quantitative	Note: values lower than limit of detection were replaced by square root of limit of detection divided by 2	All routes (indirectly)	1. Single-metal analysis, constructing separate models for each blood or urine metal 2. Multiple-metal analysis, including all metals in blood or urine simultaneously 3. Weighted quantile sum analysis, identifying important metals and estimating the mixture effect of metals (separate models built for blood and urinary metals)	Exposure occurred before outcome Note: metals were measured in NHANES 1999–2014 and mortality was assessed 1999–2015, therefore potentially short time period between exposure and outcome	Yes, other metals Weighted quantile sum regression to determine whether a mixture of blood or urine metals was associated with mortality and, if so, which metals in the mixture most likely drove the association with mortality	Non-differential misclassification: likely Timing of exposure measurement may be outside the relevant time window of exposure for cancer mortality
Dufresne et al. (1996)	Case series (*n* = 5)	Not specified	Cobalt and other inorganic particles and fibres were quantified	Lung tissue analysis was completed to quantify metal rich particles (including	Quantitative assessment was employed, but the	Exposure was assessed posthumously in a	Inhalation, primarily	Millions of particles (> 0.1 µm) per mg of lung tissue (dry weight)	The exposure was assessed	Co-exposures (including smoking, asbestos and other	N/A due to study design

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Lung; mesothelioma			in lung tissues from five deceased individuals who worked in an aluminium smelter	cobalt) in the lung tissue of 5 decedents (4 who died from mesothelioma, 1 who died from lung cancer)	cobalt analysis is reported qualitatively	small number of cases			after the outcome	non-fibrous particles) were described but there was no epidemiologic analysis; the causes of death for the cases included suggest significant asbestos exposure	
Grimsrud et al. (2005) Incidence: Lung	Nested case–control	Cobalt metal	Company administrative records to assess job histories; quantitative measurements of cobalt used to produce cobalt:nickel ratios using a previously developed nickel JEM Cobalt sampling data used to calculate 8-hour time-weighted arithmetic averages for the departments in question; ratio between cobalt and total nickel in air computed for departments and periods with measured values (cobalt amounted to approximately 4–15% of total nickel except for cobalt electrolysis, where cobalt tripled nickel); departments with no measurements used ratio of 7.1% (average for all departments exclusive of cobalt electrolysis)	Cases consisted of individuals diagnosed with lung cancer between 1952 and 1995, with minimum employment of 1 year in a Norwegian nickel refinery treating sulfidic nickel copper concentrate (consisting of approximately 45% nickel, 25% copper, 23% sulfur, 2% cobalt, < 2% iron, and precious metals) Cobalt likely always present with nickel in raw materials and intermediates at refinery Nearly 3500 personal samples analysed for cobalt between 1982 and1994, as part of routine sampling	Qualitative and quantitative	30% of measurements were below the limit of detection and substituted by 1/2 the limit of detection	All routes (indirectly)	Cumulative exposure to cobalt for each participant calculated as sum of products of time- and department-specific concentrations and corresponding durations [$\mu g/m^3$ × years]: unexposed, low, medium, and high Duration in years Time of first employment at refinery (pre-/post-1930) Duration of employment in 3 major groups of departments at the refinery	Exposure occurred before outcome	Yes Nickel (primary exposure of study interest), arsenic, asbestos, and sulfuric acid mists present in refinery Sulfuric acid mists noted in the refinery Positive correlation between cobalt and nickel (other correlations not assessed) Nickel adjusted for cobalt (but cobalt not adjusted for nickel) “A possible effect of cobalt could not be distinguished from the one earlier ascribed to insoluble forms of nickel” Occupations outside of the refinery held for 1+ year assessed for carcinogenic risk (82 cases and 182 controls reported such circumstances)	Differential misclassification: no Non-differential misclassification: yes, JEM + time trends in cobalt:nickel ratios were assumed to follow the trends of the corresponding ratio in the raw materials, or the ratio between the produced amounts of the 2 metals
Hogstedt & Alexandersson (1990) Mortality:	Retrospective cohort	Cobalt metal	Company administrative records and “consultants with long-term employment in each company” to assess job histories, as	Employment at 3 Swedish hard-metal plants for ≥ 1 year Exposure period not clearly stated; company production started in late 1930s, early	Semiquantitative	Air sampling methods not reported here (other references provided)	All routes (indirectly)	Exposure categories (eventually collapsed to “high” vs “low” and “no exposure” in final analyses) based on job/work location and air measurements collected over time (those with multiple employment	Exposure occurred before outcome	Yes Tungsten, titanium, tantalum, and niobium carbides referred to, also chromium,	Differential misclassification: unlikely Non-differential misclassification: likely (broad exposure categories

