Cohort mortality study of workers at seven beryllium processing plants: update and associations with cumulative and maximum exposure

Mary K Schubauer-Berigan, James R Couch, Martin R Petersen, et al.

Updated information and services can be found at:

http://oem.bmj.com/content/early/2010/10/14/oem.2010.056481.full.html

These include:

References	This article cites 36 articles, 10 of which can be accessed free at: http://oem.bmj.com/content/early/2010/10/14/oem.2010.056481.full.html#ref-list-1
P<P	Published online October 15, 2010 in advance of the print journal.
Email alerting service	Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

Advance online articles have been peer reviewed and accepted for publication but have not yet appeared in the paper journal (edited, typeset versions may be posted when available prior to final publication). Advance online articles are citable and establish publication priority; they are indexed by PubMed from initial publication. Citations to Advance online articles must include the digital object identifier (DOIs) and date of initial publication.

To request permissions go to:

http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:

http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:

http://journals.bmj.com/cgi/ep

Original article

Cohort mortality study of workers at seven beryllium processing plants: update and associations with cumulative and maximum exposure

Mary K Schubauer-Berigan, James R Couch, Martin R Petersen, Tania Carreón, Yan Jin, James A Deddens

ABSTRACT

Objectives To extend follow-up of cause-specific mortality in workers at seven beryllium processing plants and to estimate associations between mortality risk and beryllium exposure.

Methods 9199 workers were followed for mortality from 1940 through 2005. Standardised mortality ratios (SMRs) were estimated based on US population comparisons for lung, nervous system and urinary tract cancers, chronic obstructive pulmonary disease (COPD), chronic kidney disease, and categories containing chronic beryllium disease (CBD) and cor pulmonale. Associations with maximum and cumulative exposure were calculated for a subset of the workers.

Results Overall mortality in the cohort compared with the US population was elevated for lung cancer (SMR 1.17; 95% CI 1.08 to 1.28), COPD (SMR 1.23; 95% CI 1.13 to 1.32), and the categories containing CBD (SMR 7.80; 95% CI 6.26 to 9.60) and cor pulmonale (SMR 1.17; 95% CI 1.08 to 1.26). Mortality rates for most diseases of interest increased with time-since-hire. For the category including CBD, rates were substantially elevated compared to the US population across all exposure groups. Workers whose maximum beryllium exposure was ≥ 10 $\mu g/m^3$ had higher rates of lung cancer, urinary tract cancer, COPD and the category containing cor pulmonale than workers with lower exposure. Significant positive trends with cumulative exposure were observed for nervous system cancers (p=0.0006) and, when short-term workers were excluded, lung cancer (p=0.01), urinary tract cancer (p=0.003) and COPD (p<0.0001).

Conclusion These findings reaffirm that lung cancer and CBD, and suggest that COPD and nervous system and urinary tract cancers, are related to beryllium exposure. Cigarette smoking and exposure to other lung carcinogens are unlikely to explain these elevations.

Beryllium, a metal with unique properties, has been associated with adverse health effects. In the 1940s, beryllium exposure at high levels was observed to cause acute pneumonitis in US workers,[1][2] and lower level exposure caused an immunologically mediated, granulomatous lung disorder termed chronic beryllium disease (CBD).[3][4] These effects may be manifestations of the same disease.[5] Beryllium has also been found to cause bone and lung cancer in several species of laboratory animals[6][7] and has shown possible associations with nervous system cancer[7] and kidney disease in humans.[8][9] The International Agency for Research on Cancer

What this paper adds

- ► Beryllium has been designated a known human carcinogen by the International Agency for Research on Cancer, based upon human and animal studies of lung cancer.
- ► This cohort of workers from seven US beryllium processing facilities provides much of the human evidence regarding lung cancer risk from beryllium exposure; however, quantitative associations were available at only a single beryllium facility.
- ► In this update of mortality at the seven plants (including three with quantitative beryllium exposure estimates), we observed an association between maximum annual and cumulative beryllium exposure and lung cancer.
- ► For the first time, associations are reported between beryllium and other outcomes, including chronic obstructive pulmonary disease and cancers of the nervous system and urinary tract.

has designated beryllium a group 1 human carcinogen,[7][10] based on toxicological studies and findings of increased lung cancer risk among individuals enrolled in a beryllium case registry[11] or employed in the US beryllium processing industry.[9][12]

The largest study of beryllium-exposed workers is a pooled cohort study of 9225 workers at seven beryllium processing plants.[9] This study found a 26% elevation in risk of lung cancer (compared to the US population), which was not completely explained by differences in smoking patterns. The elevations were greatest for workers at the earliest-operating plants, which had the highest worker exposures to beryllium, and over periods associated with longer latency. Significant elevations were observed in mortality from ischaemic heart disease, chronic renal disease, and a combined category of 'pneumoconiosis and other respiratory disease'. Since the publication of this study, beryllium exposure estimates have been developed through the creation of job—exposure matrices (JEMs) at three plants in the study. A lung cancer nested case—control study at one of these plants found elevations associated with average and maximum exposure.[12][13] With quantitative exposure estimates available at two additional plants, we extended

Original article

follow-up of the cohort of workers in all seven facilities, focussing on the three plants with quantitative exposure estimates. Exposure—response associations were evaluated between two metrics of exposure (maximum and cumulative 'daily weighted average' (DWA) exposure) and several outcomes. These exposure metrics were selected because their calculation using grouped (person-years) analysis methods is straightforward, and maximum exposure was found to be associated with lung cancer in the previous nested case—control study.

The outcome of primary interest was lung cancer, given the clear evidence of lung carcinogenicity in animal studies and the focus on this outcome in previous analyses of beryllium workers.[9 12–15] Other outcomes were also of substantial a priori interest. CBD and causes related to cor pulmonale (as sequelae of CBD) have long been studied among beryllium workers.[9 16] Chronic obstructive pulmonary disease (COPD) was of interest because obstructive lung disease has been found or suggested to be related to beryllium exposure.[17–19] Malignant and non-malignant renal disease were of interest because chronic renal disease elevation was found previously in this cohort,[9] and kidney calcifications were observed among members of the Beryllium Case Registry.[20] Lastly, we included nervous system cancer because elevations were observed among beryllium-exposed workers at a US nuclear facility.[7]

For lung cancer, a Bayesian adjustment was made for differences in smoking behaviour between the US population and the cohort[21] and between a sample of low- and high-exposed workers within the cohort[22] for whom smoking data were collected in 1968.[9]

METHODS

This study was reviewed and approved by the Human Subjects Review Board of the National Institute for Occupational Safety and Health.

Cohort assembly and follow-up

The cohort, assembled for the previous study,[9] included male workers employed for at least 2 days after 1 January 1940 and before 1 January 1970. This cohort and all associated data, modified as described below, were used for the current study (online appendix table 1). Five plants (in Lorain, Lucky, Cleveland and Elmore, Ohio) are owned by company A, and two plants (in Reading and Hazleton, Pennsylvania) are owned by company B. For the Elmore, Reading and Hazleton facilities, employment records obtained from the plants were used to code complete work history information to link to the JEM. Corrections to the cohort database are described in the online appendix.

Mortality follow-up through 1988 and (for the Reading plant) through 1992 is described elsewhere.[9 13] Additional follow-up and cause-of-death ascertainment through 31 December 2005 were conducted for all cohort members using linkage to the US Social Security Administration and the National Death Index. Likely but inexact matches were manually reviewed. Both underlying and multiple causes of death were considered, as described below.

