SHORT REPORT

Is beryllium-induced lung cancer caused only by soluble forms and high exposure levels?

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ABSTRACT

Objectives The US Occupational Safety and Health Administration (OSHA) recently proposed a permissible exposure limit of 0.2 µg/m^3 for beryllium, based partly on extrapolated estimates of lung cancer risk from a pooled occupational cohort. The purpose of the present analysis was to evaluate whether cohort members exposed at lower levels to mainly insoluble forms of beryllium exhibit increased risk of lung cancer.

Methods We conducted Cox proportional hazards regression analyses among 75 lung cancer cases in age-based risk sets within two lower exposure plants in the pooled cohort followed from 1940 to 2005. We used categorical and power models to evaluate exposure–response patterns for mean and cumulative beryllium exposures in the two-plant cohort, comparing findings with the full pooled cohort. We also evaluated the distribution of exposure-years in each cohort by solubility class (soluble, insoluble and mixed).

Results 98% of workers in the two-plant cohort were hired between 1955 and 1969. The mean beryllium exposure averaged 1.3 µg/m^3 and the predominant form was insoluble. Adjusting for confounders, we observed a monotonic increase in lung cancer mortality across exposure categories in the two-plant cohort. The exposure–response coefficients (per unit ln exposure) were 0.270 (p=0.061) for mean exposure and 0.170 (p=0.033) for cumulative exposure, compared with 0.155 and 0.094 (respectively) in the full cohort.

Conclusion The low-exposure levels at these two plants and the predominance of insoluble beryllium suggest that the overall pooled cohort findings on which OSHA's lung cancer risk assessment is based are relevant for current workers exposed to any form of beryllium.

What this paper adds

- Beryllium has been designated a known human carcinogen by the International Agency for Research on Cancer, based on human and animal studies of lung cancer, but risks at low exposure levels are difficult to directly quantify. Previous quantitative exposure–response associations of beryllium-exposed workers found steep increases in lung cancer risk with exposure levels, but the influence of highly exposed individuals exposed to a variety of beryllium forms was not evaluated.
- By restricting exposure–response analyses to the facilities that began more recently and were involved in mostly insoluble beryllium handling, we demonstrate that risk per unit exposure was similar to that observed in the full cohort exposed to a wider range of beryllium forms and higher mean exposures.
- The findings of this analysis support the quantitative risk assessment that the US Occupational Safety and Health Administration has performed for lung cancer related to occupational beryllium exposure.

Beryllium metal's unique properties, including low density, high strength and thermal conductivity, have placed it in demand as a component in a variety of industrial and nuclear applications.[1] Beryllium and beryllium compounds have been designated as known human carcinogens by the International Agency for Research on Cancer (IARC).[1] The human evidence supporting this designation includes studies conducted by the National Institute for Occupational Safety and Health (NIOSH) of workers employed historically in the beryllium processing industry in the USA.[2–4] Since the IARC evaluation, new studies have evaluated cancer risk with extended follow-up in seven of these historical cohorts, including three with quantitative exposure–response evaluation.[5 6] One of these studies[6] was used recently by the US Occupational Safety and Health Administration (OSHA) in a quantitative risk assessment for lung cancer, as part of the establishment of a more protective permissible exposure limit for workers exposed to beryllium.[7]

Two criticisms have arisen since the publication of these studies. First, it has been suggested that OSHA's risk assessment for lung cancer is irrelevant to the current beryllium workforce, because 'insoluble' beryllium forms (eg, beryllium metal, beryllium oxide), to which most current beryllium workers are exposed, have not been directly observed to be associated with lung cancer. It has also been argued that the association between lung cancer and beryllium observed in the NIOSH cohort studies was driven by workers hired before 1955, when exposures were higher.[8–10] The purpose of this study was to address these criticisms by examining industrial hygiene and employment data to evaluate the contention that beryllium exposures in the NIOSH cohort study were primarily 'soluble', and by examining the

Table 1 The results of two-plant (plants 6 and 7) exposure–response modelling, compared with previously published three-plant (full cohort) estimates

