Pre-Online Release of Results from International Study of Hardmetal Production Workers

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Mortality among hardmetal production workers: A retrospective cohort study in the Austrian hardmetal industry

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Running Title: Austrian hardmetal industry cohort

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Methods: A retrospective cohort was formed of 1965 workers still employed in or after 1970. Follow-up was until end of 2014 based on national data bases. Cobalt exposure was assessed through industrial hygiene data and urine analyses. Cox proportional hazards models were calculated for selected causes of death.

Results: During 45,598 years of observation in total 177 deaths were observed. Forty-nine workers died from any cancer, 10 from lung cancer, and 3 from chronic obstructive pulmonary disease. Only the latter showed a significant association with cumulative exposure.

Conclusions: Although this is a young study population with little power to detect subtle effects, at least it does not indicate a pronounced cancer risk among tungsten carbide workers due to cobalt.

Key words: Hardmetal industry, cobalt, tungsten carbide, cohort study

Introduction

Occupational exposure to cobalt (Co) is considered a hazard because of its assumed carcinogenic potential, especially regarding lung cancer. The metal and its compounds have been classified as carcinogenic since the 1970s, with a general IARC[1] assessment of cobalt in 1991 as "possibly carcinogenic" (group 2B). In its Monograph 86 IARC[2] rated cobalt metal with tungsten carbide as probably carcinogenic to humans (Group 2A). Also according to Austrian law[3] cobalt is classified as carcinogenic. French[4-6] and Swedish[7] occupational cohort studies suggest that cobalt increased the risk of lung cancer, particularly in combination with tungsten carbide, in the hardmetal industry. Additionally, there is evidence that hardmetal particles exert genotoxic and carcinogenic activity[8,9].

One of the main uses of Co is as a binder of tungsten carbide in hardmetals. Hardmetal dust is also a known respiratory toxicant with chronic exposure leading to scarring of the lung tissue with consecutive restrictive and also obstructive lung disease[10-12]. An international consortium was set up to study the health effects of occupational exposure in the hardmetal industry in more detail[13-15]. Here we report on the results of the Austrian component of this international study[16]. Reports from the US[17], UK[18], Sweden[19] and Germany[20] appear as companion papers in that same issue.

Methods

Definition of the cohort

One large Austrian hardmetal production plant (in Tyrol) agreed to participate in the cohort study. A first examination of the personnel files indicated that data were available back as far as 1950. However, a closer investigation revealed that only employees who were still working at the plant at or after 1970 had full documentation. All workers with full documentation of occupational history at the plant were included in the original cohort providing a total of 1965 workers. Most cohort members were employed at or after 1950 but a few (11 persons) have been employed even earlier (beginning between 1946 and 1949). By definition all workers were still alive in 1970. Thus time under risk and observation started in 1970. Observation was terminated with date of death, date of leaving the country, or December 31st, 2014, whichever came first.

Because of data privacy issues only anonymous data were provided by the personnel department. Each cohort member was given a unique identifier. The researchers received the following information for each person: year and month of birth, gender, nationality, exact starting and ending dates of any job (job name, department) held at the plant, employment status (apprentice, blue collar, white collar worker). For some persons additional information (e.g. known date of death) was provided.

The study was approved by the ethics committee of the Medical University of Innsbruck (AN2014-0380 345/4.9 from 2015-01-30). Because cohort members were anonymous and some were likely already dead informed consent was not deemed necessary for the study.

Exposure assessment

The following data was available: Total aerosol measurements of dust (n = 130), tungsten (n = 141) and cobalt (n = 147) for the years 1985 to 2012 and urine tests of 253 persons (a total of 1166

records) from the years 2008 to 2014. Of these 1166 records 318 were from current non-smokers, 591 from current smokers, and 357 were missing that information.

In a first study[21] dust, tungsten, and cobalt values were found to be highly correlated with each other. All values declined over time. In a linear regression modeling ln(Co) by time (year), monitoring method, area versus personal sampling, and dummy variables for departments a significant time trend was observed, and significant differences between some departments respectively job classes. Data were lacking on some job classes that mostly were assumed to have none or only little exposure. For some job classes exposure estimates were uncertain because of only few data points. Estimated cobalt levels (after back-transformation from logarithmic values) correlated well with measured urine levels supporting the model and time trends.

Urine concentrations of cobalt were also affected by current smoking status (higher values in smokers). Workers with missing information on current smoking status resembled non-smokers in that regard. Therefore they most likely either did not (currently) smoke or at least were only very moderate smokers[20]. Based on this assumption workers with urine data (usually blue collar workers with substantial cobalt exposure) did not differ substantially in current smoking status from the population of Tyrol, although they tended to be more often smokers than the white collar workers (from whom a sub-sample had provided smoking data through a questionnaire survey)[22].