Exposure assessment

Area- and breathing zone-based air concentrations of beryllium were measured for many jobs by plant personnel on a quarterly basis from the 1950s (Elmore and Hazleton) or the 1970s (Reading) to the 1990s at three of the beryllium plants, using similar methods. From these measurements, plant personnel developed DWA values for specific operations within departments: for each task, the measured beryllium concentration was

multiplied by the time spent in that task. These exposure—time products were summed for all tasks during the work day or shift, and the sum was divided by total time (normally 8 h) for the DWA. These DWAs were used by researchers to create JEMs for the facilities using similar methods. Developing JEMs was not feasible at four plants (Lorain, Lucky, and the two in Cleveland) due to the unavailability of individual work history or exposure measurement data. JEMs that permitted linkage to work history data were available for the Reading[23], Hazleton[24] and Elmore facilities.[25] JEMs for the two former facilities were adapted as follows for use in the present study: annual department—job combinations coded from workers' employment records were linked to the appropriate combinations in the JEM. For combinations missing in the JEM, new values were assigned based on available monitoring data or were imputed from similarly exposed jobs or time periods.[25] Where multiple quarterly exposure values were given for an annual department—job combination, geometric mean estimates were used to obtain a single estimate for the year. To account for potential confounding by other carcinogenic exposures, the JEM identified jobs involving exposure to known human lung carcinogens (acid mist, asbestos, cadmium, chromium, nickel, silica).[23] We accounted for potential confounding by cigarette smoking using indirect external and within-cohort adjustments (described further below).

Statistical analysis

The cohort was analysed using a modified person-years analysis program, LTAS.NET,[26 27] to calculate standardised mortality ratios (SMRs) indirectly standardised to the US population and directly standardised rate ratios (SRRs) for internal comparisons. Person-years at risk began on the third day of employment for each worker (to account for a minimum employment duration of 2 days) or when the rate file began, whichever was later, and ended on the earliest of (1) the date of death, (2) the end of follow-up (31 December 2005) or the date the worker was last employed for workers not found to be deceased who left employment before 1979, when the National Death Index began.

In LTAS.NET, outcomes are grouped into one of 92 or 119 cause-of-death categories for rates beginning in 1940 or 1960, respectively.[28] Analyses through 2005 based on multiple causes of death (which considers all contributing causes of death mentioned on the death certificate) were preferred for outcomes with long survival times, and were used for urinary diseases, COPD, and the categories related to CBD (pneumoconiosis other than asbestosis or silicosis) and cor pulmonale (diseases of the arteries, veins and pulmonary circulation)[29]; however, the comparison rates for such analyses do not begin until 1960. Thus, for rapidly fatal outcomes (ie, lung cancer and brain and other nervous system cancers) and for the large group of pneumoconiosis and 'other' respiratory diseases, underlying-cause rates from 1940 to 2005 were used. All analyses were adjusted for race (white versus all other races), and age and calendar year in 5-year intervals. SMR and SRR analyses were also conducted by duration of employment and time since first employment (TSFE) among all workers in the analysis.

Exposure—response analyses

SMRs and SRRs related to quantitative beryllium exposure were calculated for just the subcohort of workers (n=5436) employed at the three plants with beryllium JEMs. Cumulative exposure was estimated for each worker at each time point by summing the DWA assigned from the JEM for that job and all previous jobs for each day employed in the job. In calculating cumulative exposure, the DWA was multiplied by 5/7, so that accumulated exposure

would represent the exposure received in a 5-day work week. A 10-year lag was employed for cumulative exposure, and lagged-out person-time and events were included in the lowest exposure group.[30] Person-time and events were also categorised into groups based on maximum DWA exposure, which represents the highest mean DWA exposure received to that point in time. Cutpoints were selected a priori based on approximate quartiles of exposure among workers at the Reading plant.[13] Maximum exposure was treated as a time-dependent categorical variable, in which a subject's person-time accrued to the lowest maximum exposure category ($0-10 \mu g/m^3$) until he experienced a higher exposure, when all subsequent person-time accrued to the higher exposure category(s). This exposure metric was unlagged, because lagging is not supported in LTAS.NET with such variables. Average exposure was not used in this analysis, as its computation is not straightforward in grouped data methods. Cutpoints selected to represent approximate cumulative exposure quartiles of lung cancer case distribution were used for all outcomes of a priori interest. In sensitivity analyses, professionals, workers exposed to another lung carcinogen for more than 1 year, or short-term workers (those employed for <1 year) were excluded. Some epidemiological studies completely exclude short-term workers to account for possible lifestyle differences that may affect cancer risk and because these workers generally have little exposure. However, we (as have previous authors) included all workers in primary analyses, as short-term beryllium workers often had high-intensity exposure: workers who received heavy beryllium exposure and showed evidence of dermatological or pulmonary sensitivity were frequently removed from the workforce.[31]

Confidence intervals on SMRs and SRRs were calculated by LTAS.NET, assuming a Poisson distribution of the number of observed events. A trend slope and SE for the change in standardised rate with increasing duration, TSFE and cumulative exposure were calculated as described elsewhere,[26] and Wald-type tests were used to calculate the two-sided p value for trend. No trend test could be calculated for maximum exposure; hence, an additional analysis grouping across all categories above the baseline was conducted for this metric.

Smoking comparability assessment

The previous cohort study[9] used an indirect adjustment[32] to evaluate the impact of smoking differences in the cohort (estimated from a smoking questionnaire completed by 76% of then-current employees in 1968) compared to the US population on the estimated SMR. We made several corrections to this approach, as described in the online appendix. In summary, we improved the data source used for US smoking rates.[33] Also, for analyses based upon external comparisons we allocated pipe and cigar smokers (who were known not to be current cigarette smokers) to the category of either never or former cigarette smokers, based on the distribution of never/former smokers among those of known status in the same age/birth cohort. For new analyses based on within-cohort comparisons we treated them as current pipe or cigar smokers.

To evaluate bias in the SMR by differences in smoking status, the ratio of the incidence of lung cancer in the US population to that among never smokers was estimated by summing the product of the percentage in each smoking group (age-adjusted to the cohort) and the rate ratios (compared to never smokers), obtained from data in table 21 of Hammond.[34] These rate ratios and the estimated 95% CIs were 1.0 for never smokers, 5.94 for former smokers (95% CI 4.00 to 8.83), 6.11 (95% CI 4.05 to 9.20) for current ≤1 pack/day smokers and 10.8 (95% CI 7.48 to 15.4) for current >1 pack/day smokers. These estimates are comparable

to those reported in a recent meta-analysis of cigarette smoking and lung cancer.[35] The ratio of the incidence of lung cancer in the overall cohort to that among never smokers was estimated similarly. The quotient of this ratio in the cohort and that in the US population was the estimated bias in the SMR for the cohort overall and (separately) for the plants represented in the survey (the Reading, Cleveland, Elmore and Hazleton plants). A Bayesian analysis[21] was conducted to adjust the observed SMR for this bias, including 95% credible intervals incorporating uncertainty in smoking quantities and rate ratios. Prior distributions for effect of smoking on lung cancer were specified as normal distributions with means and variances based on the log of the rate ratios and 95% CIs. The priors for smoking prevalence were specified as multivariate normal distributions based on the proportions in the smoking sample and in the US population. A non-informative prior distribution (a normal distribution with mean 0 and variance 10 000) was used for the smoking-adjusted SMR.