Mean beryllium exposure (all forms)					
	Tertile 1:	**Tertile 2:**	**Tertile 3:**		
Range (μg/m³)	0–<0.88	0.88–<1.85	≥1.85	Two-plant power model β*	Full cohort power model parameter
Mean (μg/m³)	0.42	1.32	2.94		
HR (95% CI)	1.00	1.18 (0.63, 2.19)2†	1.72 (0.92, 3.24)†	0.270 (p=0.061)†	0.155 (p<0.001)3‡
Cumulative beryllium exposure (all forms)					
Tertile #	**Tertile 1:**	**Tertile 2:**	**Tertile 3:**		
Range (μg/m³-days)	0–<723	723–<4211	≥4211	Two-plant power model β	Full cohort power model parameter
Mean (μg/m³-days)	214	2149	8943		
HR (95% CI)	1.00	1.34 (0.67, 2.68)4§	1.68 (0.78, 3.63)§	0.170 (p=0.033)§	0.094 (p=0.0017)‡

*Power model β interpretation: HR (at exposure x relative to no exposure) = $\exp(\beta*\ln(x+0.05))/\exp(\beta*\ln(0+0.05))$. Two-sided p Value indicates test of β=0.
†Adjusted for date of birth, plant, professional status and potential silica exposure.
‡From Schubauer-Berigan et al (2011).[6]
§Adjusted for date of birth, plant, professional status, potential silica exposure and short-term work status.

association of lung cancer with quantitative metrics of beryllium exposure in two low-exposure plants (6 and 7)* in the NIOSH cohort study.

METHODS

The three plants for which quantitative exposure estimates are available are described in detail elsewhere[2 5 6] and are summarised in online supplementary table 1 . At plant 2, ore refining and beryllium oxide production were done from 1935 to 1966, with copper alloy production and machining conducted from the 1930s until plant closure in 2001.[2] Plant 6 produced beryllium copper alloy since 1953 and began other operations (ore refining, beryllium oxide production, metal production and machining) in 1958.[2] At plant 7, these operations were performed from 1958 until plant closure in 1978. To estimate the solubility class of cohort exposures to beryllium at each plant, we used previously created job-exposure matrices, which used available information about the chemical form of beryllium exposure associated with each job, department and year combination at plants 2,[11†] 6[12] and 7.[13] We defined 'soluble' beryllium as beryllium salts (Be fluoride, Be hydroxide, Be sulfate) and 'insoluble' beryllium as beryllium metal, alloys or beryllium oxide.[14] 'Mixed' solubility was assigned to job/department/year combinations that involved both soluble and insoluble beryllium forms. Jobs with no available information on chemical form (eg, office work) were labelled 'indeterminate'. We multiplied the number of work days by the daily exposure level, summed across the cohort and summarised the cohort exposure-years on an annual basis.

We conducted exposure–response analyses for beryllium exposure (all forms) at plants 6 and 7, which began operations in the 1950s, to estimate whether the risk per unit exposure was similar to that observed for the three-plant cohort, which was dominated by the larger and higher-exposed plant 2. We used the same cohort definitions, cohort entry, mortality follow-up (1940–2005), exposure estimates and statistical methods as in the previous analysis,[6] conducting Cox proportional hazards regression of underlying-cause lung cancer deaths (International Classification of Diseases (ICD)-6 and ICD-7 codes 162.0, 162.1, 162.8, 163; ICD-8 and ICD-9 code 162 and ICD-10 codes C33–C34) in age-based full risk sets within the pooled plants 6 and 7. We classified exposure into tertiles of the case distribution (with cutpoints at 0.88 and 1.55 μg/m³ for mean exposure and 723 and 4211 μg/m³-days for cumulative exposure) for categorical analyses. We used categorical and power (log–log) models to evaluate exposure–response patterns for mean and cumulative beryllium exposures in the two-plant cohort, comparing findings with published estimates from the full pooled cohort.[6] The power model form was selected as it well describes the exposure–response shape within the full cohort.[6] It represents the change in the log of the HR (relative to a defined dose) per unit change in the log of the dose. We adjusted for age, birth year, professional work status,[6] potential silica exposure and (for cumulative exposure) an indicator of short-term work (<1 year) status. We evaluated but did not adjust for race and potential exposure to other lung carcinogens (acid mist, asbestos, chromium, nickel),[6] which changed risk coefficients by <10%. We evaluated potential confounding by smoking through an indirect adjustment,[15] based on the distribution of smoking (determined in a 1968 survey) across exposure categories (online supplementary material).