Annual average exposure was estimated for each worker and every year of his/her working history based on the log-linear regression model[21]. Workers from departments with missing exposure data were assigned exposure values based on expert opinion: either a department with assumed similar exposure levels was chosen or, in case of administrative departments, zero exposure was assigned.

The following exposure metrics were studied: cumulative Co exposure (mg/m^3 years), duration of exposure (years) and average exposure (mg/m^3). Also cumulative exposures up to 5 years and up to 10 years before end of follow-up were considered. All cumulative exposure metrics were highly correlated with each other. The alternative cumulative metrics did not lead to any meaningfully different point estimates and are therefore not presented.

Mortality and cause of death follow-up

Information on vital status until end of 2014 and cause of death (if applicable) was at first sought through the Austrian mortality register at the Austrian national statistics institute, Statistik Austria. The registry received a spreadsheet file including the name and birth date of each subject together with the unique identifier. The registry added mortality date and cause of death for every match. Then the name and birth date were deleted and the final file was sent to the researchers. In order to calculate age day of birth was set to mid-month. It became obvious that this information was incomplete: Some workers would have reached an implausible age. Some workers were known to have died according to the personnel department of the plant, but were missed in the mortality register. In a second approach data were compared to the central address register of Austria. This register was built around and after the year 2000. Before that date address registers were kept separately in each district. In theory old district registries have been transferred to the central register, but this procedure was likely far from complete. The register should be able to provide information if a given person is still registered in Austria and if not, when the person's permanent address was terminated and if this occurred because of death or because of relocation into a foreign country.

Many deaths already known due to the mortality register were also confirmed by the address register although the address register usually does not provide the exact date of death, but only with a precision of about one month. Many persons were not found in the address register and among these persons those that had died, according to the mortality register, their date of death was always in or before the year 2000. Persons missing in the address register therefore were primarily assumed to have died or had left Austria before or in 2000. Only for the few missing persons who had still been working in 2000 it was assumed that they were missing in the address register because of other reasons. These were, for example, persons with a German citizenship. Because the plant is located at the border to Germany they might well have worked in Tyrol, Austria and lived in Germany. They would then not be found in the Austrian address register, and for them observation had to be terminated with the end of work.

The observation of the persons was therefore terminated with the date of death (according to the mortality register, or, if this information was missing, according to the address register), the date they left Austria (according to the address register), the end of 2014, and, if the persons were neither found in the mortality nor in the address register, either by the end of 2000 or by the end of their work at the plant (if they still worked there after the year 2000).

Only the mortality register provided information on cause of death (1970-1979: ICD8; 1980-2001: ICD9, 2002-2014: ICD10). The following end-points were investigated: death according to any register data, death according to mortality register, death due to any cancer (e.g. ICD10: C00-C97), death due to respiratory cancer (e.g. ICD10: C30-C39), and death due to non-malignant respiratory disease (e.g. ICD10: J00-J99) or more specifically obstructive respiratory disease: bronchitis, emphysema, asthma (e.g. ICD10: J40-J46).

Statistical analysis

Mortality was compared within the cohort by exposure status (internal comparison), and for the whole cohort with the general population of Tyrol (external comparison). The internal comparison was run in STATA SE 13.1 (StataCorp, 4905 Lakeway Drive, College Station, Texas 77845 USA). Three different approaches were followed:

(a) Primarily Cox proportional hazard models were run. However, time varying exposure is difficult to model in STATA. Therefore only a single exposure metric (e.g. cumulative exposure at the end of follow-up) was used in these models for each cohort member.

(b) The older a person gets the greater the chance to accumulate a higher amount of exposure. So when using the same constant (cumulative) exposure as calculated at the end of follow-up due to reverse causality a beneficial effect of exposure could spuriously be found. In truth a person did not die earlier because he/she then still had a smaller cumulative exposure, but did not cumulate a higher exposure because of early death. Therefore an alternative model was built using excel macros: Each year under observation of each person was entered as a separate line with information on gender, age, employment status (apprentice, blue collar, white collar worker; in case of retirement the former status was kept), outcome status in that year (survived or died, selected causes of death, binary values each), nationality, and exposure metrics (average exposure in that year, cumulative exposure until that year). This table was imported into STATA and again Cox regressions conditional on age were performed.