Two techniques were used to evaluate potential within-cohort confounding by smoking. First, the association between cross-classified smoking categories and cumulative and maximum exposure categories among the survey respondents was assessed using a χ^2 distribution in SAS (v 9.2). Second, a Bayesian method[22] was used to adjust the rate ratio for high-exposed workers compared to low-exposed, obtained from a Poisson regression model (adjusting for race, age and calendar year categories), and assuming the lowest exposure group was the 'unexposed' group for whom the age standardisation was conducted. Non-informative prior distributions (normal with mean 0 and variance 10 000) were used for the coefficients of the Poisson model. Prior distributions for effect of smoking on lung cancer were specified as normal distributions as described above. For current pipe and cigar smokers, a rate ratio of 5.0 (95% CI 4.16 to 6.01)[36] was used. The priors for smoking prevalence in the high-exposed and low-exposed groups were specified as multivariate normal distributions based on the smoking proportions in the two exposure groups, respectively. WinBUGS software was used for the Bayesian analyses and Monte Carlo simulations; further information and the code for these simulations are provided in the online appendix.

RESULTS
Overall SMRs

Among the 9199 cohort members, 63% were deceased (online appendix table 1) and 170 (1.8%) were lost to follow-up. With 352 497 person-years and 5810 underlying-cause deaths since 1940, the all-cause SMR was 1.04 (95% CI 1.02 to 1.07). Among the causes of death of a priori interest, lung cancer, pneumoconiosis and other respiratory diseases (especially pneumoconiosis other than asbestosis and silicosis), COPD, and the category containing cor pulmonale were elevated (table 1). Urinary tract cancer and chronic renal disease SMRs were slightly, although not significantly, elevated.

Lung cancer SMRs varied substantially by plant: workers at the Lorain plant, the Reading plant, and more than one plant owned by company A showed 45%, 20% and 64% higher mortality rates, respectively, than the US population (table 1). Workers at the Reading, Elmore and Hazleton plants and those whose plant was unknown exhibited the highest SMRs for the category containing CBD (table 1).

Associations with employment duration and time since first employment

SMRs did not vary substantially by 10-year lagged employment duration category for lung cancer, urinary tract cancer, COPD,

Original article

Table 1 Standardised mortality ratios by plant*, for causes of death of a priori interest, based on (A) underlying cause of death 1940–2005 and (B) multiple causes of death 1960–2005

(A) Underlying cause-of-death analysis, 1940–2005 (ICD-10 codes)

Plant owner	Plant	Cause of death, SMR (95% CI), N		
		Lung cancer (C33–C34)	Nervous system cancer (C47, C70–C72)	Pneumoconiosis and other respiratory disease (J30–J33, J34.1–J34.8, J35–J39, J47, J60–J64, J66–J95, J98, R09.1)
Company A and B	All plants	1.17 (1.08 to 1.28), 545	0.87 (0.58 to 1.24), 29	1.99 (1.67 to 2.35), 136
Company A	1. Lorain, OH	1.45 (1.17 to 1.78), 90	0.23 (0.01 to 1.28), 1	1.83 (1.08 to 2.89), 18
Company B	2. Reading, PA	1.20 (1.04 to 1.37), 218	1.01 (0.54 to 1.73), 13	1.80 (1.34 to 2.37), 51
Company A	3. Lucky, OH	0.92 (0.59 to 1.37), 24	1.08 (0.13 to 3.91), 2	1.31 (0.42 to 3.05), 5
Company A	4, 5. Cleveland, OH	1.09 (0.88 to 1.33), 97	0.81 (0.26 to 1.89), 5	1.19 (0.67 to 1.96), 15
Company A	6. Elmore, OH	1.01 (0.74 to 1.36), 45	1.05 (0.29 to 2.69), 4	2.00 (1.00 to 3.58), 11
Company B	7. Hazleton, PA	1.03 (0.70 to 1.47), 30	0 (0 to 1.66), 0	5.12 (3.08 to 7.99), 19
Company A	>1 Plant of company A	1.64 (1.06 to 2.43), 25	1.84 (0.22 to 6.66), 2	2.28 (0.74 to 5.33), 5
	Unknown	1.05 (0.60 to 1.70), 16	1.85 (0.22 to 6.68), 2	4.36 (2.09 to 8.02), 10

(B) Multiple causes of death, 1960–2005 (ICD-10 codes)

Plant	Cause of death, SMR (95% CI), N				
	Urinary tract cancer (C64–C68)	Chronic obstructive pulmonary disease (J40–J44)	Pneumoconiosis excluding asbestosis and silicosis (J60, J63–J64)	Diseases of arteries, veins and pulmonary circulation (I26–I28, I70–I87, I89–I95, I97.2, I99, M30–M31, R58)	Chronic and unspecified renal disease (N01.9, N03, N05, N07, N14.0–N14.3, N15.0, N16.1–N16.8, N18–N19, N26)
All plants	1.07 (0.86 to 1.31), 92	1.23 (1.13 to 1.32), 670	7.80 (6.26 to 9.60), 89	1.17 (1.08 to 1.26), 656	1.11 (0.97 to 1.27), 231
1. Lorain, OH	1.19 (0.65 to 1.99), 14	1.68 (1.41 to 2.00), 130	1.14 (0.14 to 4.13), 2	1.14 (0.92 to 1.39), 95	1.30 (0.91 to 1.79), 36
2. Reading, PA	1.22 (0.88 to 1.65), 42	1.24 (1.09 to 1.39), 273	6.03 (4.07 to 8.61), 30	1.29 (1.15 to 1.44), 317	1.17 (0.94 to 1.43), 94
3. Lucky, OH	0.82 (0.22 to 2.09), 4	1.07 (0.74 to 1.50), 34	3.22 (0.39 to 11.6), 2	0.98 (0.66 to 1.41), 29	0.91 (0.45 to 1.62), 11
4, 5. Cleveland, OH	0.87 (0.48 to 1.46), 14	1.04 (0.85 to 1.26), 107	3.42 (1.38 to 7.06), 7	1.12 (0.92 to 1.35), 111	0.98 (0.70 to 1.34), 40
6. Elmore, OH	0.77 (0.28 to 1.68), 6	0.93 (0.67 to 1.26), 42	12.3 (5.62 to 23.4), 9	0.71 (0.48 to 1.02), 29	0.93 (0.55 to 1.48), 18
7. Hazleton, PA	0.79 (0.22 to 2.03), 4	1.13 (0.79 to 1.57), 35	58.0 (38.9 to 83.4), 29	1.22 (0.83 to 1.72), 32	1.64 (1.01 to 2.50), 21
>1 Plant of company A	1.78 (0.58 to 4.16), 5	1.37 (0.89 to 2.03), 25	2.57 (0.07 to 14.3), 1	1.13 (0.69 to 1.75), 20	0.75 (0.24 to 1.76), 5
Unknown	0.68 (0.08 to 2.45), 2	1.18 (0.74 to 1.78), 22	18.2 (7.31 to 37.5), 7	1.17 (0.73 to 1.77), 22	0.82 (0.30 to 1.79), 6

*Data for workers employed at both company A and B are not included because the total number of deaths from these causes was very small (n=6); however, these workers are included in 'All plants'.
ICD-10, International Classification of Diseases, 10th Revision; SMR, standardised mortality ratio.

diseases of circulation, or chronic and unspecified renal disease for all plants combined (table 2). SRRs relating longer to shorter durations of employment for these outcomes were not significantly different from unity, and no significant trend with increasing employment duration was observed. The categories containing CBD starting in 1940 and 1960 each showed sharply increasing SMRs with increased employment duration, and a highly significant trend in standardised rates with increasing employment duration was observed (table 2).

SMRs for lung cancer, pneumoconiosis and other respiratory diseases (1940–2005), urinary tract cancer, COPD and circulatory diseases tended to increase with increasing TSFE (table 3). For example, lung cancer and COPD 35 years or more since first employment showed significant 28% and 33% elevations (respectively) compared to the US population but were not significantly elevated at shorter times. Highly significant positive trends in standardised rates with increasing TSFE were observed for all evaluated outcomes except nervous system cancers and the category containing CBD (table 3).