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Lung cancer and others			well as air measurements	1940s, and 1950s (deaths were examined 1951–1982) Cobalt air concentration data (average µg/m^3 levels) collected between 1940 and 1982 were used to develop/validate exposure categories				periods placed in highest exposure category)		molybdenum, and nickel Not accounted for in analyses	limited to one period of employment for those with multiple jobs)
Kennedy et al. (2017) JEM used in McElvenny et al. (2017), Marsh et al. (2017a,b)	N/A: exposure assessment paper		JEM constructed for cobalt for period 1952–2014, consisted of job class categories (based on job titles and processes performed) and exposure estimates calculated from company IH measurements (cobalt, 6175) Site visits at 14 US and 9 European plants operated by 3 companies to review work history/IH records and observe plant operations; 8 US sites kept due to incomplete records from 4; 1 Austrian, 3 German, 3 Swedish, 2 United Kingdom Job classes created from knowledge of production processes, info from plant personnel, review of work history record job combinations (derived from job and department titles, job and department codes, and other relevant identifying info) Combined with IH data from all plants (including the 4 excluded US plants) pooled to generate exposure estimates	Workers at 3 companies and 17 manufacturing sites in 5 countries between 1926 and 2014 (varying dates across plants) Decreasing time trends identified and applied for 8 cobalt job classes (see p. e301–302 for details)	Quantitative	Different sampling devices used across countries (with impacts on fractions and aerosol properties), sensitivity analysis performed; exposure intervals were insensitive to rather large correction factors therefore both total aerosol and inhalable fraction measurements used without correction (see paper for detail)	All routes (indirectly)	Exposure intervals developed and midpoints applied to JEM job classes for use in exposure-related analyses (exposure intervals by job class presented in Table 3)	N/A	Yes JEMs for nickel and tungsten also developed by the authors; may not be possible to separate out these effects from effect of cobalt Authors identify concurrent exposures to carbon black, tungsten carbide, and WC-Co	Non-differential misclassification: likely (JEM) Some job classes with limited or completely censored data necessitated exposure interval assignment using professional judgement
Kresovich et al. (2019) Breast cancer	Case series	Not intended to be specified	Residential address in 2002 was linked with census-tract level data	Population-based study of 696 women with a breast cancer diagnosis (2005–2008) from	Quantitative	Short time window (3–6 years) between exposure assessment	Inhalation	Cobalt in air (ng/m^3)	Exposure was assessed	Yes The NATA data contain information on	Differential misclassification: unlikely

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		(general population study)	on ambient air concentrations of heavy metal from the US EPA NATA	the Breast Cancer Care in Chicago (BCCC) study were included		(2002) and outcome ascertainment (2005–2008)			before the outcome	several other metals (antimony, arsenic, beryllium, cadmium, chromium, lead, manganese, mercury, nickel, selenium) that were quantified and considered in the analyses (principal component analysis)	Non-differential misclassification: likely; census-tract level concentrations are very broad proxies for personal exposures and methods do not account for historical changes; use of a single residence at one point in time may also introduce non-differential exposure misclassification
Lasfargues et al. (1994) Mortality: Lung cancer All cancers Larynx Buccal cavity, pharynx, and larynx Oesophagus Trachea, bronchus, and lung Leukaemia	Retrospective cohort	Cobalt metal	Company administrative records to assess job histories	Employment for ≥ 1 year between 1 January 1956 and 31 December 1989, at a plant producing hard-metal tools (Workshop A included powders mixing, pressing, soft carbide machining; Workshop B included maintenance, hard carbide machining)	Qualitative for metric 1; semiquantitative for metrics 2 and 3	N/A: exposure not directly assessed	All routes (indirectly)	1. Categorical assignment based on job histories/work locations/prior atmospheric and biological measurements: - Unknown - Non-exposed directly to hard-metal dust (mainly clerical workers) - Low exposure (maintenance works outside the workshops and to hard carbide finishing working places with technical preventive measures) - Medium exposure (hard carbide finishing without protection device, soft carbide machining with protection device, workplace at oven) - High exposure (powder mixing, press, non-protected soft carbide machining) 2. Duration of employment (years)*: 1–9; 10–19; 20+ 3. Time since first employment (years)*: same as previous categories *for medium and high exposure categories only	Exposure occurred before outcome	Possibly Tungsten metal powder, tungsten, titanium, tantalium, and nobium carbides Authors state: “Possible previous exposure to hard-metal dust in another plant was also taken into account”, as discussed for one lung cancer case	Differential misclassification: unlikely Non-differential misclassification: likely; (broad exposure categories,“Nonclerical workers employed prior to 1974 and for which no detailed job history existed were all assigned to degree 3”; workers employed in several workplaces assigned highest degree of exposure)
Li et al. (2021a) Incidence: Lung Digestive Hepatobiliary	Prospective cohort (subset)	Not specified	Fasting blood samples obtained at enrolment baseline to assess plasma levels of 9 essential metals (iron, copper, zinc, selenium, chromium, manganese, molybdenum, cobalt, and nickel) and 3 heavy metals (arsenic, cadmium, and lead)	Study participants a sample (5173) from Dongfeng-Tongji cohort, an ongoing prospective study of 27 009 retired workers from Dongfeng Motor Corporation	Quantitative	Only one measurement of fasting plasma levels collected at baseline “plasma metals are not suitable biomarkers for internal exposure to all metals” Note: half of detection limit used	All routes (indirectly)	Continuous (metal levels log-transformed) Single- and multiple-metal models constructed Quantile g-computation to estimate potential joint impacts of metals and proportion of positive or negative partial effect for each metal using ln-transformed metal concentrations	Exposure occurred before outcome	Yes, other metals Spearman’s rank used to explore correlations among plasma metal levels; cobalt most strongly correlated with chromium (0.58); quantile g-computation used to assess joint impacts of metals	Differential misclassification: unlikely Non-differential misclassification: likely; the timing of exposure measurement may be outside the relevant time window of exposure for cancer outcome under study