(c) In sensitivity analyses white collar workers or all workers from Eastern European countries (mostly Turkey and former Yugoslavia) or all non-Austrian citizens were excluded. In another series of analyses only persons hired at or after 1960 were included to simulate an inception cohort. This was considered a compromise between losing too many workers with a long observation time and missing a substantial number of workers that started working after the index date (1960) but finished working before 1970. All models were controlled for sex and Austrian citizen status. The logistic regression models were additionally controlled for working status (apprentice, blue collar worker, white collar worker).

External comparisons of the cohort with the Tyrolean population were performed in a qualitative way. For each cohort member and each year (either starting in 1970 or when they entered the cohort, whichever occurred later), the chance of survival was estimated based on sex and age-specific death-rates of the Tyrolean population in the same year. The expected survival rates of the cohort were compared to the true rates in Kaplan-Meier curves. The analyses were done for the same end-points as in the internal comparisons.

Results

This is a young cohort with few deaths. Among the full cohort of 1965 persons, a total observation time of 45,598 years (average observation time of 23.2 years) and 177 deaths were observed. Of these, 159 were affirmed by the mortality register and cause of death was provided. Forty-nine died from any cancer, 10 from cancer of the respiratory system (all 10 lung cancer), and only 3 from bronchitis, emphysema, or asthma and only 1 person from “other” non-malignant respiratory disease (died in the year 2000, therefore coded by ICD9 as 507.0, i.e. aspiration pneumonia). As the latter was not likely associated with occupational exposure only the exposure related risk ratios for the 3 persons with “obstructive” respiratory diseases are reported. Including the 4th case did not alter the point estimates strongly but increased the confidence intervals.

Annual exposure was assessed by job description / department as described in table 1. Cumulative exposures ranged from 0 to 33.5 mg/m^3 years (mean ± standard deviation: 0.52 ± 2.25), average exposure from 0 to 1.8 mg/m^3 (0.05 ± 0.13), and years of exposure from 0 to 45 (6.1 ± 9.0).

Increased risks for death from obstructive lung diseases were seen with all exposure metrics. The findings were significant for the Cox regression in the full data set investigating cumulative exposure. The point estimates were similar in the conditional logistic regression but failed to reach formal significance at the 0.05 level. Risk estimates for all non-malignant respiratory diseases were generally similar but less precise and are not shown here. Neither increased nor decreased risks for any other mortality end-points were seen (Tables 2-4). Males tended to have higher risks than females. Austrian nationality did not significantly or systematically affect risks. Cox regression controlling for time varying exposures and job status (blue/white collar workers, apprentices) provided practically the same point estimates and similar confidence intervals.

Sensitivity analyses resulted in practically the same point estimates. However, case numbers were reduced and therefore point estimates were less precise. With Austrian citizens only the point estimate and the p-value for cumulative exposure on obstructive lung diseases remained stable. All three cases had been Austrian citizens.

The results of the external comparisons are presented in figures 1-4. Neither for total mortality nor for the investigated causes of death an increased risk was seen in the cohort compared to the population of Tyrol.

Discussion

We did not find increased cancer risks or increased risk of lung cancer. In comparison to the general population there was a clear indication of a "healthy worker" effect and in the internal comparison there was only a weak indication of an increasing risk of death from obstructive lung disease with increasing cumulative exposure. The latter observation was based on a very small number of cases. This cohort is of relatively young age with only 177 out of 1965 persons deceased during the observation period. This renders the cohort unfit to detect very small and subtle risks. Also the exposure estimates had several weaknesses. Exposure data were missing for some departments and/or job classes. Some of these were deemed to be unexposed or with practically no exposure. However, some (usually with only few persons affected) were likely exposed and exposure had to be estimated based on comparisons with similar job classes. Exposure data were only available for the more recent time periods. A general log-linear time trend estimated from air monitoring data was confirmed by urine data, but extrapolation to earlier times is subject to some uncertainty. Earlier exposures were likely higher and also more important because of a long latency period for some of the studied outcomes. The error would likely be non-differential and would therefore reduce the effect estimates to the null or broaden the confidence interval thus again hiding subtle effects.

Nevertheless, the cohort was able to show the increased risk of death from obstructive pulmonary diseases albeit based on a very small number of cases. This finding is plausible[23-26] but still must be treated with caution due to the small number of cases.

The within cohort models might be subject to bias by smoking behavior. It is generally known[27, 28] and has been shown for a subsample of the cohort that blue collar workers tend to smoke more often than white collar workers. Because blue collar workers are also generally more exposed this fact could confound the results and lead to spurious results. However, no increased risks were seen for lung cancer which would be the outcome most affected by confounding from smoking. On the whole the cohort members did not differ substantially in smoking prevalence from the general population of Tyrol and no meaningful differences in lung cancer rates were observed. Therefore, even when smoking data were incomplete it is not likely that this caused any strong confounding.