Associations with beryllium exposure
Lung cancer
For the subcohort of 5436 workers employed at the Reading, Elmore and Hazleton plants, lung cancer rates were significantly higher than for the US population only for cumulative beryllium exposure of 10 300 μg/m³-days or greater; however, no significant increase in trend with cumulative exposure was observed in the standardised rate (p=0.34; table 4A). Excluding workers

exposed for at least 1 year to another potential lung carcinogen or excluding professional workers gave very similar results. However, when short-term workers were excluded, the SMR in the lowest exposure group decreased substantially, and a significant positive trend (4.28×10^{-8} lung cancer deaths per μg/m³-day·person-year) was observed in the standardised rate with increasing cumulative exposure (p=0.012). These trends were even stronger when stratified by plant: the corresponding slopes and p values were 6.99×10^{-8} (p<0.0001) at the Reading plant, 3.54×10^{-7} (p<0.0001) at the Elmore plant and 1.10×10^{-7} (p=0.13) at the Hazleton plant.

Lung cancer SMRs were not elevated for the group with <10 μg/m³ maximum exposure, but were significantly and similarly elevated for higher exposure groups (table 4B). All exposure groups combined with 10 μg/m³ or higher maximum exposure showed a 40% increased risk of lung cancer compared to the general population (95% CI 21% to 61%). Standardised rates were significantly higher within each maximum exposure category above 10 μg/m³ compared to the lowest category, and as a group maximum DWA exposure at 10 μg/m³ or higher was associated with a 72% increased lung cancer rate (95% CI 32% to 124%) compared to the group receiving <10 μg/m³ maximum exposure. These results varied little when excluding short-term workers, those who were exposed for 1 year or more to another lung carcinogen, or professional workers (table 4B).

Other outcomes
The categories containing CBD showed significantly elevated SMRs across nearly all cumulative exposure categories (online

Table 2 Standardised mortality ratios compared to the US population and internally standardised rate ratios for diseases of a priori interest by duration employed (lagged 10 years)

| | Employment duration (years), 10-year lag | | | | | | | | | | | | |
| | 0 to <1 | | | 1 to <5 | | | 5 to <10 | | | ≥10 | | | Trend slope*, p value |
	N	SMR SRR	95% CI	N	SMR SRR	95% CI	N	SMR SRR	95% CI	N	SMR SRR	95% CI	
Underlying cause of death, 1940—2005†													
Lung cancer	293	1.22	1.09 to 1.37	120	1.09	0.91 to 1.31	39	1.14	0.81 to 1.56	93	1.15	0.93 to 1.41	2.70×10^{-7}, 0.98
		1.0	Referent		0.92	0.75 to 1.15		0.91	0.64 to 1.28		1.03	0.76 to 1.40	
Nervous system cancer	14	0.76	0.42 to 1.28	7	0.92	0.37 to 1.90	1	0.41	0.01 to 2.27	7	1.38	0.55 to 2.84	-1.63×10^{-6}, 0.77
		1.0	Referent		1.20	0.47 to 3.05		0.58	0.08 to 4.47		6.99	1.38 to 35.3	
Pneumoconiosis and other respiratory disease	54	1.51	1.13 to 1.96	24	1.48	0.95 to 2.20	10	2.15	1.03 to 3.96	48	4.14	3.05 to 5.48	3.16×10^{-5}, <0.0001
		1.0	Referent		1.01	0.62 to 1.65		1.49	0.71 to 3.14		2.82	1.86 to 4.29	
Multiple cause of death, 1960—2005†													
Urinary tract cancer	49	1.13	0.83 to 1.49	27	1.30	0.86 to 1.89	3	0.47	0.10 to 1.38	13	0.85	0.45 to 1.46	-1.11×10^{-5}, 0.39
		1.0	Referent		1.19	0.74 to 1.91		0.34	0.11 to 1.11		0.81	0.40 to 1.64	
Chronic obstructive pulmonary disease	382	1.38	1.25 to 1.53	137	1.04	0.87 to 1.23	38	0.97	0.69 to 1.34	113	1.14	0.94 to 1.36	-3.16×10^{-5}, 0.44
		1.0	Referent		0.73	0.60 to 0.89		0.67	0.48 to 0.95		0.81	0.65 to 1.01	
Pneumoconiosis other than asbestosis and silicosis	20	3.33	2.03 to 5.14	13	4.75	2.53 to 8.13	11	12.7	6.33 to 22.7	45	25.0	18.3 to 33.5	4.67×10^{-5}, <0.0001
		1.0	Referent		1.31	0.64 to 2.67		3.99	1.80 to 8.86		6.44	3.74 to 11.1	
Diseases of arteries, veins, pulmonary circulation	362	1.21	1.09 to 1.34	148	1.10	0.93 to 1.29	42	0.96	0.69 to 1.30	104	1.21	0.99 to 1.46	-6.56×10^{-6}, 0.87
		1.0	Referent		0.89	0.73 to 1.08		0.72	0.51 to 1.01		1.06	0.82 to 1.38	
Chronic and unspecified renal disease	131	1.28	1.07 to 1.52	47	0.92	0.67 to 1.22	7	0.49	0.20 to 1.02	46	1.15	0.84 to 1.53	-1.46×10^{-5}, 0.45
		1.0	Referent		0.83	0.53 to 1.29		0.42	0.19 to 0.91		0.82	0.58 to 1.15	

*Cause-specific deaths per year of employment·person-year.
†Cause-of-death categories as defined in table 1.
SMR, standardised mortality ratio; SRR, standardised rate ratio.

appendix table 2). COPD, urinary tract cancer and circulatory diseases showed significantly elevated SMRs in the highest cumulative exposure group. Among these other outcomes, only nervous system cancers showed a significant positive trend in standardised rates with 10-year lagged cumulative exposure (p=0.0006; online appendix table 2). When excluding those employed for less than 1 year, categories containing CBD still displayed elevated SMRs across the exposure categories (table 5). For all other outcomes, SMRs associated with the lowest exposure category were below unity. SMRs in the highest

exposure category remained significantly elevated for urinary tract cancer and COPD; highly significant positive trends with increasing cumulative exposure were observed for these two outcomes (table 5).

In analyses by stratified maximum exposure, the categories containing CBD showed significantly elevated SMRs across nearly all exposure groups (table 6). SMRs and SRRs for COPD and circulatory diseases tended to increase with increasing maximum exposure categories. For all exposure groups above $10 \mu g/m^3$ combined, significantly elevated SMRs were observed