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						to impute values below the limit of detection					
Marsh et al. (2009) Mortality: Multiple sites	Retrospective cohort	Not specified	Company administrative records to assess job histories, cross-checked with union contract books JEM based on relative exposure intensities over time; job and time-specific exposures to 6 agents: lead, sulfur dioxide, arsenic, cadmium, dust, and cobalt, assessed using a modification of the "process-based projection of exposure measurements"; process info gathered in the original Copperhill study [Enterline et al., 1986, 1987] + additional documentation from company and employee interviews relating to processes and process changes over study period	Employment for ≥ 3 years at copper smelter, mill, or sulfur operations in Copperhill, Tennessee, between 1/1/46 and 4/30/96 Cobalt assessed 54.2% of subjects had been only employed in the smelter; most had mixed employment in smelter, acid plant, or mill/mine	Qualitative, semiquantitative	N/A: exposure not directly assessed Note: 54.2% of subjects had been employed only in the smelter; most remaining subjects had mixed employment in the smelter, acid plant, or mill/mine	All routes (indirectly)	Exposed/unexposed (results of this two-category analysis used to select any cause of death category that revealed ≥ 50% (SMR, 150) mortality excess in "exposed" and corresponding baseline or deficit mortality experience (SMR, 100) in "unexposed"; none resulted in selection of cobalt exposure subgroup) (this selection criterion excluded cobalt from further analysis)	Exposure occurred before outcome	Yes "exposure to four agents (lead, arsenic, cadmium, and cobalt) never occurred alone in any job" "647 subjects (3786 person-years) were exposed at some time to jobs involving all six agents"	Non-differential misclassification: likely; "While the task involved in some job titles resulted in a very broad distribution of exposures, the personnel assigned to these tasks could not be specifically identified, resulting in high exposure potential for some subgroups in the job classes."
Marsh et al. (2017a) Mortality: Lung	Retrospective cohort + nested case–control	Cobalt metal	JEM: see Kennedy et al. (2017)	All those employed at 8 US hard-metal plants from 1952 to 2008 (last year of work histories collected); earliest year of hire was 1941 More than 70% of cohort worked > 1 year within the company; less than half worked > 5 years Tungsten, cobalt, and nickel assessed	Qualitative, quantitative See Kennedy et al. (2017)	See Kennedy et al. (2017) Across plants, mean exposure levels well below recommended standards (impacts on exposure contrast?)	All routes (indirectly)	Comparing workers exposed only to tungsten carbide with those exposed only to WC-Co Ever/never employed Duration of employment (years): < 1; 1–4; 5–19; 20+ Time since first employment (years): < 20, 20–29, 30–39, 40+ Duration of employment × time since first employment All other categories > 5 years, > 20 years > 10, > 20	Exposure occurred before outcome	Yes Tungsten, nickel, asbestos, ionizing radiation, arsenic, soot/diesel exhaust, and roof tar/asphalt fumes For tungsten, cobalt, and nickel, "all workers had some exposure to each agent in every job" Workers exposed only to tungsten carbide were	Non-differential misclassification: likely (JEM based on cross-site/country measurements) (see also Kennedy et al., 2017)

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								> 5, > 30 > 10, > 30 Cumulative exposure = number of days in each job and estimated average daily exposure (in unit-years) Average intensity of exposure = ratio of cumulative exposure to duration (in units) These metrics also computed using 15-year lag period Qualitative analysis: 3 mutually exclusive groups: tungsten carbide only; WC-Co only; mixed tungsten carbide with and without cobalt		compared with those exposed only to WC-Co (in 1 plant only)	
Marsh et al. (2017b) Mortality: Lung	Retrospective cohort + nested case–control	Cobalt metal	JEM: see Kennedy et al. (2017)	Workers at 3 companies and 17 hard-metal production sites in 5 countries with work history periods between 1926 and 2014 (varying dates across plants) Only 45% of cohort worked 5 years or more within the hard-metal companies assessed	Qualitative and quantitative	See Kennedy et al. (2017)	All routes (indirectly)	Qualitative: 4 categories of pre/post-sintering jobs examined in relation to levels of tungsten and/or cobalt and/or nickel powder exposure: pre-sintering only, post-sintering only, mixed pre/post-sintering, and no pre/post-sintering jobs Quantitative: see Marsh et al. (2017a)	Exposure occurred before outcome	Yes Nickel, tungsten carbide, and WC-Co For tungsten, cobalt, nickel, "all workers had some exposure to each agent in every job"	Non-differential misclassification: likely; (JEM based on cross-site/country measurements) (see also Kennedy et al., 2017)
McElvenny et al. (2017) Mortality: Lung	Retrospective cohort + nested case–control	Cobalt metal	Company administrative records to assess job histories; all available occupational hygiene records for factories A and B incorporated into multicountry JEM, see Kennedy et al. (2017)	Employees working at two hard-metal manufacturing sites in the United Kingdom: Factory A, manufacture started in 1931 but job histories only to 1970; between the 1970s and 2010 there were two plants, one preparing ready-to-press powder and other producing metal products using this powder; Factory B, production of hard-metal products and inserts from ready-to-press powder started in 1966 Follow-up period was 1980–2014; 8.8% of cohort was hired before 1970	Qualitative (cohort), quantitative (case–control)	See Kennedy et al. (2017)	All routes (indirectly)	Cohort: ever/never employed at Factory A or B? Case–control: ever/never not possible; duration of exposure in years assessed (unclear if JEM was actually applied?)	Exposure occurred before outcome (note: 3 of the lung cancer cases had durations of employment and time since first exposure of < 10 years)	Yes Nickel, tungsten	Non-differential misclassification: likely; JEM, also missing workers due to gaps in historic employment data (particularly early workers) for Factories A and B
Mérida-Ortega et al. (2022)	Case–control, population-based	Not intended to be	Biological samples	Urinary cobalt was assessed (along with other metals)	Quantitative	The use of spot urine samples may not	All routes	Cobalt in urine (μg/g creatinine)	Exposure was assessed after	Yes	Differential misclassification: unlikely