Hence we might conclude that in this Austrian cohort exposures did not lead to very large health risks, although small risks cannot be excluded with certainty. Smoking could be a confounder because we lacked individual smoking data for a high proportion of workers and we could not link individual data on smoking behavior to cohort members. But it was shown that white collar workers (who are also less exposed on average) tended to smoke less. Therefore any bias by smoking would have led to spuriously increased risks. Because this is why the logistic regression models that controlled for socioeconomic status (blue-/white collar workers) tended to show somewhat lower risk rates in the internal comparison. But the difference between hazard rates from cox regression and incidence rate ratios from logistic regression were very small. The external comparison with the population of Tyrol was only done in a qualitative way. Even though there is limited evidence that smoking was somewhat more prevalent among cohort members than among the general population all mortality

rates including those for lung cancer in the cohort were less than expected. This supports the null findings of the internal comparison.

Conclusion

The study was subject to many obstacles. Mostly these stemmed from considerations regarding data privacy protection. In previous studies[29, 30] we were able to collect individual mortality data through the Austrian mortality register without any problem. Detailed follow-up was also possible through local address registers in each of the Austrian districts. In special instances even social security data could be obtained. All this was no longer possible when this study was conducted. Access to the mortality register was only granted after a long campaign and many interest groups' lobbying and an amendment of the Austrian university law. Incomplete data could not be re-checked directly because only anonymous data were provided and the Federal Statistics Institute (Statistik Austria) had been obliged to destroy the data at once after completion of their initial task. For the benefit of future research the rightful concerns for data privacy should be better balanced with rightful scientific interests.

In this cohort of hardmetal workers we did not detect increased mortality rates overall or for lung cancer compared to the general population. On the contrary all-cause mortality displayed the expected healthy worker effect. In the internal comparison none of the measures of exposure (average or cumulative exposure, duration of exposure) for cobalt was associated with increased risks for either total mortality, all cancers combined, or lung cancer.

Figure Legends

Figure 1. Kaplan-Meier curves for all-cause mortality, with comparison to the population of Tyrol

Figure 2. Kaplan-Meier curves for all-cancer mortality, with comparison to the population of Tyrol

Figure 3. Kaplan-Meier curves for lung cancer mortality, with comparison to the population of Tyrol

Figure 4. Kaplan-Meier curves for obstructive pulmonary disease mortality, with comparison to the population of Tyrol