Table 3 Standardised mortality ratios compared to the US population and internally standardised rate ratios for diseases of a priori interest by time since first employment

| | Time since first employment (years) | | | | | | | | | | | | |
| | 0 to <15 | | | 15 to <25 | | | 25 to <35 | | | ≥35 | | | Trend slope*, p value |
	N	SMR SRR	95% CI	N	SMR SRR	95% CI	N	SMR SRR	95% CI	N	SMR SRR	95% CI	
Underlying causes of death, 1940-2005†													
Lung cancer	27	0.89	0.59 to 1.29	71	1.12	0.88 to 1.42	123	1.06	0.88 to 1.26	324	1.28	1.14 to 1.42	2.12×10^{-5}, <0.0001
		1.0	Referent		2.24	0.78 to 6.45		2.83	1.03 to 7.78		3.68	1.36 to 9.95	
Nervous system cancers	4	0.77	0.21 to 1.96	9	1.50	0.69 to 2.85	5	0.61	0.20 to 1.42	11	0.78	0.39 to 1.40	1.08×10^{-7}, 0.87
		1.0	Referent		1.53	0.26 to 8.89		0.77	0.12 to 5.04		1.27	0.22 to 7.35	
Pneumoconiosis and other respiratory disease	9	1.67	0.76 to 3.17	21	2.85	1.76 to 4.36	25	2.08	1.34 to 3.07	81	1.86	1.48 to 2.31	4.75×10^{-6}, 0.0002
		1.0	Referent		2.73	0.97 to 7.71		5.29	1.93 to 14.5		4.46	1.82 to 10.9	
Multiple causes of death, 1960-2005†													
Urinary tract cancer	3	0.97	0.20 to 2.83	8	0.72	0.31 to 1.42	17	0.86	0.50 to 1.37	64	1.24	0.95 to 1.58	4.91×10^{-6}, 0.002
		1.0	Referent		0.36	0.07 to 1.93		0.55	0.14 to 2.16		1.04	0.29 to 3.75	
Chronic obstructive pulmonary disease	6	0.43	0.16 to 0.94	58	0.99	0.75 to 1.28	130	1.11	0.93 to 1.32	476	1.33	1.21 to 1.46	4.88×10^{-5}, <0.0001
		1.0	Referent		11.0	4.26 to 28.1		21.8	8.76 to 54.0		24.1	10.2 to 57.4	
Pneumoconiosis other than asbestosis and silicosis	4	7.50	2.04 to 19.2	15	7.27	4.07 to 12.0	25	7.39	4.78 to 10.9	45	8.28	6.04 to 11.1	1.74×10^{-6}, 0.77
		1.0	Referent		1.94	0.53 to 7.09		4.40	1.28 to 15.2		2.14	0.66 to 6.88	
Diseases of arteries, veins, pulmonary circulation	29	0.85	0.57 to 1.22	134	1.15	0.96 to 1.36	182	1.21	1.04 to 1.40	311	1.19	1.06 to 1.33	2.03×10^{-5}, 0.02
		1.0	Referent		1.91	1.12 to 3.24		4.25	2.32 to 7.78		2.65	1.62 to 4.34	
Chronic and unspecified renal disease	4	1.27	0.35 to 3.24	12	0.95	0.49 to 1.66	43	1.26	0.91 to 1.69	172	1.09	0.94 to 1.27	1.57×10^{-5}, <0.0001
		1.0	Referent		1.02	0.15 to 7.13		4.22	0.68 to 26.2		4.54	0.77 to 26.9	

*Cause-specific deaths per year since first employment·person-year.
†Cause-of-death categories as defined as in table 1.
SMR, standardised mortality ratio; SRR, standardised rate ratio.

Original article

Table 4 Lung cancer standardised mortality ratios compared to the US population (based on underlying cause of death analysis, 1940-2005) and internally standardised rate ratios, plants 2, 6 and 7 combined: including all workers; excluding short-term workers (employed <1 year); excluding workers exposed for 1 year or more to another occupational lung carcinogen; excluding professional workers, by (A) cumulative (lagged 10 years) and (B) maximum (unlagged) beryllium exposure

(A)	Cumulative* beryllium exposure (μg/m³-days)												
	0 to <550			550 to <2500			2500 to <10300			≥10300			
	N	SMR SRR	95% CI	N	SMR SRR	95% CI	N	SMR SRR	95% CI	N	SMR SRR	95% CI	Trend slope†, p value
All workers	73	1.08	0.85 to 1.36	73	1.12	0.88 to 1.41	73	1.10	0.86 to 1.38	74	1.31	1.03 to 1.65	
		1.0	Referent		0.96	0.69 to 1.34		0.91	0.66 to 1.27		1.12	0.79 to 1.60	1.08×10^{-8}, 0.34
Excluding short-term workers	11	0.63	0.32 to 1.13	27	0.91	0.60 to 1.32	44	1.04	0.75 to 1.39	64	1.26	0.97 to 1.61	
		1.0	Referent		1.56	0.73 to 3.34		1.66	0.83 to 3.32		1.97	0.99 to 3.97	4.28×10^{-8}, 0.012
Excluding workers exposed for ≥1 year to another occupational carcinogen	72	1.13	0.88 to 1.42	68	1.16	0.90 to 1.48	55	1.10	0.83 to 1.43	38	1.48	1.05 to 2.03	
		1.0	Referent		0.99	0.71 to 1.39		0.89	0.62 to 1.27		1.11	0.73 to 1.66	5.48×10^{-9}, 0.38
Excluding professional workers	62	1.11	0.85 to 1.43	66	1.25	0.97 to 1.59	68	1.13	0.88 to 1.43	71	1.30	1.02 to 1.64	
		1.0	Referent		1.03	0.72 to 1.47		0.91	0.64 to 1.30		1.08	0.73 to 1.31	4.74×10^{-9}, 0.69

(B)	Maximum beryllium exposure (μg/m³)												
	<10			10 to <25			25 to <70			≥70			All ≥10	
	N	SMR SRR	95% CI	N	SMR SRR	95% CI	N	SMR SRR	95% CI	N	SMR SRR	95% CI	SMR SRR‡	95% CI
All workers	95	0.83	0.67 to 1.02	45	1.45	1.06 to 1.94	88	1.49	1.19 to 1.83	65	1.27	0.98 to 1.62	1.40	1.21 to 1.61
		1.0	Referent		1.83	1.26 to 2.65		1.89	1.34 to 2.66		1.50	1.08 to 2.09	1.72	1.32 to 2.24
Excluding short-term workers	70	0.85	0.66 to 1.07	22	1.80	1.13 to 2.73	21	0.96	0.60 to 1.47	33	1.40	0.97 to 1.97	1.32	1.04 to 1.65
		1.0	Referent		1.90	1.15 to 3.16		1.32	0.76 to 2.29		1.60	1.04 to 2.45	1.64	1.15 to 2.32
Excluding workers exposed for ≥1 year to another occupational carcinogen	73	0.82	0.65 to 1.04	38	1.47	1.04 to 2.02	80	1.61	1.27 to 2.00	42	1.24	0.90 to 1.68	1.46	1.24 to 1.71
		1.0	Referent		1.96	1.29 to 2.97		1.86	1.33 to 2.60		1.54	1.04 to 2.29	1.77	1.32 to 2.37
Excluding professional workers	72	0.87	0.68 to 1.09	44	1.46	1.06 to 1.97	86	1.46	1.17 to 1.80	65	1.27	0.98 to 1.62	1.39	1.20 to 1.60
		1.0	Referent		1.79	1.20 to 2.65		1.80	1.24 to 2.61		1.43	1.00 to 2.03	1.64	1.23 to 2.20

*Cumulative exposure adjusted to a 5-day exposure period per week.
†Lung cancer deaths per μg/m³-day·person-year.
‡Compared to <10 μg/m³ maximum daily weighted average exposure.
SMR, standardised mortality ratio; SRR, standardised rate ratio.

for urinary tract cancer, COPD, outcomes related to CBD, and circulatory diseases, while only the former two outcomes showed significant SRRs compared to the lowest exposure group (table 6). These results were affected little by the exclusion of short-term workers (online appendix table 3).

Smoking adjustments for lung cancer
External comparison
The bias factor for the lung cancer SMR expected from smoking-related differences between the cohort and the US population was 0.997 (95% credible interval 0.948 to 1.05). Applying this bias factor to the observed SMR for all plants combined (table 1) led to a bias-adjusted SMR of 1.18 (95% credible interval 1.06 to 1.29). Applying the bias factor to the SMR for just the plants included in the smoking survey led to an adjusted SMR of 1.13 (95% credible interval 1.01 to 1.26).