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		specified (general population study)		among women (452 cases and 439 controls) in some states of northern Mexico		have captured an appropriate exposure window for the outcome under study			the outcome, but before treatment commenced	There was potential for exposure to other metals and trace elements, which were measured in this study and accounted for in the statistical analysis (principal component analysis)	Non-differential misclassification: likely; the use of spot urine samples collected at baseline
Morfeld et al. (2017) Mortality: Lung	Retrospective cohort	Cobalt metal	Job history information and IH air measurements used to generate 2 JEMs applied in analyses: 1. 3 similar exposure groups categorized according to department, jobs, and tasks per plant; 3 categories finally collapsed into 2 (low and high) 2. 29 job class numbers verified by company Environmental Health and Safety experts Log-linear regression model fitted to the adjusted measurement data	Employment for ≥ 6 weeks at 3 German hard-metal plants (start of production in 1926, 1960, and 1971) 1443 (989 area; 454 personal) IH measurements collected 1970–2012 used to construct exposure profiles Backward extrapolation applied in two ways (see paper for detail)	Qualitative (external comparisons) and quantitative (internal)	Details on IH sampling not provided 28% of hygiene measurements (cobalt and other) reported to be below detection limits	All routes (indirectly)	External comparisons: Employment Internal comparisons: Cumulative exposure in mg/m^3 × years Long-term mean exposure Duration of exposure Exposures lagged by 0, 5, 10, 15, and 20 years	Exposure occurred before outcome	Yes Exposures to nickel, tungsten, respirable, and inhalable dust simultaneously into account applying low backward extrapolation based on similar exposure group-JEM	Differential misclassification: unlikely Non-differential misclassification: likely (JEM)
Moulin et al. (1993) Review also based on prior study by Mur et al. (1987) Mortality: Overall cancer Lung Brain Others (see paper)	Retrospective cohort	Cobalt metal Cobalt salts Cobalt oxides	Company administrative records to assess job histories	Employment for ≥ 1 year between 1950 and 1980 at an electrochemical plant specializing in cobalt and sodium production “The cobalt metal manufacturing process also includes oxides and cobalt salts production” (Mur et al., 1987)	Qualitative for metrics 1 and 2; semiquantitative for metrics 3 and 4	N/A: exposure not directly assessed	All routes (indirectly)	1. Ever employed (12+ months) (analyses examined (A) all workers, excluding person-years of foreign-born > 75, and (B) workers born in France) 2. Occupational categories (4): Cobalt production Sodium production Maintenance Administration 3. Duration of exposure (employment) (years) < 10 10–19 20–29 > 30	Exposure occurred before outcome	Yes “Cobalt ore contains arsenic and nickel, and arsenic is added during the cobalt production process” (Mur et al., 1987); “asbestos exposure may have occurred, particularly in sodium areas” (Moulin et al., 1993) (authors attempted to address asbestos issue with mutually exclusive occupational subgroups)	Differential misclassification: unlikely Non-differential misclassification: likely (broad exposure categories)