RESULTS

The vast majority of exposure-years across each plant were insoluble or mixed-solubility beryllium (online supplementary figure 1). For plant 2, overall only 9% of exposure-years were associated with soluble-only beryllium, all occurring between 1938 and 1966; insoluble beryllium exposure composed of 50% of the distribution and mixed-solubility beryllium exposure 37% of the distribution (online supplementary figure 1a). For plant 6, total beryllium exposure-years comprised 7% soluble-only, 64% insoluble-only and 29% of mixed solubility. The insoluble-only percentage increased over the years of plant operation (online supplementary figure 1b). For plant 7, overall exposure-years were 13% soluble-only, 67% insoluble-only and 17% of mixed solubility. The soluble-only contribution generally declined over time (online supplementary figure 1c).

We observed 75 lung cancer deaths in the two-plant cohort between the start of follow-up through 2005 (online supplementary table 1). The median levels of mean and cumulative exposures among cases were 1.3 μg/m³ and 1953 μg/m³-days (respectively) for the two-plant cohort and 15 μg/m³ and 2583 μg/m³-days for the three-plant cohort. We observed a monotonic increase in risk across exposure tertiles (table 1). The exposure–response coefficients for mean and cumulative exposures were 0.270 (p=0.061) and 0.170 (p=0.033), respectively, which were somewhat higher than in the three-plant cohort[6] (table 1). Indirectly adjusting

*Plant numbers correspond to those given in table 1 of Ward *et al*.[2]
†We assumed no beryllium fluoride (BeF) was used past 1966 at Plant 2.

for smoking changed HRs by <10%, compared with the HRs shown in table 1 (online supplementary table 2).

DISCUSSION

Since the publication of NIOSH's quantitative exposure–response analyses of beryllium processing workers,[5 6] two main criticisms have been directed at the studies' relevance to the current workforce[8 9]: first, it has been suggested that the three plants in the NIOSH studies were primarily handling 'soluble' forms of beryllium. In fact, as noted in table 1 of Ward *et al*,[2] all three beryllium plants were engaged in operations associated with both soluble and insoluble forms. This observation was confirmed in our detailed analysis of exposure-years associated with specific departments and operations. The predominant form of beryllium handled throughout the years of operation was insoluble, followed by mixed-solubility forms. Plant 2 (which dominated the three-plant cohort) had lower percentages of insoluble exposure than plants 6 and 7, especially during early years. The risk per unit exposure in the two-plant cohort was similar to that in the three-plant cohort, suggesting that both soluble and insoluble beryllium exposures contribute to lung cancer risk. Second, it has been suggested[8 9] that beryllium–lung cancer associations observed in the published NIOSH study were attributable to risks among highly exposed, early plant workers and are therefore not relevant to 'modern' (lower) beryllium exposures. In previous analyses,[5 6] beryllium exposure was found to be positively associated with lung cancer at each of the plants, and no evidence of effect modification was observed. The present analysis supports those findings, as the exposure–response coefficients for the two plants with more recent, lower exposure exhibited similar (or somewhat higher) risks per unit exposure compared with all three plants combined (table 1).

Limitations of the present analysis reflect those of the three-plant cohort, including lack of smoking data for the complete cohort (although our analyses suggest little confounding by smoking) and exposure uncertainty derived from the use of an annually averaged job-exposure matrix.[5 6] The relatively small number of lung cancer cases in analyses of only two plants reduced the precision of risk estimates somewhat. Further follow-up of this cohort should reduce this limitation. A number of job exposures were indeterminate with respect to solubility class; these jobs were associated with low exposure levels across the plants, suggesting this limitation had minimal impact on our findings.

In summary, we found monotonic increases in lung cancer risk with increasing mean and cumulative exposures in a pooled cohort of two plants with much lower exposure levels than previously studied.[6] The mean working lifetime exposure at these plants ($1.3\,\mu g/m^3$) was lower than the current OSHA permissible exposure limit (PEL) of $2\,\mu g/m^3$. Furthermore, risk per unit exposure for both mean and cumulative beryllium in this two-plant cohort with a higher percentage of insoluble exposure was similar to that in the three-plant cohort. These findings suggest that the pooled cohort estimates on which OSHA's lung cancer risk assessment is based are relevant for workers in the modern beryllium industry.

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Contributor MKS-B conceived of and coordinated the study and led the drafting of the manuscript. JC coordinated the estimation of the exposure-years by solubility class. JAD conducted the statistical analyses. All authors contributed to the drafting of the manuscript and approved its final version.

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Competing interests None declared.

Ethics approval The study has been conducted with the approval of the NIOSH institutional review board (Protocol no 93-DSHEFS-06).

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