Internal cohort comparison
Little association was found between either cumulative ($\chi^2_{12}=6.65$; p=0.88) or maximum beryllium ($\chi^2_{12}=11.9$; p=0.46) exposure and smoking status within the cohort. For cumulative exposure, a bias-unadjusted lung cancer rate ratio obtained from a Poisson regression model for the high-exposed (≥10 300 μg/m³-days) compared to the low-exposed group (including short-term workers) was 1.07 (95% credible interval 0.81 to 1.39). The bias factor from smoking calculated for this rate ratio was 0.96 (95% credible interval 0.88 to 1.05). Accounting for this bias and its uncertainty gave a bias-adjusted rate ratio of 1.11 (95% credible interval 0.83 to 1.47) for high compared to low cumulative exposures. Using maximum exposure as the metric, a bias-unadjusted lung cancer rate ratio

for high-exposed (≥10 μg/m³) compared to low-exposed (<10 μg/m³) groups was 1.70 (95% credible interval 1.31 to 2.20). The bias factor from smoking calculated for this rate ratio was 1.04 (95% credible interval 0.97 to 1.13), and the bias-adjusted rate ratio for maximum exposure was 1.64 (95% credible interval 1.24 to 2.13).

DISCUSSION
In this cohort mortality study, we observed strong evidence of an association between lung cancer and both employment at a beryllium plant and quantitative metrics of beryllium exposure. Lung cancer was elevated by 17% (95% CI 8% to 28%) overall in the combined cohort compared to the US population (a decrease from the SMRs observed previously[9]). The plants with earliest operation and the highest beryllium exposures, in Lorain, Ohio and Reading, Pennsylvania, exhibited significant lung cancer elevations, as did the group of workers employed at multiple plants, who tended to have lengthy employment duration (online appendix table 1). Other evidence for the lung carcinogenicity of beryllium includes the elevated SMRs observed with long TSFE (table 3), and the strong trend in internally standardised rates with increasing TSFE. More compelling is the evidence from the subcohort of 5436 workers with quantitative beryllium exposure estimates. Among these workers, lung cancer SMRs were significantly elevated for workers in the highest cumulative exposure group (≥10 300 μg/m³-days) and for workers having an annual maximum DWA of 10 μg/m³ or higher, whose lung cancer mortality rates were significantly higher than those of workers with lower maximum exposures. We note that these analyses were adjusted for birth

Table 5 Standardised mortality ratios compared to the US population and internally standardised rate ratios for causes of death of a priori interest other than lung cancer among workers employed for 1 year or more, by cumulative beryllium exposure level (lagged 10 years), assuming 5 days worked per week, for plants 2, 6 and 7 combined

	Cumulative beryllium exposure ($\mu g/m^3$-days)												
	0 to <550			550 to <2500			2500 to <10300			≥10300			
	N	SMR SRR	95% CI	N	SMR SRR	95% CI	N	SMR SRR	95% CI	N	SMR SRR	95% CI	Trend slope†, p value
Underlying causes of death, 1940-2005*													
Nervous system cancers	0	0	0 to 1.97	2	0.90	0.11 to 3.26	4	1.32	0.36 to 3.39	4	1.21	0.33 to 3.10	
		0	—		1.0	Referent		1.95	0.35 to 11.0		1.92	0.34 to 10.8	Not calculable
Pneumoconiosis and other respiratory disease	4	1.51	0.41 to 3.87	1	0.24	0.01 to 1.36	26	4.58	2.99 to 6.71	20	2.59	1.58 to 3.99	
		1.0	Referent		0.17	0.02 to 1.59		3.00	0.91 to 9.91		2.05	0.61 to 6.89	3.67×10^{-8}, 0.10
Multiple causes of death, 1960-2005*													
Urinary tract cancer	2	0.70	0.09 to 2.54	1	0.18	0.00 to 1.03	4	0.53	0.14 to 1.35	18	1.80	1.07 to 2.85	
		1.0	Referent		0.14	0.01 to 1.59		0.63	0.11 to 3.50		2.47	0.56 to 10.9	2.62×10^{-8}, 0.003
Chronic obstructive pulmonary disease	7	0.42	0.17 to 0.87	18	0.53	0.32 to 0.85	48	1.02	0.75 to 1.35	83	1.29	1.03 to 1.60	
		1.0	Referent		1.23	0.50 to 3.02		2.43	1.07 to 5.51		3.37	1.50 to 7.59	1.13×10^{-7}, <0.0001
Pneumoconiosis other than asbestosis and silicosis	3	8.78	1.81 to 25.7	3	4.98	1.03 to 14.6	31	37.8	25.7 to 53.6	18	12.5	7.38 to 19.7	
		1.0	Referent		0.65	0.13 to 3.34		4.80	1.44 to 15.9		2.47	0.71 to 8.55	2.76×10^{-8}, 0.28
Diseases of arteries, veins, pulmonary circulation	12	0.64	0.33 to 1.12	23	0.75	0.47 to 1.12	59	1.38	1.05 to 1.79	89	1.24	0.99 to 1.52	
		1.0	Referent		0.92	0.39 to 2.21		1.80	0.80 to 4.03		1.57	0.70 to 3.51	5.73×10^{-8}, 0.17
Chronic and unspecified renal disease	6	0.92	0.34 to 2.00	14	1.01	0.55 to 1.70	25	1.31	0.85 to 1.94	22	0.96	0.60 to 1.45	
		1.0	Referent		1.16	0.42 to 3.18		2.21	0.73 to 6.66		1.24	0.47 to 3.25	4.55×10^{-9}, 0.74

*Cause-of-death categories as defined in table 1.
†Cause-specific deaths per $\mu g/m^3$-day·person-year.
SMR, standardised mortality ratio; SRR, standardised rate ratio.

cohort, a potentially important confounder,[12] through adjustment on 5-year age and calendar-year periods.

A significant positive trend for lung cancer with increasing cumulative exposure was observed when excluding workers employed for less than 1 year. Such short-term workers, many of whom left the workforce due to adverse dermatological and respiratory reactions when exposed to high levels of beryllium,[8] had high maximum exposures but relatively low cumulative exposures. Although they comprised a majority of the lowest cumulative exposure group, they were an inappropriate 'baseline' group against which to compare workers with lower

exposure intensity of longer duration (hence higher cumulative exposure). When short-term workers were removed from the cumulative exposure analysis, the SMR in the baseline group decreased to below unity, and a clear association was observed between both maximum and cumulative beryllium exposure and lung cancer. The low COPD and lung cancer SMRs in the low exposure group may reflect a strong healthy worker effect related to a robust pre-employment screening program at the plants, which apparently excluded workers with evidence of prior chronic respiratory disease or lung function decrement (online appendix[31]).