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								4. Time since first exposure (employment) (years) Same categories as for duration			
Moulin et al. (1998) Mortality: Lung	Retrospective cohort + nested case–control	Cobalt metal	Company administrative records to assess job histories (cohort) + interviews with colleagues and JEM based on expert knowledge, interviews with co-workers	Employment for ≥ 3 months in any of 10 factories of the hard-metal industry, from opening (variable) to 31 December 1991 Case–control study: “qualitative definition of cobalt exposure was 1) simultaneous exposure to cobalt and tungsten carbide specific to hard-metal manufacture and 2) other cobalt exposure resulting from other production activities” Linear regression showed significant increasing trends between atmospheric cobalt levels measured 1971–1984 (see sampling and collection column) (excluding cobalt powder manufacturing workshop) and cobalt levels assigned to JEM	Qualitative (cohort), semiquantitative (case–control)	744 atmospheric concentration measurements of cobalt in 3 factories considered for matrix validation: 382 short-duration (15–20 minute) area samples gathered 1971–1983; 362 (of which 264 personal) long-duration (4–8 hours) gathered between 1982 and 1994	All routes (indirectly)	Cohort: ever/never employment Case–control: maximum intensity score coded over job history Duration of exposure (years) at intensity = / > 2: < 10, 10–20, > 20 Estimated cumulative exposure (expressed as either unweighted: intensity × duration, or frequency weighted: intensity × duration × frequency), divided into quartiles of exposure distribution among controls	Exposure occurred before outcome	Yes Case–control: 1) Simultaneous exposure to cobalt and tungsten carbide specific to hard-metal manufacture; 2) other cobalt exposure resulting from other production activities (“cobalt alone or simultaneously with agents other than tungsten carbide”)	Differential misclassification: unlikely Non-differential misclassification: likely; cohort: broadly defined exposure categories; case–control: use of JEM
Moulin et al. (2000) Mortality: Lung	Retrospective cohort + nested case–control	Cobalt metal	Cohort: company administrative records to assess employment (cohort) Case–control: administrative records for job histories and JEM based on expert knowledge, interviews with co-workers, previous measurements in French factories, literature review used to assign semiquantitative estimates of exposure to metals (iron, chromium and/or nickel, and cobalt) and/or their compounds, acid mists, polycyclic aromatic hydrocarbons, silica, and asbestos	Employment for ≥ 1 year in a French factory producing stainless and alloyed steel, between 1 January 1968 and 31 December 1991 (exposures/employment may date back to 1920s) No atmospheric measurements available for the employment period considered; JEM constructed to somewhat account for changes in exposure over time by job period (based on workplace interviews) Agent: cobalt compounds used in steel production	Qualitative (cohort), qualitative (work area) and semiquantitative (JEM) (case–control)	N/A: exposure not directly assessed	All routes (indirectly)	Cohort: ever/never employment Case–control: Categorical JEM based on: Maximum intensity score over job history (0 = none; 1 = low; 10 = medium; 100 = high) Frequency: 1–10 (i.e. 10–100% of working time) Probability of accuracy: 1 = low; 2 = medium; 3 = high Duration of exposure (years): < 10, 10–19, 20–29, 30+ Cumulative exposure: lifetime sum of either intensity × duration (i.e. “frequency-unweighted cumulative dose”), or intensity × duration × frequency (i.e. “frequency-weighted cumulative dose”) divided into quartiles based on exposure distribution among controls	Exposure occurred before outcome	Yes Cobalt moderately correlated with chromium and/or nickel as classified by JEM	Differential misclassification: unlikely Non-differential misclassification: likely: cohort: broadly defined exposure categories; case–control: use of work area categories and JEM

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Reference and outcome	What was the study design?	Relevant form(s) of cobalt in exposed population[a]	What methods were used for the exposure assessment? (including data source, environmental and biological measurements etc.)	What was the exposure context? Specify period over which exposure data gathered, and how historical exposures were accounted for (if relevant)	Was exposure assessment qualitative, semiquantitative, or quantitative?	Concerns noted on sampling and collection protocols for metal measurement	What routes of exposure were assessed?	What exposure metrics were derived for use in analyses (e.g. average exposure, exposure duration, cumulative exposure etc.)?	What was the timing of exposure relative to the outcome?	Was there potential for co-exposures to other carcinogens? If yes, were these accounted for in analyses?	Was there potential for differential or non-differential exposure misclassification?
								10-year lag period applied (last 10 years of exposure ignored)			
Niehoff et al. (2021) Incidence: Breast	Case–cohort	Not intended to be specified (general population study)	Concentrations of 15 metals (aluminium, arsenic, cadmium, cobalt, chromium, copper, iron, manganese, molybdenum, nickel, lead, antimony, selenium, tin, and zinc) assessed from toenail cuttings collected from each toe at time of enrolment into the study	Sister study is an ongoing prospective cohort of 50 884 women living in the US and Puerto Rico aged 35–74 years at time of enrolment (2003–2009) (general population study)	Quantitative	Toenail samples at study baseline may not provide accurate proxy of historical cobalt exposure	All routes (indirectly)	Average exposure at time of measurement (μg/g in toenail), split into tertiles for analysis	Exposure occurred before outcome	Yes, other metals Mixtures approach (quantile g-computation) applied to examine potential for co-metal confounding	Non-differential misclassification: likely; timing of exposure measurement may be outside the relevant time window of exposure for cancer outcome under study
O'Rorke et al. (2012) Oesophageal	Case–control, population-based	Not specified	Concentration of cobalt and five other trace elements was quantified in toenail samples (from big toe)	Trace elements, including cobalt, were assessed in a population-based case–control study of people with oesophageal adenocarcinoma	Quantitative	Timing of sample collection was after diagnosis and may not reflect exposure prediagnosis The toenail sample may not reflect exposure during relevant window of exposure; the authors note the period of exposure captured for toenails is the last 12 months (other studies suggest 7–12 months before collection)	All routes	Average exposure at time of measurement (μg/g in toenail), split into tertiles for analysis	The exposure was assessed after the outcome	Yes, other metals were considered in the analysis	Non-differential misclassification: possible; individuals with a diagnosis may have different exposures postdiagnosis than prediagnosis; additionally, the timing of exposure measurement may be outside the relevant time window of exposure for the outcomes under study
Pan et al. (2021) OPL	Case–control, nested within a surveillance programme (The Early Diagnosis and Early Treatment Project of Esophageal Cancer (EDETPEC))	Not specified	Concentration of trace elements, including cobalt in single blood (serum) and repeated diet samples (n = 3)	Cobalt was assessed in blood (plasma) and in repeated dietary samples (3 days) among 100 cases and 100 controls enrolled in a population-based case–control study of OPLs	Quantitative	Timing of sample collection was after diagnosis and may not reflect exposure pre-identification of OPL The authors note that the dietary patterns are stable, but it is unclear over which time period this refers to	All routes in blood, ingestion in diet samples	Blood: average exposure at time of measurement (μg/L in plasma), split into quartiles for analysis Daily intake (μg/day), split into quartiles for analysis	The exposure was assessed after the outcome	Data on smoking and alcohol consumption were collected and described, models were adjusted for these covariates; no other carcinogens or metals were considered	Differential misclassification: possible, but unlikely; the OPL cases were identified during the study activities Non-differential misclassification: possible; the timing of exposure measurement is likely outside the relevant time window of exposure for the outcomes under study