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Figure 1

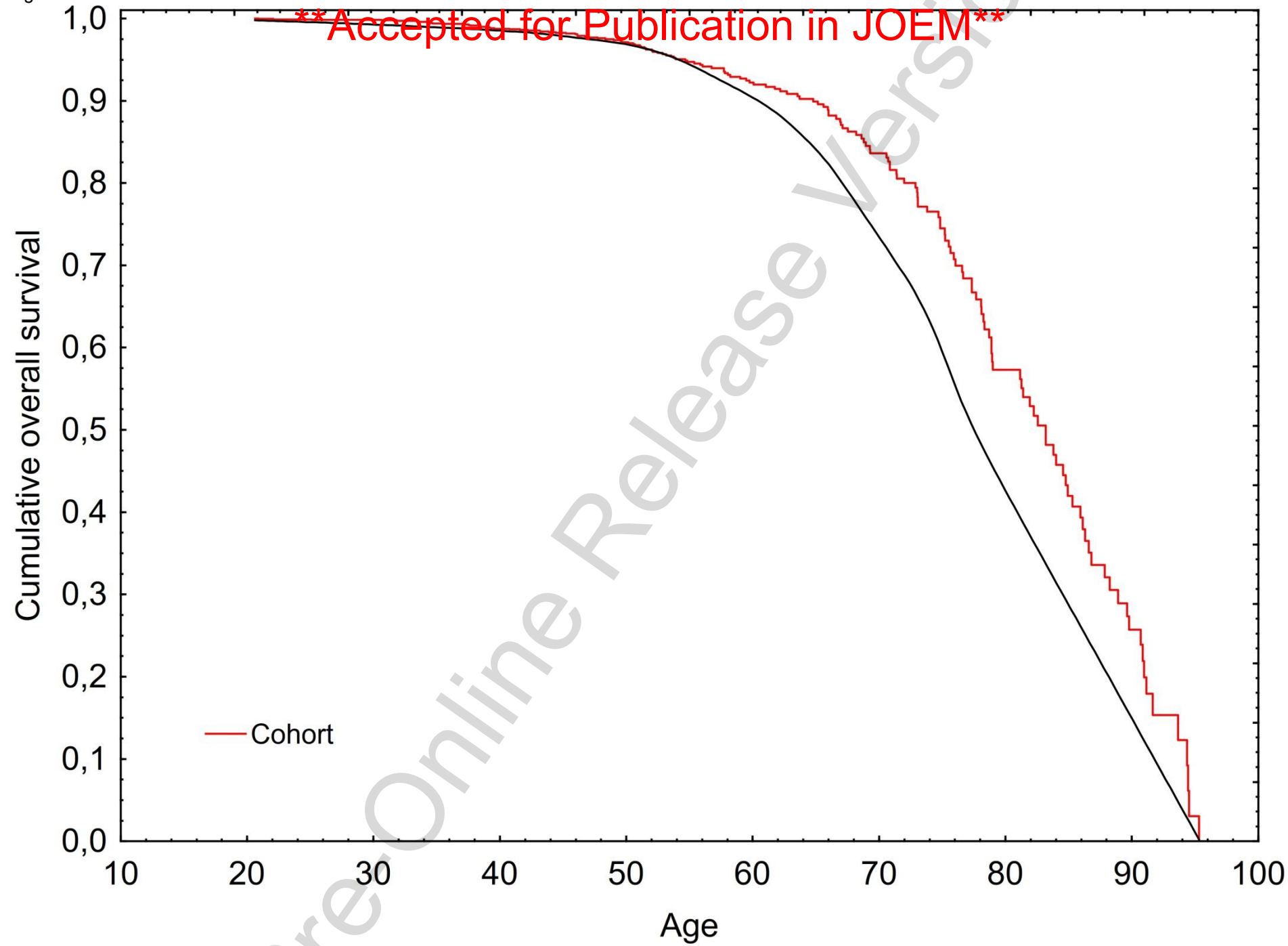

Figure 2