Table 6 Standardised mortality ratios compared to the US population and internally standardised rate ratios for other causes of death of a priori interest by maximum beryllium exposure level (unlagged), for plants 2, 6 and 7 combined

	Maximum exposure ($\mu g/m^3$)													
	<10			10 to <25			25 to <70			≥70			All ≥10	
	N	SMR SRR	95% CI	N	SMR SRR	95% CI	N	SMR SRR	95% CI	N	SMR SRR	95% CI	SMR SRR†	95% CI
Underlying causes of death, 1940—2005*														
Nervous system cancers	6	0.67	0.25 to 1.46	4	1.80	0.49 to 4.61	5	1.20	0.39 to 2.79	2	0.56	0.07 to 2.02	1.10	0.55 to 2.01
		1.0	Referent		2.64	0.71 to 9.75		1.92	0.55 to 6.72		1.29	0.25 to 6.64	1.90	0.67 to 5.37
Pneumoconiosis and other respiratory disease	39	2.51	1.78 to 3.43	3	0.61	0.13 to 1.79	21	2.20	1.36 to 3.36	18	2.41	1.42 to 3.80	1.91	1.38 to 2.59
		1.0	Referent		0.33	0.10 to 1.10		1.00	0.56 to 1.81		0.98	0.54 to 1.78	0.87	0.54 to 1.40
Multiple causes of death, 1960—2005*														
Urinary tract cancer	13	0.63	0.34 to 1.08	9	1.53	0.70 to 2.90	14	1.23	0.67 to 2.06	16	1.73	0.99 to 2.81	1.47	1.04 to 2.01
		1.0	Referent		3.14	1.30 to 7.58		2.10	0.96 to 4.58		3.64	1.51 to 8.77	2.79	1.44 to 5.40
Chronic obstructive pulmonary disease	101	0.80	0.65 to 0.97	43	1.14	0.83 to 1.54	105	1.43	1.17 to 1.73	101	1.70	1.38 to 2.06	1.46	1.28 to 1.65
		1.0	Referent		1.51	1.03 to 2.21		1.75	1.30 to 2.36		2.50	1.64 to 3.79	1.79	1.39 to 2.31
Pneumoconiosis other than asbestosis and silicosis	43	19.1	13.8 to 25.7	3	3.37	0.70 to 9.85	10	5.54	2.65 to 10.2	12	9.53	4.92 to 16.7	6.32	4.09 to 9.39
		1.0	Referent		0.34	0.10 to 1.11		0.51	0.25 to 1.04		0.68	0.36 to 1.32	0.51	0.31 to 0.85
Diseases of arteries, veins, pulmonary circulation	113	0.96	0.79 to 1.16	51	1.19	0.88 to 1.56	117	1.31	1.09 to 1.58	97	1.52	1.23 to 1.85	1.35	1.20 to 1.53
		1.0	Referent		1.20	0.81 to 1.78		1.11	0.80 to 1.54		1.73	1.09 to 2.75	1.24	0.92 to 1.66
Chronic and unspecified renal disease	58	1.12	0.85 to 1.45	17	1.24	0.72 to 1.99	26	1.04	0.68 to 1.53	32	1.44	0.98 to 2.03	1.23	0.97 to 1.55
		1.0	Referent		1.10	0.62 to 1.96		1.13	0.68 to 1.88		1.47	0.88 to 2.43	1.21	0.84 to 1.75

*Cause-of-death categories as defined in table 1.
†Compared to <10 $\mu g/m^3$ maximum daily weighted average exposure.
SMR, standardised mortality ratio; SRR, standardised rate ratio.

Original article

The cause-of-death category containing CBD showed large excesses compared to the US population. Risk was strongly related to duration of employment and was highest 25—35 years since first employment. However, this category was not positively associated with cumulative or maximum exposure, findings also observed in other studies.[37][38] Several outcomes in addition to lung cancer were associated with beryllium in this study. Urinary tract cancer, COPD, and the category related to cor pulmonale were elevated compared to the US population among higher exposed workers and showed strong associations with cumulative (when short-term workers were excluded) exposure, maximum exposure or both. Obstructive lung disease was reported in a case series of workers with CBD[17] and in early descriptions of the US Beryllium Case Registry.[39] Obstructive pulmonary effects were also found in a cross-sectional study to be related to cumulative beryllium exposure among workers at another beryllium plant,[18] and chronic bronchitis was elevated in a group of beryllium-exposed dental technicians in Israel.[40] COPD among beryllium workers may represent misdiagnosed CBD; however, this is unlikely to fully explain our findings, because: (1) a clear exposure—response association (for both cumulative and maximum beryllium) was observed for COPD, but not for CBD. If COPD represented misdiagnosed CBD, similar exposure—response patterns would be expected for the two diseases, unless heavy beryllium exposure is likely to lead to greater misdiagnosis; (2) COPD is much more common, even for a beryllium-exposed population. A very large association between CBD and beryllium exposure would need to be observed to create the magnitude of exposure—response that we observed if COPD were unrelated to beryllium, and we saw little evidence of such an association.

Bladder and renal cancer have not been previously linked to beryllium exposure, but renal toxicity is expected from high beryllium exposure.[41] Nervous system cancers, which showed a positive trend with cumulative exposure, have been found to be associated with duration of employment in high-exposed jobs among beryllium workers at a US nuclear facility.[7][42]

It is unlikely that confounding by smoking explains the elevated lung cancer and COPD rates compared to the general population or the higher lung cancer and COPD rates observed among those with higher beryllium exposure compared to the lower exposed group. There was no evidence that the cohort smoked more than the US population, and very little evidence of differential smoking patterns by beryllium exposure. Incorporating the uncertainty from source terms for the lung cancer bias adjustment addresses a criticism[43] that the smoking adjustment in the previous analysis did not consider such variability, but does not change the interpretation of the results. Removing professional workers and those exposed for at least 1 year to another lung carcinogen had little effect on the results, providing further evidence that confounding was unlikely to account for the observed excess lung cancer rates within the cohort.

Strengths of this study include the lengthy follow-up period, large cohort, increased number of plants with quantitative exposure information, and the cohort design, which permitted consideration of multiple outcomes. Some limitations of this study include the unavailability of multiple-cause-of-death population rates before 1960 (which limited the ability to evaluate associations for some outcomes during early follow-up), the lack of quantitative exposure data for the Lorain, Lucky and Cleveland plants, and the reliance on high-volume general area and breathing zone samples to estimate personal exposures. For jobs having few or no exposure estimates, exposures were extrapolated from other jobs in the same work area or with similar job duties. These limitations are unlikely to have resulted in spurious associations with the cancers and chronic diseases studied here. For CBD and cor pulmonale, the categories available in LTAS.NET were broad and included many other causes of death.[28] Within the cohort, most of the deaths in these categories were from CBD and cor pulmonale. In the 'pneumoconiosis other than asbestosis or silicosis' category, 87% of cohort deaths were from acute and chronic beryllium disease. The comparable percentage among males in the US population is 1.3% from 1999 to 2006 and even lower before then.[44] This limitation caused substantial underestimation of the true SMR; however, within-cohort comparisons were unlikely to be affected.

Because of software requirements, the unlagged maximum exposure categories were established in advance based on an expectation that they would give approximately equivalent lung cancer case distribution. This limited the ability to explore alternative lags and to evaluate risks at lower exposures. The lowest maximum exposure cutpoint we evaluated was 10 µg/m^3; however, this level should not be assumed to provide a 'threshold' below which no excess risk is observed. Lastly, exposure—response models adjusting for several factors simultaneously could not be explored in detail in this analysis. We have conducted regression models on lung cancer risk sets with cumulative, average and maximum exposure, to address these limitations (Schubauer-Berigan et al. submitted).