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Reference and outcome	What was the study design?	Relevant form(s) of cobalt in exposed population[a]	What methods were used for the exposure assessment? (including data source, environmental and biological measurements etc.)	What was the exposure context? Specify period over which exposure data gathered, and how historical exposures were accounted for (if relevant)	Was exposure assessment qualitative, semiquantitative, or quantitative?	Concerns noted on sampling and collection protocols for metal measurement	What routes of exposure were assessed?	What exposure metrics were derived for use in analyses (e.g. average exposure, exposure duration, cumulative exposure etc.)?	What was the timing of exposure relative to the outcome?	Was there potential for co-exposures to other carcinogens? If yes, were these accounted for in analyses?	Was there potential for differential or non-differential exposure misclassification?
Rodrigues et al. (2020) Incidence and mortality (mixed): Central nervous system	Nested case–control	Not specified	Administrative records to assess work histories from 1965, first year of detailed job information, or date of hire assessed using JEM: 10 PEGs based on type of production taking place, tasks performed, work environment, and potential for chemical and physical agents to be present within that environment; to the PEGs were assigned the division, department, and job title in which a participant worked (details available in Rodrigues et al., 2019); mean concentrations for each exposure matrix cell (chemical/ PEG/era) linked to subjects' work history	Employees at 3 US facilities engaged in semiconductor and electronic storage device manufacturing Changes in work environment over time addressed by dividing production history at each facility into "manufacturing eras" (described in Rodrigues et al., 2019); however, historical data were sparse for most combinations of agent/facility/era/PEG, precluding development of facility-specific estimations	Qualitative (PEG analysis), quantitative (JEM)	IH data from the 3 facilities used to estimate the mean concentration (mg/m^3) of cobalt in each PEG; this was based on ≥ 6 long-term personal samples per matrix cell; see Rodrigues et al. (2019) for detailed description of sampling limitations	All routes (indirectly)	PEG categories (10, see Table 3) Longest held job categories (5, see Table 4) JEM: each subject's cumulative exposure (mg/m^3-years or fibres/mL-years) calculated by multiplying mean concentrations by durations (years) worked in each job (classified according to PEG and era) and summing over all jobs in the subject's work history Cumulative exposure: continuous variable, also tertiles of mg/m^3-years based on distribution of all subjects by cumulative exposure, among those with non-zero exposure to the agent for all 3 facilities combined Latency analysis removed 5 years before index data for each subject's work history	Exposure occurred before outcome	Yes Various carcinogenic agents assessed via JEM but co-exposure with cobalt not accounted for in analyses	Differential misclassification: unlikely Non-differential misclassification: likely (JEM); "For many exposure matrix cells numbers were small and may not have been representative of exposure occurring in a facility-specific PED/Era combination." (Rodrigues et al., 2019); available IH samples were not collected with the aim of representative sampling and were not facility-specific
Rogers et al. (1993) Oral; oesophagus; and larynx	Case–control, population-based	Not specified	Cobalt was quantified in both halluces (big toenails) as part of a population-based case–control study of upper aerodigestive tract cancers	Cobalt exposure was assessed among 661 cases and 466 controls as part of a population passed case–control study of upper aerodigestive tract cancers	Quantitative	Timing of sample collection was after diagnosis and may not reflect exposure prediagnosis The toenail sample may not reflect exposure during relevant window of exposure; the authors note the period of exposure captured for toenails is the last 7–24 months (other studies suggest 7–12 months before collection)	All routes (indirectly)	Average exposure at time of measurement (ppm in toenail), split into three groups for analysis (0–25%, 25–75%, 75–100% corresponding to < 0.05 ppm, 0.5–0.17 ppm, > 0.17 ppm)	The exposure was assessed after the outcome	Smoking, alcohol use, and education level were assessed and accounted for in analyses Exposure to other metals was assessed and considered separately	Differential misclassification: possible; individuals with a diagnosis may have different exposures postdiagnosis than prediagnosis Non-differential misclassification: likely as the timing of exposure measurement may be outside the relevant time window of exposure for cancer outcomes under study (oral, oesophageal, and laryngeal)