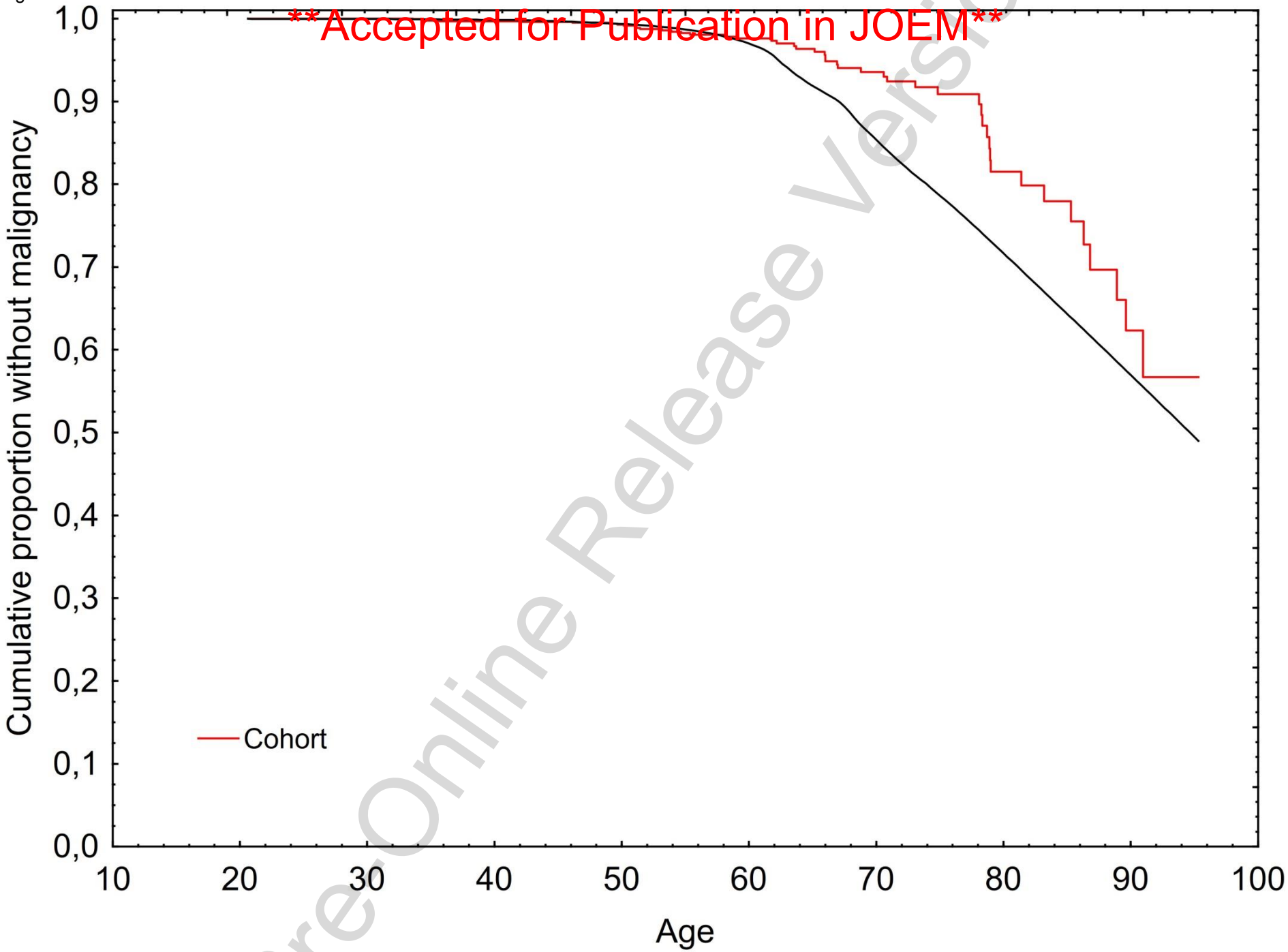

Figure 3

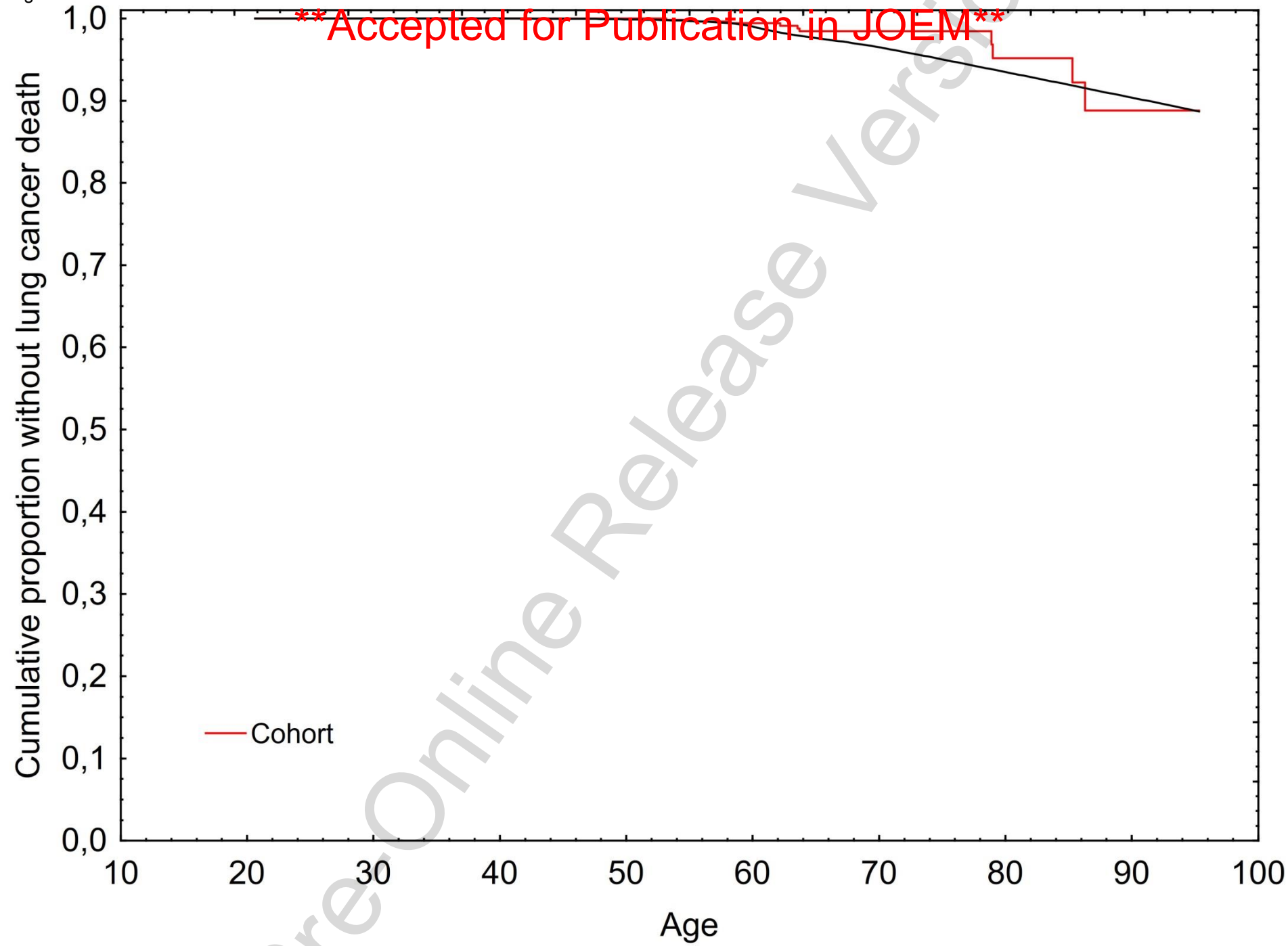

Figure 4

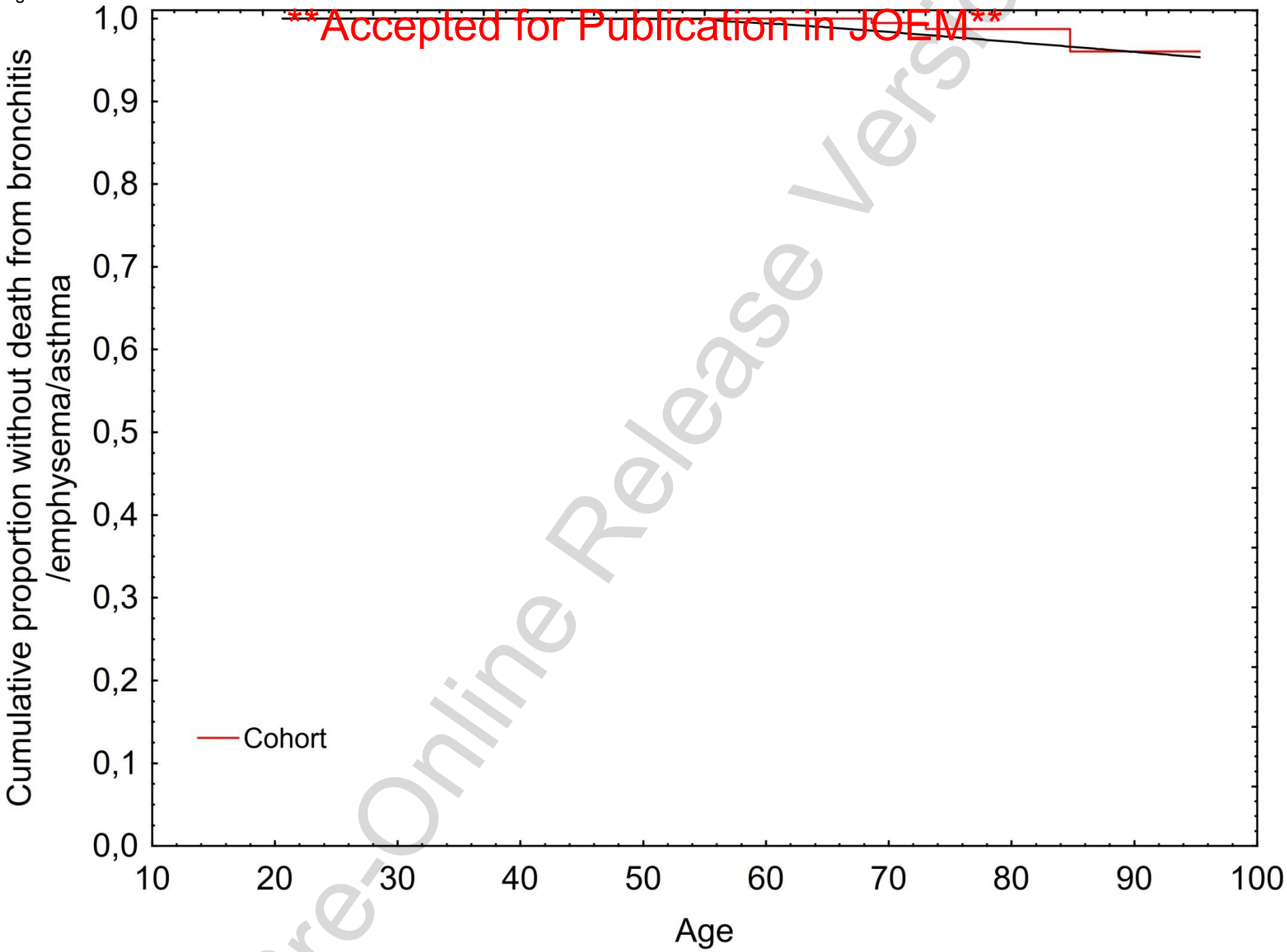

Table 1: Annual estimates of personal cobalt concentration (mg/m³) either derived from [20] or based on expert opinion.