REFERENCES

1. **Eisenbud M,** Berghout CF, Steadman LT. Environmental studies in plants and laboratories using beryllium; the acute disease. *J Ind Hyg Toxicol* 1948;**30**:281—5.
2. **VanOrdstrand HS,** Hughes R, DeNardi JM, et al. Beryllium poisoning. *JAMA* 1945;**129**:1084.
3. **Metzner FN,** Lieben J. Respiratory disease associated with beryllium refining and alloy fabrication; a case study. *J Occup Med* 1961;**3**:341—5.
4. **Cullen MR,** Kominsky JR, Rossman MD, et al. Chronic beryllium disease in a precious metal refinery. *Am Rev Resp Dis* 1987;**135**:201—8.
5. **Cummings KJ,** Stefaniak AB, Virji MA, et al. A reconsideration of acute beryllium disease. *Environ Health Perspect* 2009;**117**:1250—6.
6. **Finch GL,** Hoover MD, Hahn FF, et al. Animal models of beryllium-induced lung disease. *Environ Health Perspect* 1996;**104**:973—9.
7. **International Agency for Research on Cancer (IARC).** *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Beryllium, Cadmium, Mercury, and Exposures in the Glass Manufacturing Industry*. Lyon, France: IARC, 1993:41—117.
8. **Stokinger HE.** Introduction. In: Stokinger HE, ed, *Beryllium: Its Industrial Hygiene Aspects*. New York, NY: Academic Press, 1966:1—7.
9. **Ward E,** Okun A, Ruder A, et al. A mortality study of workers at seven beryllium processing plants. *Am J Ind Med* 1992;**22**:885—904.
10. **Straif K,** Benbrahim-Tallaa L, Baan R, et al. A review of human carcinogens—part C: metals, arsenic, dusts, and fibres. *Lancet Oncol* 2009;**10**:453—4.
11. **Steenland K,** Ward E. Lung cancer incidence among patients with beryllium disease: a cohort mortality study. *J Natl Cancer Inst* 1991;**83**:1380—5.
12. **Schubauer-Berigan MK,** Deddens JA, Steenland K, et al. Adjustment for temporal confounders in a reanalysis of a case-control study of beryllium and lung cancer. *Occup Environ Med* 2008;**65**:379—83.

13. **Sanderson WT,** Ward EM, Steenland K, et al. Lung cancer case-control study of beryllium workers. Am J Ind Med 2001;**39**:133—44.
14. **Mancuso TF.** Relation of duration of employment and prior respiratory illness to respiratory cancer among beryllium workers. Environ Res 1970;**3**:251—75.
15. **Mancuso TF.** Mortality study of beryllium industry workers' occupational lung cancer. Environ Res 1980;**21**:48—55.
16. **Wagoner JK,** Infante PF, Bayliss DL. Beryllium: an etiologic agent in the induction of lung cancer, nonneoplastic respiratory disease, and heart disease among industrially exposed workers. Environ Res 1980;**21**:15—34.
17. **Andrews JL,** Kazemi H, Hardy HL. Pattern of lung dysfunction in chronic beryllium disease. Am Rev Resp Dis 1969;**100**:791—800.
18. **Kriebel D,** Sprince NL, Eisen EA, et al. Beryllium exposure and pulmonary function: a cross sectional study of beryllium workers. Occup Environ Med 1988;**45**:83—92.
19. **Nemery B.** Metal toxicity and the respiratory tract. Eur Respir J 1990;**3**:202—19.
20. **Freiman DG,** Hardy HL. Beryllium disease. The relation of pulmonary pathology to clinical course and prognosis based on a study of 130 cases from the U.S. beryllium case registry. Hum Pathol 1970;**1**:25—44.
21. **Steenland K,** Greenland S. Monte Carlo sensitivity analysis and Bayesian analysis of smoking as an unmeasured confounder in a study of silica and lung cancer. Am J Epidemiol 2004;**160**:384—92.
22. **deVocht F,** Kromhout H, Ferro G, et al. Bayesian modelling of lung cancer risk and bitumen fume exposure adjusted for unmeasured confounding by smoking. Occup Environ Med 2009;**66**:502—8.
23. **Sanderson WT,** Petersen MR, Ward EM. Estimating historical exposures of workers in a beryllium manufacturing plant. Am J Ind Med 2001;**39**:145—57.
24. **Chen MJ.** Development of beryllium exposure matrices for workers in a former beryllium manufacturing plant. [Dissertation]. Cincinnati, OH: University of Cincinnati, 2001:1—99.
25. **Couch JR,** Petersen MR, Rice CR, et al. Development of retrospective quantitative and qualitative job exposure matrices for exposures at a beryllium processing plant. Occup Environ Med 2010;xx:(In press).
26. **Steenland K,** Spaeth S, Cassinelli R 2nd, et al. NIOSH life table program for personal computers. Am J Ind Med 1998;**34**:517—18.
27. **Schubauer-Berigan MK,** Raudabaugh WR, Ruder AM, et al. LTAS.NET: a life table analysis system for the windows environment [abstract]. Ann Epidemiol 2005;**15**:656.
28. **Robinson CF,** Schnorr TM, Cassinelli RT 2nd, et al. Tenth revision U.S. mortality rates for use with the NIOSH Life Table Analysis System. J Occup Environ Med 2006;**48**:662—7.
29. **Steenland K,** Nowlin S, Ryan B, et al. Use of multiple-cause mortality data in epidemiologic analyses: US rate and proportion files developed by the National Institute for Occupational Safety and Health and the National Cancer Institute. Am J Epidemiol 1992;**136**:855—62.
30. **Hein MJ,** Deddens JA, Schubauer-Berigan MK. Bias from matching on age at death or censor in nested case-control studies. Epidemiol 2009;**20**:330—8.
31. **VanOrdstrand HS,** Zielinski JF, DeNardi JM. Medical management of beryllium workers. In: Stokinger HE, ed. Beryllium: Its Industrial Hygiene Aspects. New York, NY: Academic Press, 1966:323—8.
32. **Axelson O,** Steenland K. Indirect methods of assessing the effects of tobacco use in occupational studies. Am J Ind Med 1988;**13**:105—8.
33. **National Center for Health Statistics (NCHS).** Changes in Cigarette Smoking Habits Between 1955 and 1966. Rockville, MD: U.S. Department of Health, Education, and Welfare, 1970:1—33.
34. **Hammond EC.** Smoking in relation to the death rates of one million men and women. In: Haenszel W, ed. Epidemiological Study of Cancer and Other Chronic Diseases. Washington DC: U.S. Government Printing Office, 1966:127—204.
35. **Gandini S,** Botteri E, Iodice S, et al. Tobacco smoking and cancer: a meta-analysis. Int J Cancer 2008;**122**:155—64.
36. **Henley SJ,** Thun MJ, Chao A, et al. Association between exclusive pipe smoking and mortality from cancer and other diseases. J Natl Canc Inst 2004;**96**:853—61.
37. **Schuler CR,** Kent MS, Deubner DC, et al. Process-related risk of beryllium sensitization and disease in a copper-beryllium alloy facility. Am J Ind Med 2005;**47**:195—205.
38. **Rosenman K,** Hertzberg V, Rice C, et al. Chronic beryllium disease and sensitization at a beryllium processing facility. Environ Health Perspect 2005;**113**:1366—72.
39. **Hasan FM,** Kazemi H. Chronic beryllium disease: a continuing epidemiologic hazard. Chest 1974;**65**:289—93.
40. **Fireman E,** Kramer MR, Priel I, et al. Chronic beryllium disease among dental technicians in Israel. Sarcoidosis Vasc Diffuse Lung Dis 2006;**23**:215—21.
41. **Wedeen RP.** Occupational and environmental renal disease. Semin Nephrol 1997;**17**:46—53.
42. **Carpenter AV,** Flanders WD, Frome EL, et al. Chemical exposures and central nervous system cancers: a case-control study among workers at two nuclear facilities. Am J Ind Med 1988;**13**:351—62.
43. **Levy PS,** Roth HD, Hwang PM, et al. Beryllium and lung cancer: a reanalysis of a NIOSH cohort mortality study. Inhal Toxicol 1988;**14**:1003—15.
44. **Centers for Disease Control and Prevention (CDC).** National Center for Health Statistics. Compressed Mortality File 1999-2006. CDC WONDER On-line Database, compiled from Compressed Mortality File 1999-2006 Series 20 No. 2L, 2009, Atlanta, USA 2009.