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Reference and outcome	What was the study design?	Relevant form(s) of cobalt in exposed population[a]	What methods were used for the exposure assessment? (including data source, environmental and biological measurements etc.)	What was the exposure context? Specify period over which exposure data gathered, and how historical exposures were accounted for (if relevant)	Was exposure assessment qualitative, semiquantitative, or quantitative?	Concerns noted on sampling and collection protocols for metal measurement	What routes of exposure were assessed?	What exposure metrics were derived for use in analyses (e.g. average exposure, exposure duration, cumulative exposure etc.)?	What was the timing of exposure relative to the outcome?	Was there potential for co-exposures to other carcinogens? If yes, were these accounted for in analyses?	Was there potential for differential or non-differential exposure misclassification?
Sauni et al. (2017) Incidence : Multiple sites	Retrospective cohort	Not specified [inferred by the Working Group to possibly include cobalt-bearing metals and oxides]	Company administrative records to assess job histories Subcohorts by exposure level developed according to first department of employment at the plant, assessed with IH measurements collected since 1966 (area and personal samples) and biological monitoring	Employment for ≥ 1 year between 1968 and 2004, at a Finnish cobalt plant producing cobalt powder from pyrite ore concentrate (1966–1987) and producing cobalt powder, inorganic cobalt, and nickel compounds using by-products of metallurgic industry as raw material (1987–1999) Cobalt assessed	Semiquantitative	Note sampling details are available in other publications (Linna et al. 2003, 2004, cited in paper)	All routes (indirectly)	1. Duration (> 1 year and > 5 year employment) 2. Exposure groupings assigned by department: variable exposure with peaks (factory maintenance); low (leaching and solution purification); moderate (chemical department, test plant); high (sulphatizing roasting, reduction, and powder production)	Exposure occurred before outcome Cancer risk calculated starting from date of 5 years of work at the cobalt plant	Yes Nickel not accounted for in analyses (posited by authors to be relatively low in this work setting): "In sulphatising roasting, dust in the ambient air was found to contain 15–20% iron, 1% zinc, 0.4% cobalt, and 0.2% nickel" "The highest exposure levels of nickel (0.12 mg/m^3) were measured in the chemical department during 1987–1999, otherwise exposure levels have been ≤ 0.04 mg/m^3."	Differential misclassification: unlikely Non-differential misclassification: likely, particularly in duration metric without accounting for department
Svartengren et al. (2017) Incidence : Lung	Retrospective cohort	Cobalt metal	Company administrative records to assess employment and job histories Aggregated job classes defined on basis of similar exposure groups and measurement data; log-linear modelling performed for all aggregated jobs between 1950 and 2012	Workers with ≥ 1 year employment at 3 Swedish hard-metal production sites; job periods assessed from 1950 to 2012 Personal and area air measurements (*n* = 1230 cobalt) covered 1970–2012; estimates for previous time periods (1950–1969) modelled by linear extrapolation for each job class	Quantitative Log-linear model analysis of air concentrations to calculate cumulative and mean exposure measures; modelling based on personal and area air (total dust) measurement data extracted from company records; cobalt was represented in 1230 of 2693 samples	Air measurement data only covered period from "early 1970 to 2012", which may have underestimated exposures in earlier time periods	All routes (indirectly)	Ever/never exposed Duration Cumulative (mg/m^3) = exposure level × exposure time, quartiles Mean concentrations (cumulative exposure/exposure duration), quartiles	Exposure occurred before outcome	Yes, tungsten and nickel (not accounted for in cobalt analyses)	Differential misclassification: unlikely Non-differential misclassification: likely (JEM); exposures in earlier time periods extrapolated from later data
Tüchsen et al. (1996) Incidence : Multiple sites	Retrospective cohort	Cobalt oxides and cobalt silicates	Company administrative records	Employment in plate underglazing departments of 2 porcelain factories (employment years: factory 1, 1943–1987; factory 2, 1962–1987) in Copenhagen, Denmark Agent under investigation was cobalt aluminate spinel (plate underglazing); note: from 1907 to 1972 only cobalt aluminate spinel was used	Qualitative	N/A, exposure not directly assessed	All routes (indirectly)	Ever/never employment	Exposure occurred before outcome	Yes Dusts (quartz?) Nickel (assessed to be "insignificant") Asbestos mentioned as being absent in reference group; unclear if this was a concern for cobalt-exposed	Differential misclassification: unlikely Non-differential misclassification: likely (employment in both departments classified according to the first exposed employment period)

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Reference and outcome	What was the study design?	Relevant form(s) of cobalt in exposed population[a]	What methods were used for the exposure assessment? (including data source, environmental and biological measurements etc.)	What was the exposure context? Specify period over which exposure data gathered, and how historical exposures were accounted for (if relevant)	Was exposure assessment qualitative, semiquantitative, or quantitative?	Concerns noted on sampling and collection protocols for metal measurement	What routes of exposure were assessed?	What exposure metrics were derived for use in analyses (e.g. average exposure, exposure duration, cumulative exposure etc.)?	What was the timing of exposure relative to the outcome?	Was there potential for co-exposures to other carcinogens? If yes, were these accounted for in analyses?	Was there potential for differential or non-differential exposure misclassification?
				(factory 1 changed from cobalt aluminate spinel to cobalt silicate in 1972)							
Wallner et al. (2017) Mortality: Lung	Retrospective cohort	Cobalt metal	Company administrative records to assess employment and job histories Annual average exposure estimated for each worker based on a prior log-linear regression model (see Hutter et al., 2016); workers with missing exposure data assigned exposure values based on expert opinion: either a department with assumed similar exposure levels was chosen or zero exposure assigned (i.e. administrative departments)	Employees working at an Austrian hard-metal production plant between 1970 and 31 December 2014 (most employed at or after 1950 with 11 employed in 1940s)	Qualitative (external comparison), semiquantitative (internal comparison)	N/A, exposure not directly assessed Prior total aerosol measurements of cobalt (*n* = 147) between 1985 and 2012, and urine concentrations of 253 persons from 2008 to 2014, used to inform job exposure categories	All routes (indirectly)	External comparison: employment Internal comparison: cumulative cobalt exposure (mg/m^3 years) Duration of exposure (years) Average exposure (mg/m^3) 5-year and 10-year cutoffs before end of follow-up were assessed but did not change point estimates much	Exposure occurred before outcome	Yes Tungsten (prior study found high correlations between dust, tungsten, and cobalt)	Non-differential misclassification: likely; exposure data missing for some departments and/or job classes “Cohort members held up to 10 jobs consecutively” Exposure data only available for more recent time periods while earlier exposures were likely higher (and more important given latency)
Westberg et al. (2017) Mortality: Lung	Retrospective cohort	Cobalt metal	Company administrative records to assess employment and job histories Each worker’s job and time period extracted and assigned a job class according to classifications from international study (see Kennedy et al., 2017); aggregated job classes (A–I) defined based on similar exposure group considerations and measurement data (see paper for categories) Modelling developed estimates of exposures by time period, site, and job grouping	Work at 3 Swedish hard-metal production plants between 1935 and 2012 42% of cohort employed for < 1 year Personal and area air measurements (*n* = 1230 cobalt) covered 1970–2012; estimates for previous time periods (1950–1969) modelled by linear extrapolation for each job class	Qualitative, semiquantitative, quantitative	Air measurement data only covered period from “early 1970 to 2012”, which may have underestimated exposures in earlier time periods	All routes (indirectly)	Ever/never exposed Duration of exposure (employment) Log-linear model analysis of air measurements used to develop: cumulative exposure (mg/m^3-year) (quartiles and exposure classes) and mean concentrations (quartiles and exposure classes)	Exposure occurred before outcome	Yes, tungsten and nickel (not accounted for in cobalt analyses)	Non-differential misclassification: likely (JEM); exposures in earlier time periods extrapolated from later data