Job description	N*	Conc.	Rationale
Accountant, secretary, student, cook, watchman	437	0	Expert
Lab technician, metallurgical technician, development engineer	217	0	Expert
Foreman, group supervisor, production supervisor	369	0	Expert
Sevice engineer, Industrial engineer, plant engineer	103	0	Expert
Painter, custodian, electrician, tool room mechanic	140	0	Expert
Material handler, shipping clerk, order filler	33	0	Expert
Mark-pack-lid, inspect/mark/pack, markem packer	59	0	Expert
Inspector, inspection clerk, inspect/shipping, inspect/mark/pack	266	0	Expert
Press set-up	60	Exp(0.297-0.047*year+87.79)	Like press
Press	168	Exp(0.297-0.047*year+87.79)	[20]
Shape (any green machining)	289	Exp(1.124-0.047*year+87.79)	Like press
Extrude	237	Exp(-0.047*year+87.79)	[20]
Cold isostatic press (CIP)/Slug form	3	Exp(0.297-0.047*year+87.79)	[20]
Furnace (heat treat, sinter, carburize, etc.)	175	Exp(-0.715-0.047*year+87.79)	[20]
Hone	45	Exp(4.428-0.047*year+87.79)	Like grind
Grind (Wet Grinding)	492	Exp(4.428-0.047*year+87.79)	[20]
Slow moving operations (drill, mill, bore, etc.)	219	Exp(0735-0.047*year+87.79)	[20]
Electro-discharge machining (EDM)	8	0	Expert
Blast (sandblast, gritblast, Vaqua blast, etc.)	17	Exp(0.297-0.047*year+87.79)	Like press
Coat (CVD, PVD, plasma, etc.)	91	Exp(0.297-0.047*year+87.79)	Like press
Braze	3	0	Expert
Powder room operations	128	Exp(1.369-0.047*year+87.79)	[20]
Graphite Service Operator	6	Exp(2.398-0.047*year+87.79)	[20]

*N … Number of jobs held with that description. Cohort members held up to 10 jobs consecutively.

Table 2: Relative risk (hazard ratio HR and confidence interval) by cumulative exposure (mg/m³ years) in Cox proportional hazards regression; in comparison HR from Cox regression with annually changing exposure status. All models controlled for nationality and gender, the second model also controlling for job status.

End-point	(n)	HR	Conf.-Interv.	p-value	HR time dependent variables
Death	(177)	1.01	0.98-1.04	0.558	1.01
Death with ICD	(159)	1.01	0.98-1,04	0.524	1.01
Any cancer	(49)	0.99	0.93-1.06	0.786	0.99
Lung cancer	(10)	1.03	0.94-1.13	0.516	1.01
Obstructive	(3)	1.12	1.02-1.22	0.019	1.10

Table 3: Relative risk (hazard ratio HR and confidence interval) by average exposure (mg/m³) in Cox proportional hazards regression; in comparison HR from Cox regression with annually changing exposure status. All models controlled for nationality and gender, the second model also controlling for job status.

End-point	(n)	HR	Conf.-Interv.	p-value	HR time dependent variables
Death	(177)	1.27	0.652-2.48	0.482	1.18
Death with ICD	(159)	1.23	0.612-2.466	0.562	1.13
Any cancer	(49)	0.77	0.186-3.163	0.714	0.62
Lung cancer	(10)	4.83	0.701-33.316	0.110	3.25
Obstructive	(3)	18.77	0.782-451.33	0.071	14.65

Table 4: Relative risk (hazard ratio HR and confidence interval) by duration of exposure (years) in Cox proportional hazards regression; in comparison HR from Cox regression with annually changing exposure status. All models controlled for nationality and gender, the second model also controlling for job status.

End-point	(n)	HR	Conf.-Interv.	p-value	HR time dependent variables
Death	(177)	0.99	0.980-1.004	0.194	1.01
Death with ICD	(159)	0.99	0.981-1.006	0.301	1.01
Any cancer	(49)	1.0	0.978-1.022	0.976	1.02
Lung cancer	(10)	1.02	0.981-1.07	0.275	1.04
Obstructive	(3)	1.05	0.969-1.127	0.249	1.06

Statement of clinical significance, not exceeding 50 words

Cobalt dusts, which occur in the carbide industry during manufacture and processing, are considered "probably carcinogenic". A retrospective cohort study in a company of the Austrian hard metal industry as part of an international multi-center study has shown that the employees are not subject to an increased health risk.