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White et al. (2019) Incidence: Breast	Prospective cohort	Not intended to be specified (general population study)	Census-tract level air concentrations from US EPA NATA database linked to each study participant's geocoded baseline residence at the census-tract level	Air dispersion models used to estimate concentrations for 177 ambient toxic pollutants in air, using 2005 US EPA NATA data release; this compiles information on major point source emissions (e.g. factories), non-point sources (e.g. small manufacturers), and vehicular sources (e.g. cars, trucks) Cobalt metal concentrations (μg/m^3) assessed	Quantitative	Modelled exposure limitations, 2005 modelling does not necessarily reflect historical exposures	Inhalation	Estimates of personal airborne cobalt (based on census-level air dispersion models) categorized into quintiles Weighted quantile sum analysis used to examine combined association of correlated compounds (10 airborne metals)	Air dispersion models may not reflect relevant prediagnosis exposure window (i.e. if participant moved or if exposures changed over time)	Yes, US EPA NATA database includes antimony, arsenic, cadmium, chromium, cobalt, lead, manganese, mercury, nickel, and selenium Cobalt and chromium correlation = 0.7 Weighted quantile analysis assessed combined association effect of airborne metals and those driving association	Differential misclassification: unlikely Non-differential misclassification: likely; census-tract level concentrations are very broad proxies for personal exposures and do not account for historical changes
Wild et al. (2000) Mortality: Lung	Retrospective cohort	Cobalt metal	Company administrative records to assess job histories + 14 workshops grouped into: powder production, hard-metal production before sintering, same (after sintering), other sintered alloy production, maintenance, and other non-exposed workshops JEM used to assign exposure intensity, duration, and cumulative exposure	Employment ≥ 3 months in a French factory producing stainless and alloyed steel, between 1 January 1950 and 30 June 1992 (limited to those still alive on 1 January 1968) "all past or present workplaces were… assessed divided in up to 3 consecutive periods in which the exposure was considered to be different in level" Exposure measurements (details unavailable) used to validate JEM coding, "concentrations increased in a similar way as in the job exposure matrix"	Qualitative + semiquantitative (JEM)	N/A, exposure not directly assessed	All routes (indirectly)	Ever/never, workshop-based categories examining "ever employed in" as well as "only employed in" JEM: 1. Ever/never 2. Highest exposure score experienced in work history 3. Duration at exposure score > 2; recoded into non-exposed, exposed < 10, 10–20, and > 20 years 4. Cumulative exposure (sum of score by duration) 5. Cumulative exposure (score weighted by frequency code, by 0.05 for < 10%, 0.3 for 10–50%, 0.75 for > 50%) Exposures lagged by 10 years	Exposure occurred before outcome	Yes Exposure "consisting of simultaneous exposure to cobalt and tungsten carbide" "several other simultaneous productions existed in this industrial site in which several potential carcinogens were assessed by the expert group", however this issue may mostly concern maintenance workers Exposures to other substances (asbestos, polycyclic aromatic hydrocarbons, certain chromium compounds, certain nickel compounds, and silica) coded as present or absent	Differential misclassification: unlikely Non-differential misclassification: likely (broadly defined exposure categories; use of JEM)

ICP-MS, inductively coupled plasma mass spectrometry; IH, industrial hygiene; JEM, job-exposure matrix; N/A, not applicable; NHANES, National Health and Nutrition Examination Survey; OPL, oesophageal precancerous lesion; PEG, primary exposure group; ppm, parts per million; SMR, standardized mortality ratio; US EPA NATA, United States Environmental Protection Agency National Air Toxics Assessment; vs, versus.

[a] Includes forms of cobalt explicitly described within the study; may not comprehensively describe all cobalt forms present.

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